Exploring the Substitution of Exenatide for Insulin in Patients With Type 2 Diabetes Treated With Insulin in Combination With Oral Antidiabetes Agents

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OBJECTIVE — This 16-week study explored the safety of substituting exenatide for insulin in patients with type 2 diabetes using insulin in combination with oral antidiabetes agents.

RESEARCH DESIGN AND METHODS — Successful maintenance of glycemic control was predefined as an A1C increase of <0.5%. A total of 49 patients (aged 53 ± 8 years, with BMI 34 ± 4 kg/m^2, A1C 8.1 ± 1.1%, and duration of diabetes 11 ± 7 years) were randomized to either substitute exenatide for insulin or remain on their current insulin regimen. Patients who either completed ≥8 weeks of study or discontinued because of loss of glycemic control were included in primary efficacy analysis.

RESULTS — A total of 62% (18 of 29) of the exenatide-treated patients maintained glycemic control compared with 81% (13 of 16) of the insulin-treated patients. Of the 11 exenatide-treated patients who did not maintain control, 5 discontinued before week 16 because of loss of glucose control. The overall safety profile was generally consistent with previous exenatide trials. The mean overall hypoglycemia rates were 1.72 and 0.97 events/patient-year for the exenatide and insulin reference groups, respectively.

CONCLUSIONS — This pilot study suggests that it is feasible to sustain glycemic control when substituting exenatide for insulin. Although it is not possible to characterize clear predictors of outcome given the size and exploratory nature of the study, the data suggest that patients with longer disease duration, who are taking higher doses of insulin and have less endogenous β-cell function, may experience deterioration in glucose control if exenatide is substituted for insulin therapy.

Diabetes Care 30:2767–2772, 2007

Progressive loss of β-cell function (1) and mass (2) makes it difficult for patients to maintain glycemic control (3–5). Historically, insulin therapy is considered the treatment of choice when diet, exercise, and oral antidiabetes agents fail to maintain adequate glycemic control. Initiation of therapy can include once-daily intermediate or long-acting insulin or a formulation containing both basal and rapid-acting components (6–8). However, intensification of insulin therapy is often accompanied by weight gain and hypoglycemia, well-recognized barriers to improvement of glycemic control (9,10).

Exenatide is a first-in-class incretin mimetic indicated for use with metformin and/or a sulfonylurea but is not approved as a substitute for insulin in insulin-requiring patients. The mechanism whereby exenatide improves glycemic control is quite different from that of exogenous insulin. Exenatide stimulates endogenous insulin secretion in a glucose-dependent manner, suppresses glucagon, slows gastric emptying, and reduces food intake (11,12). Noninferiority studies (13,14) of patients failing to maintain glycemic control on oral antidiabetes agents have shown that it is feasible to attain similar A1C improvement with exenatide and insulin. Exenatide also lowers postprandial and fasting glucose but, unlike insulin, is associated with a reduction in body weight. However, there are few data supporting the potential substitution of insulin with exenatide in patients with type 2 diabetes (15–17). Therefore, the primary objective of this study was to explore the safety of substituting exenatide for insulin in patients with type 2 diabetes who were using insulin in combination with oral antidiabetes medications.

RESEARCH DESIGN AND METHODS

— This exploratory, multicenter, two-arm, parallel-design, open-label trial was conducted over 16 weeks at five centers in the U.S. Patients randomized to the exenatide group used a multi-use pen to subcutaneously inject a fixed dose of 5 μg b.i.d. for 4 weeks and 10 μg b.i.d. for the remaining 12 weeks of the study (before morning and evening meals). Patients in the reference group remained on their insulin regimens throughout the 16-week study. No specific glycemic goals were set for insulin patients during the trial. Patients in both treatment arms continued their oral antidiabetes medications and were instructed to continue their current diet and exercise regimens. As per protocol instructions, the sulfonylurea dose was decreased by ~50% in response to one confirmed or two suspected (symptoms without confirmatory blood

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Received for publication 14 December 2006 and accepted in revised form 19 June 2007.

