Baseline Factors Associated With Glycemic Control and Weight Loss When Exenatide Twice Daily Is Added to Optimized Insulin Glargine in Patients With Type 2 Diabetes

Julio Rosenstock, md[1]
Sylvia K. Shenouda, phd[2]
Richard M. Bergenstal, md[3]
John B. Buse, md, phd[4]
Leonard C. Glass, md[2]
Cory R. Heilmann, phd[2]
Anita Y.M. Kwan, ms[5]
Leigh A. MacConell, phd[6]
Byron James Hoogwerf, md[5]

OBJECTIVE—To determine variables associated with glycemic and body weight responses when adding exenatide to basal insulin–treated type 2 diabetes.

RESEARCH DESIGN AND METHODS—Exploratory subgroup analyses based on baseline A1C, disease duration, and BMI of a 30-week study comparing exenatide twice daily to placebo, added to optimized insulin glargine (intent-to-treat analysis: 137 exenatide; 122 placebo).

RESULTS—Exenatide participants had greater A1C reductions compared with optimized insulin glargine alone, irrespective of baseline A1C ($P < 0.001$). Exenatide participants with longer diabetes duration and those with lower BMI had greater A1C reductions ($P < 0.01$). Exenatide participants lost more weight, regardless of baseline A1C or BMI ($P < 0.05$). Exenatide participants with longer diabetes duration lost the most weight ($P < 0.001$).

CONCLUSIONS—Exenatide added to optimized basal insulin was associated with improved glycemic control and weight loss, irrespective of baseline A1C, diabetes duration, and BMI. Changes were evident in modestly obese patients and in those with longer diabetes duration.

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The combined use of glucagon-like peptide 1 (GLP-1) receptor agonists and insulin is of growing clinical interest (1–6), and the combined use of insulin glargine with exenatide is now approved in the U.S. In this recent study, exenatide twice daily added to optimized titration of glargine resulted in greater A1C improvements with weight loss and lesser increase in insulin dose than placebo plus optimized glargine (5). The current exploratory post hoc analysis assessed the relationship of baseline A1C, duration of diabetes, and BMI with glucose control, body weight changes, and insulin doses in that study.

RESEARCH DESIGN AND METHODS

—A full study description has been published (5). The study was approved by institutional review boards in accordance with the Declaration of Helsinki.

Participants were on ≥20 units/day of insulin glargine, alone or plus metformin and/or pioglitazone, with A1C 7.1–10.5% and BMI ≤45 kg/m^2. At randomization, if A1C >8.0%, insulin glargine dose continued unchanged, but if A1C ≤8.0%, the dose was decreased by 20%. After 5 weeks, participants began weekly structured insulin titrations to achieve a fasting glucose <100 mg/dL (7) guided by self-monitoring of blood glucose.

Subgroups

Participant subgroups included baseline A1C (≤8 and >8%), duration of disease (<9, 9–15, and >15 years), and baseline BMI (<30, 30–36, and >36 kg/m^2).

Statistical methods

Mixed models with repeated measures similar to the original analyses (5) were fitted separately to subgroups.

RESULTS

—Out of 261 randomized participants, 2 discontinued without receiving study medication, leaving 137 exenatide and 122 placebo participants to be included in the intent-to-treat analysis. Baseline characteristics were similar between the two treatment groups (5).

Glycemic control

Both exenatide and placebo participants had significant A1C reductions regardless of baseline A1C, duration of diabetes, or baseline BMI (Supplementary Table 1 and Supplementary Fig. 1). Exenatide participants had significantly greater A1C reductions compared with placebo participants at end point regardless of baseline A1C (least square [LS] mean difference, A1C ≤8%: −0.52%; A1C >8%: −0.75%; $P < 0.001$). Exenatide participants with 9–15 and >15 years of diabetes had greater A1C reductions compared with placebo participants at end point (LS mean difference, −0.78 and −0.82%, respectively; $P < 0.001$); exenatide participants with <9 years of diabetes had lesser A1C reduction (LS mean difference, −0.31%; $P = 0.124$). Exenatide

From the [1]Dallas Diabetes and Endocrine Center at Medical City, Dallas, Texas; [2]Eli Lilly and Company, Indianapolis, Indiana; the [3]International Diabetes Center at Park Nicollet, Minneapolis, Minnesota; the [4]University of North Carolina School of Medicine, Chapel Hill, North Carolina; [5]Lilly USA, LLC, Indianapolis, Indiana; and [6]Amylin Pharmaceuticals, Inc., San Diego, California.
Corresponding author: Byron James Hoogwerf, hoogwerf_byron_james@lilly.com.
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participants with <30 and 30–36 kg/m^2 BMI had greater reductions in A1C compared with placebo (LS mean difference, −0.62 and −0.85%, respectively; $P <$ 0.01); exenatide participants with BMI >36 kg/m^2 had less reduction (LS mean difference, −0.39%; $P = 0.05$) (Fig. 1).

