Effects of Exenatide (Exendin-4) on Glycemic Control and Weight Over 30 Weeks in Metformin-Treated Patients With Type 2 Diabetes

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OBJECTIVE — This study evaluates the ability of the incretin mimetic exenatide (exendin-4) to improve glycemic control in patients with type 2 diabetes failing to achieve glycemic control with maximally effective metformin doses.

RESEARCH DESIGN AND METHODS — A triple-blind, placebo-controlled, 30-week study at 82 U.S. sites was performed with 336 randomized patients. In all, 272 patients completed the study. The intent-to-treat population baseline was 53 ± 10 years with BMI of 34.2 ± 5.9 kg/m² and HbA1c of 8.2 ± 1.1%. After 4 weeks of placebo, subjects self-administered 5 μg exenatide or placebo subcutaneously twice daily for 4 weeks followed by 5 or 10 μg exenatide, or placebo subcutaneously twice daily for 26 weeks. All subjects continued metformin therapy.

RESULTS — At week 30, HbA1c changes from baseline ± SE for each group were −0.78 ± 0.10% (10 μg), −0.40 ± 0.11% (5 μg), and +0.08 ± 0.10% (placebo; intent to treat; adjusted P < 0.002). Of evaluable subjects, 46% (10 μg), 32% (5 μg), and 13% (placebo) achieved HbA1c ≤7% (P < 0.01 vs. placebo). Exenatide-treated subjects displayed progressive dose-dependent weight loss (−2.8 ± 0.5 kg [10 μg], −1.6 ± 0.4 kg [5 μg], P < 0.001 vs. placebo). The most frequent adverse events were gastrointestinal in nature and generally mild to moderate. Incidence of mild to moderate hypoglycemia was low and similar across treatment arms, with no severe hypoglycemia.

CONCLUSIONS — Exenatide was generally well tolerated and reduced HbA1c with no weight gain and no increased incidence of hypoglycemia in patients with type 2 diabetes failing to achieve glycemic control with metformin.
the effects of exenatide on glycemic control over a 30-week period in patients with type 2 diabetes failing to achieve glycemic control with metformin.

**RESEARCH DESIGN AND METHODS**— Subjects were 19–78 years of age with type 2 diabetes treated with metformin monotherapy. General inclusion criteria were screening fasting plasma glucose concentration of ≤13.3 mmol/l (≤240 mg/dl), BMI of 27–45 kg/m², and HbA₁c of 7.1–11.0%. The metformin dose was ≥1,500 mg/day for 3 months before screening. Subjects were weight stable (±10%) for 3 months before screening with no clinically significant (for a type 2 diabetes population) abnormal laboratory test values (>25% outside normal laboratory values). Female subjects were postmenopausal, surgically sterile, or using contraceptives for 3 months before screening and continuing throughout the study. Exclusion criteria included use of sulfonylureas, meglitinides, thiazolidinediones, α-glucosidase inhibitors, exogenous insulin therapy, weight loss drugs, corticosteroids, drugs known to affect gastrointestinal motility, transplantation medications, or any investigational drug, or evidence of clinically significant co-morbid conditions for 3 months before screening.

Adults (n = 336) with type 2 diabetes treated with metformin participated at 82 sites in the U.S. (January 2002 to June 2003). A common clinical protocol was approved for each site by an institutional
review board in accordance with the principles described in the Declaration of Helsinki, including all amendments through the 1996 South Africa revision (26). All subjects provided written informed consent before participation.