Published ahead of print at http://care.diabetesjournals.org on 26 June 2007. DOI: 10.2337/dc06-2532. Clinical trial reg. no. NCT00099333, clinicaltrials.gov.

Additional information for this article can be viewed in an online appendix at http://dx.doi.org/10.2337/dc06-2532.

Abbreviations: SMBG, self-monitored blood glucose.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

See accompanying Editorial on p. 2972.

Table 1—*Baseline demographic and metabolic characteristics*

Patient characteristics	Exenatide ITT	Insulin ITT	Exenatide (maintained control)	Exenatide (lost control)
n	33	16	18	11
Age (years)	54 ± 8	52 ± 8	54 ± 8	54 ± 10
Sex (% women)	54	50	61	36
Body weight (kg)	95 ± 17	102 ± 19	93 ± 19	98 ± 18
BMI (kg/m^2)	33 ± 4	35 ± 4	33 ± 5	32 ± 4
Fasting serum glucose (mmol/l)	8.8 ± 2.6	8.6 ± 2.7	8.6 ± 2.4	8.4 ± 2.6
A1C (%)	8.0 ± 1.2	8.3 ± 0.9	8.1 ± 1.1	8.0 ± 1.3
Diabetes duration (years)	10.4 ± 6.2	11.9 ± 7.4	9.9 ± 7.1	11.7 ± 5.4
Insulin treatment duration (years)	2.9 ± 3.1	3.0 ± 3.2	2.5 ± 2.9	3.8 ± 3.3
Insulin dose (unit/day)	41 ± 24	54 ± 38	37 ± 25	52 ± 25
C-peptide (nmol/l)	1.0 ± 0.5	0.9 ± 0.5	1.2 ± 0.5	0.8 ± 0.5
Background therapy				
Metformin only	13	8	4	8
Sulfonylurea only	4	0	2	0
Metformin and sulfonylurea	16	8	12	3
Glargine	8	2	4	4
NPH insulin	0	1	0	0
Ultralente	1	0	0	1
Mixtures	6	4	3	1
Multiple insulin therapies	4	3	1	3

Data are means ± SD or *n* unless otherwise indicated. ITT, intent to treat.

glucose <3.4 mmol/l) hypoglycemic events.

Eligible patients were between 30 and 75 years of age, had been diagnosed with type 2 diabetes for ≥2 years, and had been treated with one of the following for ≥3 months to 12 years: once- or twice-daily NPH insulin, once-daily insulin glargine, once- or twice-daily ultralente insulin, or an insulin mixture. All patients were on oral antidiabetes regimens consisting of an immediate- or extended-release metformin and/or a sulfonylurea for at least 3 months before screening or a fixed-dose sulfonylurea/metformin combination therapy. Additional inclusion criteria included, at the time of screening, an A1C level ≤10.5%, BMI >27 and <40 kg/m^2, and a history of stable body weight. Patients were excluded if they had more than three episodes of severe hypoglycemia within 6 months before screening, had used any prescription drug to promote weight loss within 3 months, or had previously received exenatide or glucagon-like peptide 1 analogs.

Study measurements

A common clinical protocol was approved by an institutional review board at each site and was conducted in accordance with the principles described in the Declaration of Helsinki (18). Patients were recruited according to local practices, and all participants gave written informed consent before participation. A1C levels were measured at weeks −2, 0 (randomization and study initiation), and 16 (or at early discontinuation). Blood chemistries and fasting serum lipids were assessed at weeks −2 and 16 (or at early discontinuation). Fasting serum glucose and fasting C-peptide were assessed at weeks −2, 2, 4, and 8. Weight, vital signs, concomitant medications, and drug doses were collected at week 0 and at each subsequent visit. Patients performed 5-point self-monitored blood glucose (SMBG) profiles at study weeks 2, 4, 8, and 16.