At end point, both treatment groups had significant reductions in glucose profiles across the assessed baseline parameters (Supplementary Fig. 2), with exenatide consistently associated with significantly lower postprandial, but not fasting, glucose levels.

Change in weight

At end point, there was a weak but statistically significant correlation between weight loss and A1C reduction in exenatide participants ($R^2 = 0.07$; $P = 0.002$) and no significant correlation for placebo ($R^2 = 0.002$; $P = 0.637$). Both exenatide and placebo showed a relatively stronger, but still weak, correlation ($R^2 = 0.137$ and 0.144, respectively; $P < 0.001$) between weight gain and increase in insulin dose, which was attenuated when analyzed by total daily insulin dose, instead of change in insulin dose.

Exenatide participants lost weight during the 30-week study regardless of baseline A1C (≤8 and >8%) (Fig. 1 and Supplementary Table 1), with significant reductions in weight compared with placebo at end point (LS mean difference, −1.9 and −3.0 kg, respectively; $P <$ 0.05). Placebo participants, with baseline A1C ≤8%, showed no change in weight, while those with A1C >8% gained weight. At study end, exenatide participants with >15 years of diabetes had the greatest weight loss during the study (LS mean difference at end point, −3.9 kg;

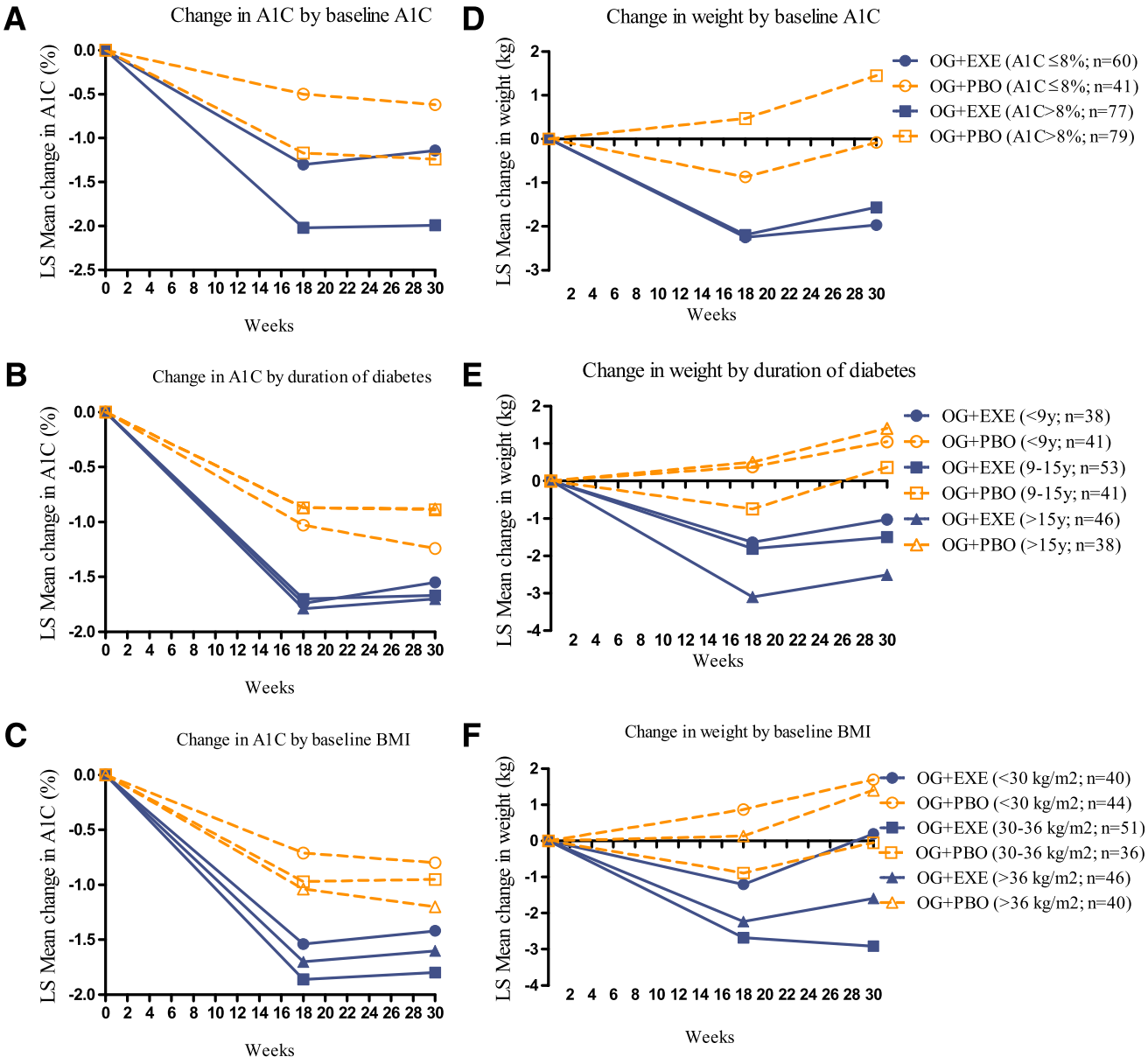

Figure 1—*LS mean change of A1C during 30 weeks in exenatide and placebo participants with baseline A1C ≤8 and >8%* (A), *<9, 9–15, and >15 years' duration of diabetes* (B), *and baseline BMI <30, 30–36, and >36 kg/m^2* (C). *LS mean change of weight during 30 weeks in exenatide and placebo participants with baseline A1C ≤8 and >8%* (D), *<9, 9–15, and >15 years' duration of diabetes* (E), *and baseline BMI <30, 30–36, and >36 kg/m^2* (F). *OG+EXE, optimized insulin glargine + exenatide twice daily; OG+PBO, optimized insulin glargine + placebo. Data presented as LS mean change in A1C and weight from baseline.*

$P < 0.001$). In participants with <9 and 9–15 years of diabetes, treatment differences were of smaller magnitude compared with placebo (LS mean difference at end point −2.1 and −1.9 kg, respectively; $P < 0.05$). Placebo participants with >15 years of diabetes gained weight. Exenatide participants with higher baseline BMI (30–36 and >36 kg/m^2) lost weight, while placebo participants with baseline BMI <30 and >36 kg/m^2 gained weight. Across baseline BMI tertiles (<30, 30–36, and >36 kg/m^2), greater weight loss was observed in exenatide participants compared with placebo participants (LS mean difference, −1.5, −2.9, and −3.0 kg, respectively; $P < 0.05$) (Fig. 1).