This was a balanced, randomized, triple-blind, placebo-controlled, parallel-group clinical study (30-week duration) designed after consultation with the U.S. Food and Drug Administration to evaluate glycemic control, as assessed by HbA1c, and safety. The study commenced with a 4-week, single-blind, lead-in period with subcutaneous injection of placebo twice daily. Thereafter, subjects were randomly assigned to one of four treatment arms. Nausea had been the most frequent treatment-emergent adverse event in earlier clinical trials, but gradual dose escalation has been shown to attenuate this side effect (27). Therefore, the present study design included an acclimation period (4 weeks) at a lower exenatide fixed dose (5 μg twice daily) in treatment arms A and B before the fixed dose of exenatide was either increased to 10 μg twice daily (arm B) or kept at 5 μg twice daily (arm A) for the duration of the study. Volumes of placebo equivalent to those administered to arms A and B were administered in treatment arms C and D. Study medication was self-injected subcutaneously in the abdomen within 15 min before meals in the morning and evening. All subjects continued their current regimen of metformin treatment (≥1,500 mg/day).

Subjects were instructed to fast overnight during the study. Any subject with either an HbA1c change of +1.5% from baseline at any clinic visit or an HbA1c ≥11.5% at week 18 or 24 could be terminated from the study for safety reasons at the investigator’s discretion (loss of glucose control). Similarly, subjects could be withdrawn if fasting plasma glucose values were >13.3 mmol/l (>240 mg/dl) on two consecutive study visits or if recorded fingerstick fasting blood glucose values were >14.4 mmol/l (>260 mg/dl) for at least 2 weeks, not secondary to a readily identified illness or pharmacological treatment.

A subset of subjects (meal cohort) underwent a standardized meal tolerance test on weeks 0, 4, and 30. After an overnight fast (≥8 h), subjects took their morning dose of metformin within 1 h of their clinic visit. Exenatide or placebo was injected 15 min before a standardized breakfast. Meal size was calculated individually at screening to provide 20% of a subject’s total daily caloric requirements with a macronutrient composition of 55% carbohydrate, 15% protein, and 30% fat based on body weight and activity level. The size of the standardized breakfast was the same on each test day for each individual subject.

Study end points
Primary end points included glycemic control, as assessed by HbA1c, and safety. Secondary end points included percentage of patients achieving HbA1c ≤7% by week 30, effect of exenatide on fasting and postprandial (meal cohort only) plasma glucose concentrations, body weight, fasting and postprandial concentrations of blood insulin, fasting proinsulin, and lipids.

Statistical analysis
Randomization was stratified according to screening HbA1c values (<9.0% and ≥9.0%) to achieve a balanced distribution of subjects across treatment arms (A, B, C, and D).
A minimum sample size of 300 subjects with at least one postbaseline HbA1c measurement was estimated to provide ~90% power to detect a difference of 0.6% in the change from baseline to each visit in HbA1c and weight across treatments (28,29). Factors in the model included treatment (placebo and two active treatment arms), strata of baseline HbA1c (<9.0% and ≥9.0%), and study site as fixed effects. Before data analysis, sites were pooled according to geographic location to prevent loss of too many degrees of freedom in the model. This pooling took into account the number of endocrinologists, patient accessibility to specialty diabetes care, and quality of managed care in the geographic locations.

The intent-to-treat population was defined as all randomized subjects who received at least one injection of medication starting from the evening of day 1. All efficacy and safety analyses were performed on the intent-to-treat population with the exception of the percentage of subjects achieving HbA1c ≤7% (evaluable population) and the meal tolerance cohort. For intent-to-treat subjects, missing data (including missing values at intermediate visits) were imputed from scheduled visits using the last-observation-carried-forward method. The least square means and SE were derived from the general linear model for each treatment. Pairwise comparisons of the treatment effects were performed using Fisher’s protected testing procedure to control type I errors due to multiple comparisons (30). Similar analyses were performed for each fasting metabolic parameter and for postprandial plasma glucose concentrations without adjusting for the multiple comparisons. Post hoc evaluation of change in body weight versus duration of nausea was performed using regression analysis. The proportion of subjects achieving HbA1c ≤7% was compared across treatment groups using the Cochran-Mantel-Haenszel test, wherein strata of baseline HbA1c values served as the stratification factor. Results are given as means ± SE unless otherwise indicated.

The evaluable population was defined as all randomized subjects who completed treatment through week 30 and received at least 80% of the study medication injections. Subjects who missed 7 consecutive days of injections during the last 2 months of the study were excluded.