Adverse events were assessed at each visit and were reported as preferred terms from the Medical Dictionary for Regulatory Activities. A clinical trial adverse event was defined as any untoward medical occurrence, without regard to the possibility of a causal relationship. A hypoglycemic episode was defined as any time a patient felt that he or she was experiencing a sign or symptom of hypoglycemia or noted a blood glucose level <3.4 mmol/l (60 mg/dl) during self-monitoring, regardless of whether this level was associated with signs, symptoms, or treatment.

Statistical analysis

The primary hypothesis was that >60% of the patients who stopped insulin therapy and initiated exenatide twice daily would maintain glycemic control. It was estimated that 30 patients, randomized in a 2:1 ratio (exenatide to insulin reference), would be sufficient to verify the probability of observing >60% success in the exenatide group. The function of the reference group was to provide additional confidence in the validity of changes in A1C observed in those using exenatide. SAS (version 8.2; SAS Institute, Cary, NC) was used to conduct all statistical analyses. Tests of within-group change (last observation carried forward) were based on the Wilcoxon's signed-rank test (with a two-sided significance level of 0.05). Student's *t* tests (with a two-sided significance level of 0.05) and Fisher's exact tests were used for between-group comparisons. We conducted a post hoc analysis of hypoglycemia based on events confirmed by glucose measurement. The overall exposure rate (total confirmed events divided by total exposure) was calculated using two criteria: *1*) the American Diabetes Association criteria (confirmed blood glucose <3.9 mmol/l) and *2*) the a priori study design criteria (confirmed blood glucose <3.4 mmol/l).

The intention-to-treat sample included all randomized patients with type 2 diabetes who received at least one dose of the study drug. Patients were considered to have maintained glycemic control if they did not experience a clinically relevant rise in A1C (an increase of ≥0.5%) at end point. Patients were also considered to have maintained glycemic control if they maintained their A1C levels below the prespecified limit but discontinued from the study after week 8 for reasons other than loss of glucose control. Patients were considered to have lost glycemic control if they experienced a clinically relevant rise in A1C or if they discontinued from the study at any time because of loss of glycemic control (as determined by the investigator). A stepwise logistic regression procedure was used to identify variables associated with maintenance of glycemic control in the exenatide group.

RESULTS

Patient disposition and clinical characteristics

A total of 51 patients with type 2 diabetes were randomized (2:1) to exenatide or insulin reference therapy (online appendix

Fig. 1 [available at http://dx.doi.org/10.2337/dc06-2532]). A total of 45 patients (29 in the exenatide and 16 in the insulin reference groups) had sufficient data for the primary efficacy analysis; 4 discontinued before their true glycemic control outcome could be determined. Table 1 presents baseline demographics, clinical characteristics, and background therapy. Exenatide-treated patients who successfully maintained glycemic control ($n = 18$) had (on average) shorter disease duration, higher pretreatment fasting C-peptide levels, were taking comparatively less insulin, and were observed to have been receiving insulin therapy for a shorter period of time.

