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Clinical effects of long-term metreleptin treatment in patients with lipodystrophy

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Abstract

Objective—To evaluate the long-term clinical effect of treatment with metreleptin (an analogue of human leptin) on glycemic and lipid abnormalities and markers of hepatic steatosis in patients with inherited or acquired lipodystrophy.

Methods—Fifty-five patients (36 with generalized lipodystrophy and 19 with partial lipodystrophy) with at least 1 of 3 metabolic abnormalities (diabetes mellitus, fasting triglyceride level ≥ 200 mg/dL, and insulin resistance) and low leptin levels received subcutaneous injections of metreleptin once or twice daily in an ongoing clinical trial at the National Institutes of Health.

Results—At baseline, hemoglobin A_{1c}— $8.5\% \pm 2.1\%$ (mean $\pm$ standard deviation [SD])—and triglycerides— 479 ± 80 mg/dL (geometric mean $\pm$ standard error [SE])—were substantially elevated. Robust and sustained reductions in both variables were evident for the observed patient population during a 3-year metreleptin treatment period ($-2.1\% \pm 0.5\%$ [mean $\pm$ SE] and $-35.4\% \pm 13.7\%$ [mean $\pm$ SE], respectively). Mean alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels were elevated at baseline (100 ± 120 U/L and 71 ± 77 U/L [mean $\pm$ SD], respectively) and decreased by -45 ± 19 U/L and -33 ± 14 U/L (mean $\pm$ SE), respectively, during the 3-year metreleptin treatment period. Improvements in hemoglobin A_{1c}, triglycerides, ALT, and AST were more pronounced in the subsets of patients having elevated levels at baseline. The most notable adverse events observed in this patient population were likely attributable to underlying metabolic abnormalities or comorbidities.

Conclusion—Metreleptin treatment substantially reduced glycemic variables, triglycerides, and liver enzymes (ALT and AST) and demonstrated durability of response throughout a 3-year treatment period. These results support metreleptin as a potential treatment for certain metabolic disorders (for example, diabetes mellitus and hypertriglyceridemia) associated with lipodystrophy.

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DISCLOSURE

All patient studies and data acquisition described in this report were conducted at the Clinical Center of the NIH (clinical trial registration number: NCT00025883). Thus, all the data presented were derived from the NIH study, and subsets of the data have been previously reported. The manuscript was conceptualized and written by representatives from Amylin Pharmaceuticals, Inc. (Drs. Jean L. Chan, Karen Lutz, Wenying Huang, Yvette Peters, and Christian Weyer) and the NIH (Elaine Cochran and Dr. Phillip Gorden), and the work was performed under the auspices of a Cooperative Research and Development Agreement. All the Amylin authors (Drs. Jean L. Chan, Karen Lutz, Wenying Huang, Yvette Peters, and Christian Weyer) are employees and stockholders of Amylin Pharmaceuticals, Inc.

INTRODUCTION

Inherited or acquired lipodystrophies are rare disorders characterized by a generalized or partial loss of adipose tissue in association with severe metabolic disturbances that can be monogenetic, autoimmune-related, or idiopathic (1,2). On the basis of the clinical presentation (more generalized versus partial loss of subcutaneous fat) as well as the identification of specific mutations in genes encoding enzymes and proteins involved in proper differentiation and function of adipocytes, lipodystrophy has been classified into 4 main categories: congenital generalized lipodystrophy (CGL), familial partial lipodystrophy (FPL), acquired generalized lipodystrophy (AGL), and acquired partial lipodystrophy (APL). Of note, this general classification scheme is not inclusive of all lipodystrophies; rare types of lipodystrophy exist that may not fit into this classification (for example, mandibuloacral dysplasia, neonatal progeria, and atypical progeria). In addition, not all lipodystrophies fit exactly within one of the 4 main subgroups because of the heterogeneity of initial manifestations, variable distribution of fat loss, and genetic markers yet to be identified, but this classification serves as a useful general framework (1,2).

Because of the loss of adipose tissue, levels of the adipocyte-secreted hormone leptin are low (3). The syndromes of lipodystrophy are associated with deposition of fat in ectopic locations (such as liver and muscle) and metabolic abnormalities (such as insulin resistance, hypertriglyceridemia, and diabetes). These abnormalities are often severe and can result in life-threatening comorbidities—for example, acute pancreatitis, hepatic steatosis or steatohepatitis (which can progress to cirrhosis), or accelerated atherosclerosis (1,2). The relative leptin deficiency has been implicated as a key pathogenic mechanism underlying the aforementioned abnormalities and can also contribute to hyperphagia, another feature of this disorder, which further exacerbates the metabolic abnormalities as patients are driven to ingest excessive calories (including fat).