Safety analysis
All safety analyses were performed using the intent-to-treat population. Safety end points included adverse events, clinical laboratory tests, physical examination, 12-lead electrocardiogram, vital signs, and titering of anti-exenatide antibodies. Treatment-emergent adverse events were defined as those occurring upon or after receiving the first randomized dose. The intensity of hypoglycemic episodes was

Figure 3—Meal tolerance subgroups. Postprandial plasma glucose concentrations after a standardized meal at week 0 (A) and at week 30 (B) and postprandial plasma insulin levels at week 30 (C). Exenatide or placebo were administered at time zero. Evaluable population: 10 μg exenatide, n = 16; 5 μg exenatide, n = 7; placebo, n = 13. Data are mean ± SE.
defined as mild/moderate or severe. For mild/moderate hypoglycemia, subjects reported symptoms consistent with hypoglycemia that may have been documented by a plasma glucose concentration value \(<3.3\) mmol/l. For severe hypoglycemia, subjects required the assistance of another person to obtain treatment for their hypoglycemia, including intravenous glucose or intramuscular glucagon.

**Assays**

Plasma analytes and HbA1c were quantitated by Quintiles Laboratories (Smyrna, GA) using standard methods. HbA1c was measured using a high-performance liquid chromatography methodology (31,32). Serum insulin and proinsulin were quantitated by Esoterix Endocrinology (Calabasas Hills, CA) by two-site immunochemiluminometric assays. Intra-assay variability ranged from 3 to 12% and interassay variability from 7 to 14%. Cross-reactivities for the insulin assay were \(<0.001\%\) with IGF-I and IGF-II, \(<0.01\%\) with C-peptide, and \(<0.1\%\) with proinsulin. There was no significant cross-reaction for the proinsulin assay with IGF-I, IGF-II, C-peptide, or insulin. Plasma exenatide and anti-exenatide antibodies were measured as described previously (12).

**RESULTS**

Study population demographics were evenly balanced across treatment arms (Fig. 1). The intent-to-treat population comprised 336 subjects with 272 subjects completing the study (81%) and 64 withdrawing early (19%). Withdrawal rates were equally distributed across treatment arms. Other than metformin, the most frequently used concomitant medications were ACE inhibitors (114 subjects, 34%), hydroxymethylglutaryl-CoA reductase inhibitors (102 subjects, 30%), and statins (89 subjects, 26%).

**Figure 4**—Body weight in the intent-to-treat population. A: Change in body weight from baseline. Baseline weights were \(101.2 \pm 2.0\) kg in the 10-µg exenatide arm, \(100.2 \pm 2.0\) kg in the 5-µg exenatide arm, and \(100.2 \pm 2.0\) kg in the placebo arm. B: Change in weight from baseline stratified by baseline BMI \(<30\) and \(\geq 30\) kg/m². For baseline BMI \(<30\) kg/m², baseline body weights were \(84.0 \pm 1.9\) kg in the 10-µg exenatide arm, \(80.8 \pm 2.0\) kg in the 5-µg exenatide arm, and \(80.3 \pm 2.2\) kg in the placebo arm. For baseline BMI \(\geq 30\) kg/m², baseline body weights were \(106.9 \pm 2.1\) kg in the 10-µg exenatide arm, \(108.3 \pm 2.3\) kg in the 5-µg exenatide arm, and \(105.8 \pm 1.8\) kg in the placebo arm. *P \(\leq 0.05\) compared with placebo treatment. **P \(\leq 0.001\) compared with placebo treatment. Data are mean ± SE.
inhibitors (112 subjects, 33%), and platelet aggregation inhibitors, excluding heparin (101 subjects, 30%).

HbA1c and plasma glucose

HbA1c values declined in all treatment arms during the placebo lead-in period and the initial 2 weeks of the study after randomization (Fig. 2A). At week 4, significant reductions in HbA1c from baseline were observed in both exenatide treatment arms compared with placebo ($P < 0.0005$). At week 30, a significant dose-dependent reduction in HbA1c was observed in both exenatide-treated arms compared with placebo ($P < 0.001$, overall $F$ test).