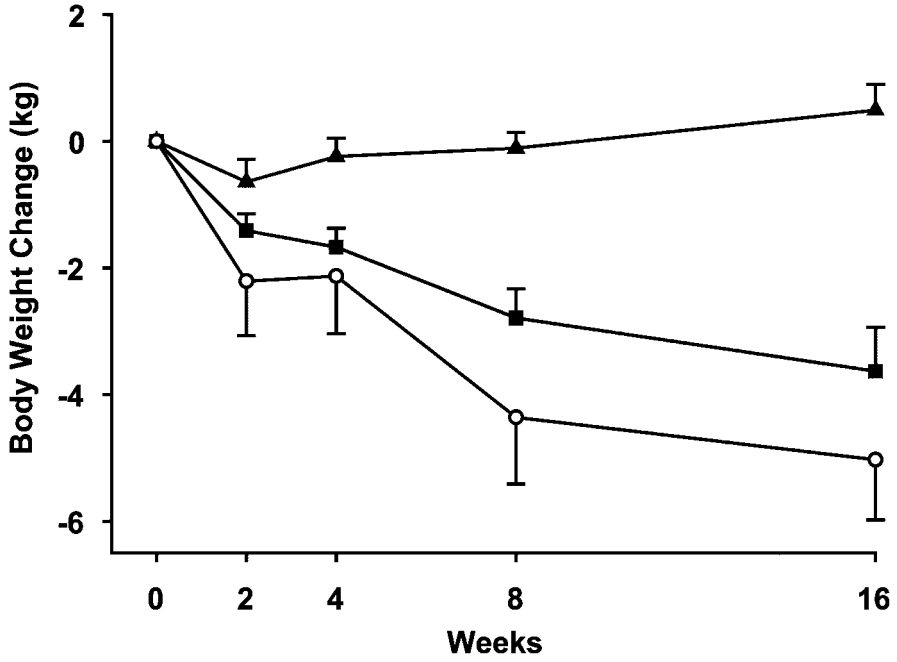

Figure 1— *Mean ± SE body weight change over time in the insulin and exenatide patient groups. ▲, insulin group; ■, exenatide group that maintained glycemic control; ○, exenatide group that lost glycemic control.*

Primary efficacy results: glycemic control

The overall mean A1C change in the exenatide group ($n = 29$) was $+0.3 \pm 1.5\%$ (within-group change, P = NS). The overall mean A1C change in the insulin group ($n = 16$) was $-0.1 \pm 0.7\%$ (within-group change, P = NS). The mean changes in A1C were not significantly different between groups at end point. Of the patients who substituted exenatide for insulin, >60% (18 of 29, mean A1C change $-0.5 \pm 0.7\%$, $P = 0.003$) successfully maintained glycemic control as defined a priori, supporting the primary hypothesis of the study. Of the 16 patients in the insulin reference group, 13 (81%) maintained glycemic control. Individual changes in A1C and fasting serum glucose are shown in online appendix Fig. 2. The majority of exenatide-treated patients who maintained control also completed the 16-week study (14 of 18) and had reductions in A1C from baseline (12 of 18). Four patients were observed to have successfully maintained glycemic control at week 8 but discontinued before week 16 for reasons other than loss of glycemic control (nausea [one patient] or patient decision [three patients]).

Of the 11 exenatide-treated patients who did not maintain glycemic control (mean A1C change $+1.6 \pm 1.5\%$, $P = 0.001$), 5 discontinued the study before week 16 because of loss of glycemic control (as determined by the investigator) and 6 lost glycemic control as evidenced by exceeding the predefined A1C criterion. Within-group analyses demonstrated that the subset of exenatide-treated patients unable to maintain glycemic control had a significant increase in fasting glucose by week 2 ($+3.9 \pm 2.7$ mmol/l, $P = 0.005$), which increased through week 8 ($+5.2 \pm 3.3$ mmol/l, $P = 0.008$). However, neither an end point rise in fasting glucose nor an earlier rise in week 2 fasting glucose was significantly associated with treatment failure in logistic regression analyses. Of the characteristics described in Table 1, pretreatment C-peptide (maximum likelihood estimate 2.96, $P = 0.024$) and baseline body weight (maximum likelihood estimate -0.07, $P = 0.088$) were identified as the best predictors of successful glycemic control.

Secondary efficacy results: body weight and SMBG profiles

Most of the exenatide-treated patients (27 of 29, 93%) lost weight during the study. Less than one-half of the patients (6 of 16, 38%) in the insulin reference group lost weight. Exenatide patients experienced a steady decline (Fig. 1) in mean body weight (end-point change -4.2 ± 3.0 kg; within-group change, $P < 0.001$), while the mean body weight with insulin was not substantially changed (end-point change $+0.5 \pm 1.7$ kg, P = NS). The between-group comparison of mean changes in body weight at end point was statistically significant ($P < 0.001$). The mean changes in body weight observed in the two exenatide groups (those who maintained vs. those who lost glycemic control) were similar (between-group change, P = NS). We conducted a post hoc analysis to determine the degree of correlation between change in A1C and change in body weight. The Pearson correlation coefficients were -0.29 and -0.25 for the exenatide and insulin reference groups, respectively.

