Efficacy and Safety of Metreleptin Therapy in Patients With Type 1 Diabetes: A Pilot Study

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Diabetes Care 2017;40:694–697 | DOI: 10.2337/dc16-1553

OBJECTIVE

To study the efficacy and safety of metreleptin therapy in patients with suboptimally controlled type 1 diabetes mellitus (T1DM).

RESEARCH DESIGN AND METHODS

After a baseline period of 4 weeks, five female and three male patients with T1DM (mean age 33 years, BMI 23.8 kg/m^2) received metreleptin (0.08 mg/kg/day in females and 0.04 mg/kg/day in males) subcutaneously twice daily for 20 weeks followed by an off-therapy period of 4 weeks.

RESULTS

Metreleptin therapy did not lower HbA_{1c} significantly compared with the baseline value (mean difference −0.19% [−2.0 mmol/mol] and −0.04% [−0.5 mmol/mol] at 12 and 20 weeks, respectively). Mean body weight reduced significantly by 2.6 and 4.7 kg (P = 0.003) and daily insulin dose by 12.6% and 15.0% at week 12 and 20 (P = 0.006), respectively.

CONCLUSIONS

Metreleptin is safe but may not be efficacious in improving glycemic control in patients with T1DM, although it reduces body weight and daily insulin dose modestly.

Recombinant methionyl human leptin (metreleptin) has been safe and efficacious in improving metabolic complications in patients with marked hypoleptinemia and congenital leptin deficiency (1) and generalized lipodystrophies (2). Given the recent preclinical studies demonstrating the potential of leptin to improve type 1 diabetes mellitus (T1DM) in animal models (3,4), we designed this proof-of-concept study to determine the efficacy and safety of metreleptin in patients with suboptimally controlled T1DM.

RESEARCH DESIGN AND METHODS

Subjects

Patients with T1DM between the 18 and 50 years of age and with a BMI $<$27 kg/m^2 and an HbA_{1c} of 7.0–10.0% (53–86 mmol/mol) were eligible for the study. The study was approved by the institutional review board of The University of Texas (UT) Southwestern Medical Center (Dallas, TX), and each patient gave written informed consent. Exclusion criteria were hypertriglyceridemia, hypoglycemia unawareness, drug or alcohol abuse, uncontrolled hypertension, chronic renal insufficiency, active cardiopulmonary or infectious disease, and malignancy.

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Received 18 July 2016 and accepted 28 January 2017.

Clinical trial reg. no. NCT01268644, clinicaltrials.gov.

This article contains Supplementary Data online at http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc16-1553/-/DC1.

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Study Design

After a 4-week lead-in period in which subjects monitored capillary blood glucose levels and recorded basal and prandial daily insulin doses, baseline evaluation was conducted at week 0. The study period was divided into the following three phases:

- Phase A (weeks 0–12): Metreleptin therapy was initiated by keeping the concomitant insulin therapy at stable doses.
- Phase B (weeks 12–20): With ongoing metreleptin therapy, the concomitant basal insulin dose was actively reduced by 50%.
- Phase C (weeks 20–24): Metreleptin therapy was discontinued (off drug).

Insulin Dose Adjustment

During the study, capillary blood glucose values were monitored closely. Insulin dose adjustments were made to avoid hypo- and hyperglycemia and was likely to be reduced if preprandial blood glucose was <80 mg/dL or the postprandial value was <99 mg/dL and to be increased if preprandial blood glucose was >200 mg/dL or the postprandial value was >250 mg/dL.

Metreleptin Therapy

Metreleptin (Amylin Pharmaceuticals, San Diego, CA [now Aegerion, Cambridge, MA]) was administered subcutaneously in the abdomen before breakfast and dinner. During the first 4 weeks, the starting dose for female patients was 0.04 mg/kg/day and for male patients, 0.02 mg/kg/day (in two divided doses). After 4 weeks, the metreleptin dose was doubled for an additional 16 weeks.

Study End Points

The primary end point was HbA_{1c} at 12 weeks. We also examined metreleptin's safety and tolerability and its effect on daily insulin requirements.

Methods

All patients were admitted to the inpatient unit for 2–4 days at baseline and at the end of each phase when a history and physical examination were performed. Blood glucose, triglycerides, glucagon, and free fatty acids were tested every 2 h for 24 h. Capillary blood glucose data were acquired from a OneTouch Ultra 2 Blood Glucose Monitoring System, and insulin use data were acquired from insulin diaries.