Mouse models have provided valuable insights into the pathophysiologic processes of lipodystrophy and have demonstrated that the metabolic abnormalities associated with this disease develop as a consequence of loss of adipose tissue and low leptin levels (4). Administration of leptin, a key regulator of energy homeostasis as well as fat and glucose metabolism, has been shown to ameliorate metabolic abnormalities dramatically in a transgenic mouse model of generalized lipodystrophy (5). These animal studies formed the scientific rationale for testing the hypothesis that administration of recombinant human leptin (metreleptin) would improve the insulin resistance, diabetes, hypertriglyceridemia, or a combination of these disorders in patients with lipodystrophy.

Indeed, in an open-label pilot study in 9 patients with lipodystrophy (3 with AGL, 5 with CGL, and 1 with FPL) with severe metabolic abnormalities conducted at the National Institutes of Health (NIH), administration of metreleptin resulted in substantial improvements in hypertriglyceridemia, hyperglycemia, or both (6). On the basis of these results, an open-ended, open-label study of metreleptin treatment in patients with lipodystrophy was initiated more than 10 years ago and is currently ongoing. Results from this protocol have been reported in several publications during the past decade and have demonstrated substantial improvements in glucose and lipid metabolism, liver volume, food intake, and endocrine assessments in patients with lipodystrophy (6–14). In their most recent publication, Chong et al (11) presented 1-year efficacy data from a cohort of 48 patients (35 of whom had data at baseline and through 1 year of metreleptin treatment), and they reported glycemic and lipid effects for the overall analysis population. The clinical effects of metreleptin at specific time points beyond 1 year of treatment, and in subsets of patients with diabetes or hypertriglyceridemia at baseline, have not been reported to date.

Because lipodystrophy is a chronic and clinically heterogeneous condition, it is important to describe the longterm safety and metabolic effects of a specific treatment approach and to provide a comprehensive characterization of its effects in clinically relevant subgroups of patients. The purposes of the current analysis were (1) to present longer-term efficacy data in a larger cohort of patients (N = 55 as of a data cut performed in July 2009), (2) to report data on those patients who had elevated hemoglobin A_{1c} (A1C) or triglyceride levels (or both) at baseline, and (3) to provide longer-term safety data (metreleptin exposure up to 9 years). Such data are highly relevant for enhancing the understanding of the long-term safety and effects of an investigational agent that is intended for prolonged administration.

RESEARCH DESIGN AND METHODS

Study Population

The study population consisted of patients with acquired or inherited lipodystrophy who were >5 years of age and who presented with at least 1 of 3 metabolic abnormalities—diabetes mellitus based on 1997 American Diabetes Association (ADA) criteria, insulin resistance based on a fasting insulin level >30 μ IU/mL, and hypertriglyceridemia—in conjunction with fasting leptin levels of <8.0 ng/mL for male patients and <12.0 ng/mL for female patients. The data set described in this report is based on the intent-to-treat (ITT) population of 55 patients (as of a data cut performed in July 2009) who enrolled in the study and received at least 1 dose of metreleptin. Although data are presented for the first 3 years of metreleptin treatment, some patients have received treatment for several years (31% for more than 6 years), and some patients have received up to 9 years of treatment as of the July 2009 data cut. The focus in this efficacy analysis on data up to 3 years was based on achieving the best balance between presentation of longer-term data and robustness of analysis, inasmuch as the number of patients with longer-term data becomes progressively less with longer duration of treatment (based on the ongoing nature of the protocol) and thus the analysis becomes less robust. The study population was composed entirely of patients with rare forms of genetic, idiopathic, or autoimmune-related lipodystrophy and did not include patients with human immunodeficiency virus (HIV)-associated adipose redistribution syndrome.

Study Design

This open-label, currently ongoing study was initiated in August 2000 to examine the long-term safety and clinical effects of metreleptin treatment in patients with lipodystrophy. Metreleptin was self-administered subcutaneously once or twice daily in accordance with a previously described weight-based protocol (with different weight-based dosing based on sex and age), with specified titration during the first few months of treatment and subsequent adjustment based on individual response (6,7,11). Because of these variations and differences in metabolic profiles at baseline and in responses to metreleptin, the actual metreleptin milligram dose administered varied for each patient. To provide greater insight into actual metreleptin doses administered over time, we calculated a weighted average dose as follows: sum [daily dose*dose duration in days]/total days. The mean $\pm$ standard error (SE) weighted average daily dose of metreleptin treatment for the course of the study was 2.75 ± 0.43 mg (male patients) and 5.55 ± 0.33 mg (female patients). Before the initiation of metreleptin treatment, patients' concomitant medications used to treat diabetes or hypertriglyceridemia were optimized by the treating physician, as previously described (11). Standard medications and dietary changes were recommended by the treating physician preceding the initiation of metreleptin treatment. During the first year of the study, patients were to keep diet and medications unchanged, with the exception of a decrease in or discontinuation of antihyperglycemic therapies to minimize the occurrence of hypoglycemia

in response to improved insulin sensitivity. After the first year of metreleptin treatment, standard therapies may have been added or dietary improvements may have been suggested.