As observed in the SMBG profiles (Table 2), patients in the insulin reference group demonstrated consistently better prebreakfast blood glucose control ($P < 0.05$) at all study follow-up visits (weeks 2, 4, 8, and 16) compared with that in exenatide-treated patients. Conversely, exenatide-treated patients demonstrated better postprandial glucose control after breakfast ($P < 0.05$) at study weeks 2, 8, and 16, with less consistent improvement demonstrated following the evening meals (i.e., better postprandial control compared with insulin only at week 8, $P < 0.05$).

Safety findings

In the exenatide group, 26 of 33 (79%) patients reported a treatment-emergent adverse event compared with 9 of 16 (56%) in the insulin reference group. Most of the adverse events reported in this study were mild to moderate in intensity. Adverse events considered possibly related to exenatide treatment were predominantly gastrointestinal in nature (e.g., nausea, diarrhea, vomiting, abdom-

Table 2—*Five-point self-monitored blood glucose profiles*

	Prebreakfast	Breakfast excursion	Predinner	Dinner excursion	Bedtime
Week 2					
Exenatide group	10.21 ± 0.458	−0.84 ± 0.578	8.94 ± 0.587	0.34 ± 0.632	9.51 (0.632)
Insulin group	7.81 ± 0.533	1.42 ± 0.661	8.27 ± 0.671	2.08 ± 0.722	9.15 (0.717)
Difference	2.403	−2.263	0.673	−1.736	0.363
P	0.0018	0.0155	0.4568	0.0812	0.7070
Week 4					
Exenatide group	10.06 ± 0.441	−0.06 ± 0.653	9.34 ± 0.532	−0.47 ± 0.563	8.54 (0.543)
Insulin group	7.03 ± 0.497	1.72 ± 0.735	8.08 ± 0.620	0.71 ± 0.638	7.99 (0.611)
Difference	3.039	−1.784	1.261	−1.173	0.555
P	<0.001	0.0791	0.1328	0.1782	0.5021
Week 8					
Exenatide group	9.58 ± 0.507	−0.86 ± 0.653	9.12 ± 0.681	−1.38 ± 0.536	8.43 (0.733)
Insulin group	7.54 ± 0.571	1.74 ± 0.735	8.54 ± 0.766	1.15 ± 0.587	9.21 (0.831)
Difference	2.033	−2.607	0.579	−2.533	−0.775
P	0.0120	0.0123	0.5760	0.0033	(0.4895)
Week 16					
Exenatide group	9.35 ± 0.485	−0.39 ± 0.522	9.00 ± 0.685	−0.70 ± 0.635	8.23 (0.731)
Insulin group	7.58 ± 0.549	2.07 ± 0.592	8.64 ± 0.777	0.52 ± 0.720	8.71 (0.829)
Difference	1.744	−2.460	0.368	−1.213	−0.479
P	0.0217	0.0040	0.7253	0.2165	(0.6678)

Data are means ± SD unless otherwise indicated. The units for all glucose values and excursions are expressed in millimoles per liter. Between-group differences represent exenatide minus the insulin reference. Exenatide group, $n = 19$; insulin group, $n = 15$.

inal pain, gastroesophageal reflux disease), with nausea the most common (48.5% incidence). Five exenatide-treated patients discontinued from the study because of an adverse event (nausea [three patients], bronchitis, and hyperglycemia). Two serious adverse events (chest pain and excessive hyperglycemia) were reported in the study, both occurring in the same exenatide-treated patient; this patient required hospitalization and discontinued because of hyperglycemia before completing the week-16 study visit. There were no adverse events considered possibly related to insulin treatment. Headache was the most common adverse event (31.3% incidence) reported in the insulin reference group, followed by nausea (12.5%) and cough (12.5%)