Biochemical Analyses

Fasting blood samples were analyzed for biochemical variables. Serum glucose, lipids, and HDL cholesterol were measured by the photometric method (Beckman Coulter AU clinical analyzer). HbA_{1c} and 1,5-anhydroglucitol (GlycoMark) levels were measured by the immunoturbidimetric method (Roche Integra 800 chemistry analyzer). Plasma glucagon and leptin levels were determined by using radioimmunoassay kits (Millipore, St. Charles, MO). Plasma free fatty acids were measured by an auto analyzer (Quest Diagnostics, Irving, TX).

Assessment of Intramyocellular and Intrahepatic Lipid Concentration

Intramyocellular lipid at the soleus muscle and intrahepatic lipid concentrations were determined by ^1H magnetic resonance spectroscopy using a 1.5-T Gyroscan ACS-NT whole-body system (Philips Medical Systems, Best, the Netherlands) (5).

DEXA

Total body fat was estimated from DEXA scan (QDR 2000 densitometer; Hologic, Waltham, MA) (6).

Statistical Methods

All available data were used in the analysis, including data from one patient who withdrew at 12 weeks. Linear mixed-effects repeated-measures models were used to compare continuous measurements collected from week 0 (baseline) to week 24. The study subject was modeled as a random effect. Analyses were performed with SAS 9.4 statistical software (SAS Institute, Cary, NC).

Table 1—Metabolic variables during the study

	Baseline	Leptin therapy		Off leptin	Omnibus *P* value
Variable	Week 0	Week 12	Week 20	Week 24	(weeks 0–24)
Weight (kg)	70.7 (5.9)	68.1 (6.9)[b,c]	66.0 (7.8)[b]	67.8 (7.4)[b,c]	0.003
Systolic BP (mmHg)	115 (10.7)	114 (6.1)	116 (10.5)	115 (6.1)	0.99
Diastolic BP (mmHg)	73 (11.0)	73 (7.9)	76 (8.6)	72 (3.6)	0.95
Leptin (ng/mL)	23 (6–34)	39 (7–172)[b]	49 (6–371)[b]	27 (6–134)[b,c]	0.049
Insulin dose (units/day)	45.9 (11.5)	40.1 (12.3)[b]	39.4 (11.3)[b]	43.8 (11.3)[c]	0.006
Triglycerides (mg/dL)	100 (50)	85 (44)	82 (31)	93 (31)	0.45
Cholesterol (mg/dL)	151 (24)	141 (26)	140 (15)	143 (16)	0.11
HDL-C (mg/dL)	52 (14)	49 (15)[d]	50 (15)	53 (16)	0.04
HbA_{1c}					
%	7.6 (0.4)	7.4 (0.5)	7.7 (0.3)	7.6 (0.6)	
mmol/mol	60 (4.8)	58 (5.0)	61 (3.0)	60 (6.3)	0.48
Fasting glucose (mg/dL)	159 (69)	151 (36)	116 (56)	131 (39)	0.68
Glucose meter mean[a] (mg/dL)	172 (29)	168 (22)	176 (19)	177 (21)	0.44
Glucose meter SD[a] (mg/dL)	83 (15)	81 (19)	79 (15)	85 (10)	0.77
1,5-Anhydroglucitol (μg/mL)	4.6 (3.2)	5.2 (2.7)	3.7 (0.9)	3.3 (0.7)	0.59
Hepatic fat (%)	0.05 (0.0–0.07)	0.02 (0.0–0.20)	0.0 (0.0–0.25)	0.0 (0.0–0.01)	0.57
IMCL lipid (%)	1.53 (0.55–2.30)	0.98 (0.77–3.85)	1.51 (0.79–2.20)	2.34 (0.64–2.94)	0.82
Body fat (%)	30.8 (5.7)	28.6 (5.0)	28.3 (4.7)	26.8 (4.9)	0.001

Data are mean (SD) or median (minimum–maximum). BP, blood pressure; HDL-C, HDL cholesterol; IMCL, intramyocellular fat. [a]Extracted from the OneTouch Ultra 2 Blood Glucose Monitoring System; [b]$P < 0.05$ compared with week 0; [c]$P < 0.05$ compared with week 20; [d]$P < 0.05$ compared with week 24.

RESULTS

Patient Characteristics

Three male and five females patients (mean ± SD: age 33 ± 10 years; BMI 23.8 ± 1.4 kg/m^2; HbA_{1c} 7.6 ± 0.4% [60 ± 4.8 mmol/mol]) were studied. On the basis of self-report, all patients were fully compliant to metreleptin therapy except one who withdrew after 12 weeks as a result of injection site reaction.