For intent-to-treat subjects at week 30 with baseline HbA1c greater than 7%, 40% (41 subjects) in the 10-μg exenatide arm and 27% (27 subjects) in the 5-μg exenatide arm reached an HbA1c ≤7%. This proportion of the population was significantly greater than in the placebo arm (11% [11 subjects]; $P < 0.01$ for pairwise comparisons). Similarly, for the evaluable population with baseline HbA1c values greater than 7%, 46% (39 subjects) in the 10-μg exenatide arm and 32% (25 subjects) in the 5-μg exenatide arm achieved an HbA1c ≤7% by week 30. These proportions of the evaluable population were significantly greater than in the placebo arm (13% [10 subjects]; $P < 0.0001$ and $P < 0.01$, respectively) (Fig. 2B).

Fasting plasma glucose concentrations were equivalent among treatment arms at baseline (Fig. 1). At week 30, fasting plasma glucose concentrations were $-0.6 \pm 0.2$ mmol/l ($-10.1 \pm 4.4$ mg/dl; $P = 0.0001$) and $-0.4 \pm 0.3$ mmol/l ($-7.2 \pm 4.6$ mg/dl; $P < 0.005$) for the 10- and 5-μg exenatide arms, respectively, compared with $+0.8 \pm 0.2$ mmol/l ($+14.4 \pm 4.2$ mg/dl) for the placebo arm. The end of study difference from baseline observed in both exenatide-treated arms compared with placebo ($P < 0.001$, overall $F$ test).

In subjects who underwent a standardized meal tolerance test, baseline data at week 0 (all arms received placebo) showed a similar rise in postprandial plasma glucose concentrations across treatment arms (Fig. 3A). Geometric mean area under the curve 15–180 min values at baseline were similar. At week 4, postprandial plasma glucose concentrations were reduced in both exenatide arms compared with placebo ($P = 0.006$). Postprandial plasma glucose geometric mean area under the curve 15–180 min values averaged 34% lower than baseline in each exenatide arm, compared with only 9% lower than baseline in the placebo arm. This pattern was sustained to week 30 with a robust lowering of postprandial glucose concentrations in the 10-μg ($P = 0.004$) and 5-μg exenatide arms ($P = 0.03$; Fig. 3B). At week 30, there was a rise in plasma insulin in response to the meal in all three arms, with a greater early increment noted in the 10-μg exenatide arm compared with placebo, despite lower baseline and postprandial glucose concentrations (Fig. 3C).

Body weight

Body weight averaged 100 kg across all treatment arms at baseline (Fig. 1). During the study, exenatide arms had progressive weight loss from baseline (Fig. 4A). Reductions in body weight were observed regardless of baseline BMI (Fig. 4B).

Insulin and proinsulin

Baseline fasting insulin and proinsulin concentrations were similar across treatment arms (Fig. 1). Despite the reduction in fasting plasma glucose concentrations in the exenatide arms, there were no significant differences in fasting plasma insulin concentrations from baseline in any treatment arm ($+2.1 \pm 7.8$ pmol/l [10 μg], $-3.5 \pm 14.7$ pmol/l [5 μg], $-5.6 \pm 10.4$ pmol/l [placebo]). There was a trend toward a decline in fasting plasma proinsulin concentrations from baseline ($-9.6 \pm 3.8$ pmol/l [10 μg], $-5.2 \pm 5.9$ pmol/l [5 μg], $-0.9 \pm 4.5$ pmol/l [placebo]) and a significant decrease in the proinsulin-to-insulin ratio toward more physiological proportions in the 10-μg exenatide arm ($P < 0.001$), with a similar trend observed in the 5-μg exenatide arm (Fig. 5).