The incidence of hypoglycemia was 39% (13 of 33) and 38% (6 of 16) in the exenatide and insulin reference groups, respectively. Most of the hypoglycemia was reported to have occurred during the daytime (exenatide, 11 of 13 patients; insulin, 4 of 6 patients). Of the 13 exenatide-treated patients who reported hypoglycemia, 10 were taking concomitant sulfonylurea. A total of 12 hypoglycemia events (8 in the exenatide and 4 in the insulin groups) were confirmed by glucose measurement (<3.4 mmol/l). The overall hypoglycemia rates were 1.72 and 0.97 events/patient-year for the exenatide and insulin reference groups, respectively. The rates were slightly higher in the subgroups that maintained glycemic control (exenatide, 2.54 events/patient-year; insulin, 1.18 events/patient-year). There were no episodes of serious hypoglycemia (i.e., requiring medical intervention). One patient treated with exenatide and sulfonylurea had three severe hypoglycemic episodes (i.e., episodes that required assistance of another person and were associated with either a blood glucose level <50 mg/dl or prompt recovery after oral carbohydrate, intravenous glucose, or glucagon injection), which were treated with food or drink; this patient discontinued after week eight because of nausea.

CONCLUSIONS — In this exploratory study, substitution of exenatide for insulin therapy resulted in no deterioration in glycemic control in ~62% of the type 2 diabetic patients studied. The remaining 38% of patients did experience deterioration in glycemic control. In some, this deterioration manifested as a rise in A1C noted at study end (after 16 weeks), and in others the worsening of hyperglycemia occurred by 2–8 weeks after insulin withdrawal. In those patients where there was no deterioration in glycemic control, a potential benefit for carrying out such substitution of therapy was the observed weight loss. Although A1C was not increased at end point in the majority (15 of 29, 52%) of the exenatide-treated patients, A1C remained above target (>7.0%) in many (20 of 29, 69%). Most of the insulin-treated patients (9 of 16, 56%) also did not experience an increase in A1C; however, all but 1 patient (15 of 16, 94%) remained above target (A1C > 7%) at end point. The number of exenatide-treated patients who both improved glycemic control and lost weight (11 of 29) through this therapeutic substitution was relatively small. The adverse event profile in patients who switched to exenatide was consistent with the predominance of gastrointestinal side effects observed in prior phase III, placebo-controlled trials. The overall incidence of hypoglycemia was similar between the exenatide and insulin reference groups, and most of the patients in the exenatide group who experienced hypoglycemia were taking concomitant sulfonylurea. It is known from the phase III trials studies of exenatide that hypoglycemia occurs, most commonly, when exenatide is used with sulfonylurea.

Several factors should be considered when interpreting our results. First, the glycemic control results may have been

better if we had added exenatide to the treatment of patients on insulin and decreased insulin doses gradually rather than replacing insulin with exenatide abruptly. This choice may have also contributed to the relatively high dropout rate in the exenatide group. Secondly, this study was not designed to compare insulin treatment with exenatide; thus, there were no specific glycemic goals set for insulin patients during the trial. The small number of patients in the trial also makes drawing conclusions from between-group statistical comparisons problematic. Finally, given the small sample size and exploratory nature of this study, it was not possible to adequately answer all clinically relevant questions related to this type of therapy substitution. For example, since only five patients treated with exenatide had a baseline A1C <7%, it would be difficult to conclusively determine whether it is possible to sustain glycemic control below the target level.

It should be noted that while stable glucose control was observed in a majority of patients, deterioration in glycemic control was observed in some patients, and many patients remained above target (A1C >7.0%). Exenatide elicits its glucose-lowering effect in part by glucose-dependent stimulation of insulin release from pancreatic β-cells (11,19). It is not clear whether glucose-dependent stimulation of insulin is the dominant glucose-lowering mechanism compared with suppression of glucagon or slowing of gastric emptying, for example, but it has been observed to be an important action in the hierarchy of possible mechanisms. Given that type 2 diabetes is a progressive disease where β-cell function gradually diminishes over time (1), it is possible that exenatide may have a diminished capacity to exert a glucose-lowering effect in patients with more advanced disease and minimal β-cell function. For example, patients who require insulinization during the night may be more likely to experience deterioration in glycemic control if cessation of insulin is attempted. It is therefore interesting to note that exenatide-treated patients less likely to have a favorable outcome in the current study had (on average) longer disease duration, lower pretreatment fasting C-peptide levels, were taking comparatively more insulin, and were observed to have been receiving insulin therapy for a longer period of time. However, it is not possible to characterize clear predictors of outcome given the size and exploratory nature of the study.