Effect of Metreleptin Therapy

No statistically significant change was observed in HbA_{1c} after 12 weeks of metreleptin therapy compared with baseline values, with a mean difference (95% CI) of −0.19% (−0.44, 0.07%) or −2.0 mmol/mol (−4.8, 0.7 mmol/mol; P = 0.14). However, in five patients, HbA_{1c} values at week 12 were lower by 0.1–0.7% (1.1–7.7 mmol/mol) compared with baseline values; in one patient, HbA_{1c} increased by 0.2% (2.2 mmol/mol), and two experienced no change (Supplementary Fig. 1). No significant change in HbA_{1c} (%) was seen even at week 20 and 24 when the subjects were off metreleptin (Table 1). Other glycemic parameters also did not improve.

Fasting plasma triglyceride values were not lower at week 12 and 20 compared with baseline. Metreleptin treatment led to a mean weight loss of 2.6 kg (95% CI −4.6, −0.6 kg) at week 12 and of 4.8 kg by week 20 (95% CI −7.4, −2.2 kg). Metreleptin therapy also resulted in a significant decrease in body fat. However, no changes were noted in hepatic and intramyocellular fat with metreleptin therapy (Table 1).

Total daily insulin dose was significantly reduced by week 12 ($P < 0.05$). After week 12, the basal insulin dose was reduced by 50%, and although the dose was adjusted upward on the basis of self-monitored blood glucose, the daily insulin dose was still low compared with the baseline dose. Upon discontinuation of metreleptin therapy, daily insulin dose increased by a mean of 4.4 units (Table 1).

Median serum leptin levels increased from a baseline value of 22 ng/mL to 39 and 49 ng/mL at weeks 12 and 20, respectively. By week 24, serum leptin levels decreased to 27 ng/mL. At week 0, the geometric mean area under the curve (AUC) for plasma glucose (3,768 mg/dL · h) was not significantly different from week 12 (3,508 mg/dL · h), whereas plasma glucose AUC at week 20 (4,136 mg/dL · h) was higher than that at week 12 (P = 0.004). A comparison of AUC values for plasma triglycerides, free fatty acids, and glucagon showed no changes during metreleptin treatment (Fig. 1).

CONCLUSIONS

In contrast to preclinical studies (3,4), this pilot study did not reveal significant improvements in HbA_{1c} with the addition of metreleptin to insulin monotherapy for a period of 12 weeks. Some patients may be more responsive to metreleptin therapy than others, but identifying the factors predicting response to metreleptin from the pilot data is not possible.

Because leptin replacement therapy in animal models was particularly efficacious in severely hyperglycemic states (3), in phase B of the current study (12–20 weeks), we intentionally reduced the dose of basal insulin by 50% to further exacerbate hyperglycemia in these patients. However, metreleptin therapy did not prevent the induction of hyperglycemia, and insulin dose had to be titrated upward to avoid persistent hyperglycemia according to the predesigned algorithm. Thus, by week 20, the total daily dose of insulin was nearly the same as it was at the end of week 12, and no improvement in HbA_{1c} levels were observed. In fact, 24-h plasma glucose values were significantly higher at week 20 than at week 12. Metreleptin therapy also was unable to improve other measures of glycemic control; however, total daily insulin dose was 12.6% lower at week 12 and 15% lower at week 20 than at baseline.