Clinical laboratory findings and safety

Exenatide treatment was not associated with an increased incidence of cardiovascular, hepatic, or renal adverse events. No changes in plasma lipids, laboratory safety parameters, heart rate, blood pres-
Table 1—Treatment-emergent adverse events

<table>
<thead>
<tr>
<th>Event</th>
<th>Placebo</th>
<th>5-μg exenatide</th>
<th>10-μg exenatide</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>113</td>
<td>110</td>
<td>113</td>
</tr>
<tr>
<td>Nausea</td>
<td>26 (23)</td>
<td>40 (36)</td>
<td>51 (43)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>9 (8)</td>
<td>13 (12)</td>
<td>18 (16)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>12 (11)</td>
<td>15 (14)</td>
<td>11 (10)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>4 (4)</td>
<td>12 (11)</td>
<td>13 (12)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>7 (6)</td>
<td>10 (9)</td>
<td>5 (4)</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>6 (5)</td>
<td>5 (5)</td>
<td>7 (6)</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>6 (5)</td>
<td>5 (5)</td>
<td>6 (5)</td>
</tr>
<tr>
<td>Back pain</td>
<td>3 (3)</td>
<td>3 (3)</td>
<td>7 (6)</td>
</tr>
</tbody>
</table>

Data are n (%). Adverse events had an overall incidence ≥5% in any treatment arm and a higher incidence in an exenatide arm for the intent-to-treat population.

Exenatide and glycemic control

sure, or electrocardiogram variables were observed between treatment arms.

The incidence of serious (2.7, 4.5, and 3.5% for 10-μg, 5-μg, and placebo arms, respectively) and severe (9.7, 11.8, and 8.8% in the 10-μg, 5-μg, and placebo arms, respectively) treatment-emergent adverse events was low and evenly distributed across treatment arms. The most frequent adverse events were mild or moderate and were gastrointestinal in nature (Table 1). Nausea was the most frequent severe adverse event, and it was higher in exenatide-treated subjects than in placebo-treated subjects. Nausea was generally mild or moderate in intensity, with the incidence of severe nausea (3.5, 2.7, and 1.8% in the 10-μg, 5-μg, and placebo arms, respectively) and withdrawals due to nausea low (4 of 11 withdrawals [1.8%] in the exenatide arms). Nausea was reported at a higher incidence during the initial weeks of therapy (weeks 0–8) and declined thereafter (Fig. 6). There was no correlation between change in body weight and duration of nausea. Post hoc analysis of nausea and body weight change showed a lack of correlation between change in body weight and nausea duration (10 μg exenatide: \( Y = -0.006X - 3.538, R^2 = 0.009 \); 5 μg exenatide: \( Y = +0.004X - 2.182, R^2 = 0.004 \); placebo: \( Y = +0.002X - 0.435, R^2 = 0.0002 \)). Moreover, subjects who never experienced nausea also lost weight: 2.2 ± 0.7 kg (10-μg exenatide arm) and 1.4 ± 0.4 kg (5-μg exenatide arm).

There were no cases of severe hypoglycemia. The overall incidence of mild to moderate hypoglycemia was 5.3% (six subjects) in the 10-μg exenatide arm, 4.5% (five subjects) in the 5-μg exenatide arm, and 5.3% (six subjects) in the placebo arm. The incidence of anti-exenatide antibodies (43% at 30 weeks) had no predictive effect on glycemic control or adverse events. Most treatment-emergent anti-exenatide antibodies were low titer (1/125) and of unknown biological relevance.

CONCLUSIONS — The data demonstrate that when exenatide at doses of 5 and 10 μg twice daily is added to a background of metformin for 30 weeks in a group of type 2 diabetic patients with less-than-optimal glycemic control (baseline HbA1c ~8.2%), there was an overall improvement in glycemia (end of study HbA1c ~7.4%), with nearly 50% of patients able to reach an HbA1c treatment goal of ≤7% when treated with the 10-μg dose. The magnitude of HbA1c reduction was notable, as the baseline HbA1c was relatively low (8.2%). Many previous trials in this disease population have studied patients with higher baseline HbA1c levels, where it is possible to exert a greater HbA1c-lowering effect (33,34). Reduction of HbA1c was the result of a modest decrease in fasting plasma glucose concentrations in keeping with the pharma-cokinetic profile of exenatide and, more importantly, a sustained robust glucose-lowering effect postprandially, as indicated by the meal challenge cohort.