The weight effect observed in this study is also of interest. Prior clinical trials have shown that exenatide treatment results in weight loss as a monotherapy and when added to a variety of background oral therapies including metformin, sulfonylureas, and thiazolidinediones (20–23). Greater weight loss is seen in exenatide-treated individuals with metformin background therapy. Data from 2-year open-label extension trials have demonstrated that the weight reduction associated with exenatide is progressive over time and is associated with improvements in a number of cardiovascular risk factors (24). In the current study, early (week 2) weight reduction was observed in the patients who maintained glycemic control after coming off insulin, suggesting that the weight effect may be associated with both exenatide treatment and insulin withdrawal. The current study demonstrates that a substantial number of patients treated with insulin will experience deterioration in glucose control when exenatide is substituted. However, the study does not ascertain the mechanism by which weight loss occurs.

In conclusion, this exploratory study gives some insight into the outcome of substituting one injectable therapy (exenatide) for another (insulin) in patients with long-standing type 2 diabetes. The majority of patients maintained glycemic control, although most did not fully optimize control. Several patients experienced deterioration in glycemic control, indicating that therapy substitution is not feasible for all patients currently treated with insulin. In this study, patients who transitioned from insulin to exenatide needed to perform SMBG and were given parameters as to when to contact their physician. Although the exploratory nature of this study limits its predictive power, the results suggest that patients with longer disease duration who are taking higher doses of insulin and who have less endogenous β-cell reserves are less likely to have a favorable outcome with this therapy substitution. Further investigation is warranted.

Acknowledgments— We wish to thank the patients, investigators, and their staffs for participating in the study.

References

1. U.K. Prospective Diabetes Study Group: U.K. Prospective Diabetes Study 16: Overview of 6 years' therapy of type II diabetes: a progressive disease. *Diabetes* 44:1249–1258, 1995
2. Butler AE, Janson J, Bonner-Weir S, Ritzel R, Rizza RA, Butler PC: β-cell deficit and increased β-cell apoptosis in humans with type 2 diabetes. *Diabetes* 52:102–110, 2003
3. UK Prospective Diabetes Study (UKPDS) Group: Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). *Lancet* 352:854–865, 1998
4. UK Prospective Diabetes Study (UKPDS) Group: Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 352:837–853, 1998
5. Turner RC, Cull CA, Frighi V, Holman RR, the UK Prospective Diabetes Study (UKPDS) Group: Glycemic control with diet, sulfonylurea, metformin, or insulin in patients with type 2 diabetes mellitus: progressive requirement for multiple therapies (UKPDS 49). *JAMA* 281:2005–2012, 1999
6. International Ddiabetes Federation Clinical Guidelines Task Force: *Global Guideline for Type 2 Diabetes*. Brussels, International Diabetes Federation, 2005
7. Janka HU, Plewe G, Riddle MC, Kliebe-Frisch C, Schweitzer MA, Yki-Jarvinen H: Comparison of basal insulin added to oral agents versus twice-daily premixed insulin as initial insulin therapy for type 2 diabetes. *Diabetes Care* 28:254–259, 2005
8. Raskin P, Allen E, Hollander P, Lewin A, Gabbay RA, Hu P, Bode B, Garber A, the INITIATE Study Group: Initiating insulin therapy in type 2 diabetes: a comparison of biphasic and basal insulin analogs. *Diabetes Care* 28:260–265, 2005
9. American Diabetes Association: Standards of medical care in diabetes–2006. *Diabetes Care* 29 (Suppl. 1):S4–S42, 2006
10. Garber AJ: Premixed insulin analogues for the treatment of diabetes mellitus. *Drugs* 66:31–49, 2006
11. Keating GM: Exenatide. *Drugs* 65:1681–1692, 2005
12. Nielsen LL, Young AA, Parkes DG: Pharmacology of exenatide (synthetic exendin-4): a potential therapeutic for improved glycemic control of type 2 diabetes. *Regul Pept* 117:77–88, 2004
13. Heine RJ, Van Gaal LF, Johns D, Mihm MJ, Widel MH, Brodows RG, the GWAA Study Group: Exenatide versus insulin glargine in patients with suboptimally controlled type 2 diabetes: a randomized