Insulin dose

At end point, no treatment differences in insulin dose with respect to baseline A1C or duration of diabetes were observed (Supplementary Table 1). Insulin dose was significantly lower in exenatide participants with baseline BMI 30–36 and >36 kg/m^2 compared with placebo participants (LS mean difference, −9.2 and −12.2 units, respectively; $P < 0.05$). No difference in insulin dose was observed in participants with baseline BMI <30 kg/m^2 (LS mean difference at end point, −1.2 units; $P = 0.791$).

CONCLUSIONS

—Intensive basal insulin replacement, with structured insulin titration is often associated with weight gain (8–12). Understanding the relationships of weight changes and A1C improvements associated with clinical characteristics such as A1C, duration of diabetes, and BMI may assist physicians in individualizing specific therapies for patients with type 2 diabetes (1–4).

Higher baseline A1C is associated with reduced ability to achieve glycemic targets, although higher A1C values are associated with greater reductions from baseline (13,14). The current study demonstrates the latter observation, and regardless of baseline A1C, exenatide had greater reduction relative to insulin glargine alone.

It has been theorized that incretin-based therapies have diminished efficacy with long-standing disease and fewer β-cells (15). However, the current study shows that participants with >9 years' duration of diabetes had better glycemic responses to the combination of exenatide and basal insulin than insulin glargine alone.

Weight gain was observed in placebo participants, while exenatide participants lost weight at end point (5), with a significant, but weak, correlation between A1C reduction and weight loss. Differences in weight loss between the treatment groups seemed to be more prominent in participants with higher baseline A1C, higher BMI, and a longer duration of diabetes.

This post hoc analysis must be interpreted cautiously. Nevertheless, these data provide a basis to question the common perceptions that exenatide works best in the heaviest patients with a short duration of diabetes (15).

In summary, exenatide added to optimized insulin glargine was associated with greater A1C and weight reductions compared with optimized insulin glargine alone, including modestly obese patients with a longer duration of diabetes.

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