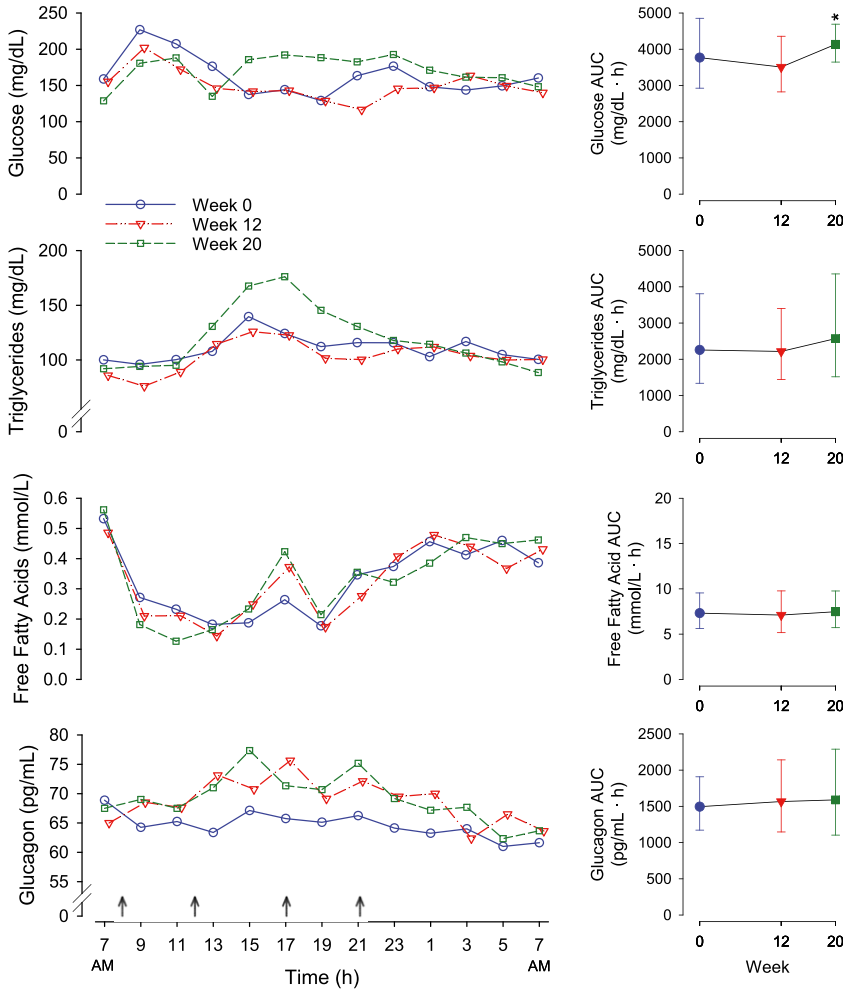

Figure 1—Twenty-four–hour plasma glucose, triglycerides, free fatty acids, and glucagon levels at weeks 0, 12, and 20. Each symbol represents the mean value at that collection point. Arrows indicate times at which the standardized breakfast, lunch, dinner, and snack were consumed. Insulin dose was kept the same during this period. The right panel shows geometric mean and 95% CIs for the AUC values for each variable. *$P < 0.05$ compared with week 12.

Metreleptin treatment led to 3.7% and 6.6% weight loss by week 12 and 20, respectively, compared with baseline. Consistent with weight loss, an 8% reduction in body fat was observed with metreleptin treatment. Leptin therapy may, in some ways, stimulate forced starvation by signaling a decreased need for food (7).

Data from NOD mice suggested that leptin-mediated suppression of diabetic hyperglucagonemia may contribute to improvement of hyperglycemia (3,4). However, metreleptin therapy in the current study did not suppress serum glucagon or free fatty acid levels at week 12 or 20. The optimal conditions to see a beneficial response to metreleptin therapy in T1DM may include markedly low serum insulin levels and hyperglucagonemia (e.g., during severe hyperglycemia and ketoacidosis) (8–10).

In contrast to the preclinical studies (3,4) the enrolled patients had normal leptin and glucagon levels and had better glycemic control, which may partly explain the difference in response. The heterogeneity in individual response may be a potential limitation. Whether higher doses of metreleptin are more efficacious in improving hyperglycemia in T1DM by more potently suppressing plasma glucagon remains to be explored in future studies with larger cohorts and different study designs. We used relatively low metreleptin doses in this pilot study that were similar to those used in patients with lipodystrophy (2,11) to maximize safety and reduce the likelihood of hypoglycemia.

In conclusion, metreleptin therapy was safe but may not be efficacious in improving glycemic control in suboptimally controlled patients with T1DM. However, metreleptin therapy reduced body weight and daily insulin dose modestly.

Acknowledgments. The authors thank Dr. Roger H. Unger (UT Southwestern Medical Center) for valuable suggestions about the design of the study. The authors also thank Drs. Daniel Foster, Michael Brown, Philip Raskin, and Scott Grundy for serving as the internal UT Southwestern Advisory Committee and Drs. Jay Skyler (University of Miami Leonard M. Miller School of Medicine), Irl B. Hirsch (University of Washington School of Medicine), and Jeffrey Friedman (Rockefeller University) for serving on the Data and Safety Monitoring Committee. The authors thank Sarah Masood for conducting the serum leptin assay, Kay McCorkle and Xinxin Yu for performing plasma glucagon assays, and Pei-Yun Tseng for help in data collection and preparing the illustration (all from UT Southwestern Medical Center).
Funding. The authors acknowledge the support of JDRF and Amylin Pharmaceuticals for providing funding for the study.
Duality of Interest. This work has been partially funded by Amylin Pharmaceuticals. Metreleptin was acquired by Aegerion Pharmaceuticals after the conclusion of this study. A.G. has received consulting fees from Amylin and Aegerion. No other potential conflicts of interest relevant to this article were reported.
Author Contributions. C.V. collected and organized data and wrote the manuscript. G.O.C. ascertained patients and followed them during the trial, collected data, and reviewed/edited the manuscript. B.A.-H. provided statistical expertise and analyzed the data. C.Q. recruited patients and conducted the study procedures. A.G. designed the study, recruited patients, interpreted data, and reviewed/edited the manuscript. A.G. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Prior Presentation. Presented in poster and late-breaking abstract form at the 76th Scientific Sessions of the American Diabetes Association, New Orleans, LA, 10–14 June 2016.

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