trial. *Ann Intern Med* 143:559–569, 2005
14. Nauck MA, Duran S, Kim D, Johns D, Festa A, Trautmann M: Effects of exenatide compared with twice-daily biphasic insulin aspart in patients with type 2 diabetes using metformin and a sulphonylurea (Abstract). *Diabetologia* 49:A1, 2006
15. Bhatia R, Viswanathan P, Chaudhuri A, Mohanty P, Bhatia M, Dandona P: Exenatide causes weight loss and a reduction in the insulin dose along with an improvement in A1C in obese type 2 diabetics on insulin (Abstract). *Diabetes* 55 (Suppl. 1): A105, 2006
16. Hood RC: Exenatide (EXE) use in T2DM with A1C ≤7%. (Abstract). *Diabetes* 55 (Suppl. 1):A116, 2006
17. Oyer DS, Crawford RS, Shah A, Bettenhausen S: Exenatide in diabetic patients on insulin and TZDs (Abstract). *Diabetes* 55:A471–472, 2006
18. World Medical Association: Declaration of Helsinki: recommendations guiding physicians in biomedical research involving human subjects. *JAMA* 277:925–926, 1997
19. Fehse F, Trautmann M, Holst JJ, Halseth AE, Nanayakkara N, Nielsen LL, Fineman MS, Kim DD, Nauck MA: Exenatide augments first- and second-phase insulin secretion in response to intravenous glucose in subjects with type 2 diabetes. *J Clin Endocrinol Metab* 90:5991–5997, 2005
20. Buse JB, Henry RR, Han J, Kim DD, Fineman MS, Baron AD, the Exenatide-113 Clinical Study Group: Effects of exenatide (exendin-4) on glycemic control over 30 weeks in sulfonylurea-treated patients with type 2 diabetes. *Diabetes Care* 27: 2628–2635, 2004
21. DeFronzo RA, Ratner RE, Han J, Kim DD, Fineman MS, Baron AD: Effects of exenatide (exendin-4) on glycemic control and weight over 30 weeks in metformin-treated patients with type 2 diabetes. *Diabetes Care* 28:1092–1100, 2005
22. Kendall DM, Riddle MC, Rosenstock J, Zhuang D, Kim DD, Fineman MS, Baron AD: Effects of exenatide (exendin-4) on glycemic control over 30 weeks in patients with type 2 diabetes treated with metformin and a sulfonylurea. *Diabetes Care* 28:1083–1091, 2005
23. Zinman B, Hoogwerf B, Duran Garcia S, Milton D, Giaconia J, Kim D, Trautmann M, Brodows R: Safety and efficacy of exenatide in patients with type 2 diabetes mellitus using thiazolidenediones with or without metformin (Abstract). *Diabetes* 55 (Suppl. 1):A28, 2006
24. Blonde L, Klein EJ, Han J, Zhang B, Mac SM, Poon TH, Taylor KL, Trautmann ME, Kim DD, Kendall DM: Interim analysis of the effects of exenatide treatment on A1C, weight and cardiovascular risk factors over 82 weeks in 314 overweight patients with type 2 diabetes. *Diabetes Obes Metab* 8:436–447, 2006