It is also noteworthy that the improvement in glycemia was coupled with overall weight loss and no increase in hypoglycemia. Exenatide treatment elicited dose-dependent reductions in body weight (~3% at the 10-μg dose) that did not appear to fully plateau by week 30. This occurred in the setting of a significant improvement in overall glycemia, where one would ordinarily see weight gain with most other therapies. Weight loss occurred in subjects who had not experienced nausea and was independent of nausea in the cohort at large, as weight loss was sustained over the course of the study but nausea was more pronounced during the first weeks of therapy.

Figure 6—Time-dependent incidence of subjects experiencing treatment-emergent nausea in the intent-to-treat (ITT) population.
The improvement in the proinsulin-to-insulin ratio noted in the exenatide-treated patients is an indication of a beneficial effect on the β-cell. In addition, the meal challenge data indicate a robust insulin secretory response to the meal stimulus despite lower fasting and postprandial glucose concentrations. More detailed analysis of pancreatic β-cell function in long-term treatment with exenatide will be necessary to better characterize the potential positive effects of exenatide on the β-cell.

These results are consistent with those reported in a similar 30-week placebo-controlled phase III study of the effects of exenatide on glycemic control and safety in subjects with type 2 diabetes failing to achieve glycemic control with sulfonylureas (35). In that study, at week 30 the 10-µg exenatide arm had significant placebo-adjusted reductions of −1.0% in HbA1c and −1.0 kg in weight. In addition, a reduction in the proinsulin-to-insulin ratio in the 10-µg exenatide arm indicated that exenatide had a beneficial effect on the β-cell (32). In a parallel, 30-week placebo-controlled phase III study in subjects with type 2 diabetes failing to achieve glycemic control with metformin and a sulfonylurea, the 10-µg exenatide arm had significant placebo-adjusted reductions of −1.0% in HbA1c and −0.7 kg in weight at week 30 (36). Thus, exenatide appears to elicit similar glyemic effects whether patients are on background metformin or sulfonylurea or a combination of both.

Combining exenatide with metformin did not increase the risk of hypoglycemia. It is acknowledged that metformin is antihyperglycemic in its action and has little or no hypoglycemic potential. That noted, although there was a background incidence of hypoglycemia in the metformin-plus-placebo group, it was mild or moderate in nature and of questionable clinical significance. Importantly, despite a decrease of nearly 1% in HbA1c with exenatide, there was no increase in hypoglycemia above that seen in the placebo arm and no severe hypoglycemic events. This is a clear representation of the glucose-dependent action of exenatide and offers a potential advantage over other therapies in this area, such as the oral insulin secretagogues and exogenously administered insulin.

The most common treatment-emergent adverse event was dose-related nausea. Nausea was mostly mild-to-moderate in intensity with a low incidence of severe nausea; only 3% of subjects in the 10-µg exenatide arm withdrew from the clinical trial due to nausea. The incidence of treatment-emergent nausea was highest at initiation of the maintenance dose (weeks 4–8 for 10 µg and weeks 0–4 for 5 µg) and became less frequent with subsequent dosing. Lastly, anti-exenatide antibodies were detected in a subset of patients but this was not associated with any apparent loss of efficacy or increased incidence of immune system-associated adverse events.

In summary, in patients treated with metformin who are not achieving adequate glycemic control, exenatide elicited a substantial reduction in HbA1c with no increase in the incidence of hypoglycemia and was associated with significant and sustained weight loss. This combination of beneficial effects suggests that long-term use of exenatide at subcutaneous doses of 5 µg and 10 µg twice daily has potential for the treatment of patients with type 2 diabetes not adequately controlled with metformin.

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