Study End Points

For the purpose of this analysis, key glycemic and lipid variables including A1C, fasting plasma glucose (FPG), triglyceride concentrations, low-density lipoprotein (LDL), high-density lipoprotein (HDL), and total cholesterol levels, as well as liver enzymes (alanine aminotransferase [ALT] and aspartate aminotransferase [AST]) as surrogates of hepatic steatosis (a common feature of lipodystrophy) are presented not only for the entire ITT population but also for those subgroups presenting with unsatisfactory glucose control (A1C $\geq 7\%$, based on 1997 ADA criteria), elevated triglycerides (≥ 200 mg/dL), elevated ALT levels (≥ 41 U/L), or elevated AST levels (≥ 34 U/L) at baseline. Additional detailed assessments (for example, dynamic tests of insulin sensitivity, liver volume, liver fat, liver biopsies, body composition assessment, and dynamic endocrine testing) were completed as part of this intensive protocol but are not presented herein (7,8,12–15). Safety and tolerability of metreleptin were assessed by spontaneous adverse event reporting, physical examination, and standard laboratory studies.

Biochemical Analyses

At baseline, fasting plasma leptin concentrations were measured by immunoassay with use of a commercially available kit (Linco Research, Inc., St. Charles, Missouri; now Millipore, 2006). A1C, glucose, triglyceride, ALT, and AST values were measured in the clinical laboratory according to standard methods (6).

Data Analyses

The data presented herein are based on an on-treatment analysis, with data provided for all patients as available. Student paired *t* tests to compare measures after baseline with the documented baseline values were performed for A1C, FPG, lipids, AST, and ALT for the overall ITT population and for patients in the ITT population with abnormal baseline values for A1C ($\geq 7\%$, based on 1997 ADA criteria), triglyceride concentrations (≥ 200 mg/dL), ALT (≥ 41 U/L), or AST (≥ 34 U/L). Unless indicated otherwise, glycemic variables and ALT and AST measurements are presented as mean $\pm$ SE. The change from baseline and 95% confidence interval (CI) are listed for glycemic factors, ALT, and AST. Because of the nonnormal distribution of the triglyceride data as a result of some extremely high values, triglycerides are presented as the geometric mean $\pm$ SE. The geometric mean is the *n*th root of the product of “*n*” positive values and is more representative of the central tendency in skewed data than is the mean. The mean $\pm$ SE percentage change from baseline and 95% CI are listed. Significance levels are not adjusted for multiplicity of efficacy end points. All statistical analyses were performed by using SAS, version 9.2 (SAS Institute Inc., Cary, North Carolina). All efficacy and safety analyses were performed on the ITT population.

RESULTS

Patient Demographics and Disposition

The ITT population (*N* = 55) was 80% female and 67% white, with a mean age of 25 years (range, 7 to 68) (Table 1). Approximately half of the patients (53%) were of pediatric age (<18 years) at the time of enrollment. The study population included patients in the 4 main subgroups of lipodystrophy: CGL (*n* = 23; 42%), FPL (*n* = 14; 25%), AGL (*n* = 13; 24%), and APL (*n* = 5; 9%). The mean $\pm$ standard deviation (SD) body mass index at baseline was 22.2 ± 3.4 kg/m², and the mean $\pm$ SD baseline leptin level was 2.8 ± 2.8 ng/mL.

Patient disposition and duration of exposure to metreleptin treatment are summarized in Table 2. At the time of the 2009 data cut, there were 42 patients actively treated in the study. Thirteen patients withdrew from the study, with the most common reason for withdrawal being noncompliance ($n = 5$; 9%). There was a wide range of exposure to metreleptin (6 months to 9 years as of the 2009 data cut) since the study was initiated in 2000 (Table 2). Importantly, 76% of patients had received more than 1 year of treatment, and 31% had received more than 6 years of treatment. The median duration of exposure in the ITT population was 2.5 years. Because the study is open-ended, and treatment remains ongoing, patients who enrolled later in the protocol had less data available in comparison with the early enrollees, a fact that primarily accounts for the decreasing number of patients with available data over time (rather than patients terminating the study early).

Effect of Metreleptin Treatment on Glycemic Control

In the overall ITT population, the baseline A1C was well above accepted treatment goals at $8.5\% \pm 2.1\%$ (mean $\pm$ SD). Metreleptin treatment led to reductions in A1C from baseline during the 3-year treatment period. A reduction of $-1.2\% \pm 0.2\%$ (95% CI, -1.6% to -0.8%) to $7.3\% \pm 0.3\%$ (Fig. 1 A) was observed in patients completing 4 months of metreleptin treatment ($n = 40$) with available data. A1C continued to improve over time, averaging $6.0\% \pm 0.3\%$ in patients who completed 3 years of metreleptin treatment ($n = 18$) with available data and reflecting a decrease in A1C of $-2.1\% \pm 0.5\%$ (95% CI, -3.2% to -1.1%). The baseline concentration of FPG was 184 ± 91 mg/dL (mean $\pm$ SD). Sustained improvements in FPG were observed during the 3-year metreleptin treatment period (146 ± 14 mg/dL and 124 ± 13 mg/dL at month 4 and year 3, respectively), representing reductions of -46.3 ± 11.5 mg/dL (95% CI, -69.6 to -23.0) and -55.1 ± 18.7 mg/dL (95% CI, -94.4 to -15.8) for patients with available data ($n = 40$ and $n = 19$), respectively.

In patients ($n = 41$; 75%) with elevated A1C at baseline ($9.4\% \pm 1.5\%$ [mean $\pm$ SD]), A1C decreased by $-1.4\% \pm 0.2\%$ (95% CI, -1.8% to -0.9%) to $7.7\% \pm 0.3\%$ after 4 months of metreleptin treatment (for the observed population, $n = 31$). Further improvements from baseline of $-2.6\% \pm 0.6\%$ (95% CI, -3.8% to -1.3%) to $6.3\% \pm 0.3\%$ were noted for the observed population ($n = 14$) after 3 years of treatment (Fig. 1 B).

Effect of Metreleptin Treatment on Triglycerides and Other Lipids

At baseline, the triglyceride levels were substantially elevated at 479 ± 80 mg/dL. The mean percentage change in triglyceride levels was $-36.7\% \pm 6.4\%$ (95% CI, -49.7% to -23.7%) after 4 months of metreleptin treatment and $-35.4\% \pm 13.7\%$ (95% CI, -64.1% to -6.7%) at 3 years. Resulting triglyceride levels were 254 ± 40 mg/dL after 4 months and 164 ± 26 mg/dL after 3 years of metreleptin treatment in the observed populations ($n = 40$ and $n = 19$, respectively) (Fig. 2 A).

In patients ($n = 41$; 75%) with abnormal triglyceride levels (> 200 mg/dL) at baseline, the baseline triglyceride concentration was 743 ± 123 mg/dL. The mean percentage change from baseline to month 4 of metreleptin treatment was $-44.4\% \pm 7.1\%$ (95% CI, -58.8% to -29.9%) to 326 ± 59 mg/dL in the observed population ($n = 30$). Improvements were sustained during the 3-year metreleptin treatment period. The mean percentage change from baseline to year 3 of metreleptin treatment was $-51.2\% \pm 16.7\%$ (95% CI, -87.5% to -14.8%) to 197 ± 35 mg/dL for the observed population ($n = 13$) (Fig. 2 B).

Mean changes and resulting concentrations in other fasting lipid variables, including LDL, HDL, and total cholesterol, are presented in Table 3. Decreases in LDL and total cholesterol were observed during 3 years of metreleptin treatment, whereas mean HDL concentrations did not change.

Effect of Metreleptin Treatment on Hepatic Enzymes

Hepatic steatosis, hepatomegaly, and nonalcoholic steatohepatitis are commonly observed in patients with lipodystrophy (15). Although direct measures of liver fat were not available for the purpose of this analysis, the effect of metreleptin treatment on hepatic enzymes ALT and AST, surrogate markers of hepatic steatosis, was evaluated and is shown in Figures 3 and 4.

The ITT population had a baseline ALT value of 100 ± 120 U/L (mean $\pm$ SD; N = 55), which is more than 2-fold above the upper limit of normal (41 U/L). In the patient population with available data (n = 40), ALT concentrations improved by approximately 50%, with a reduction of -37 ± 12 U/L (95% CI, -62 to -12) to 46 ± 7 U/L after 4 months of metreleptin treatment. After 3 years of metreleptin treatment, the change from baseline ALT concentrations was -45 ± 19 U/L (95% CI, -86 to -4) to 29 ± 4 U/L for the observed patient population (n = 19) (Fig. 3 A).

Patients (n = 33; 60%) with elevated baseline ALT levels (> 41 U/L) (150 ± 134 U/L [mean $\pm$ SD]) had the following distribution of lipodystrophy subtypes: AGL (n = 12; 22%), APL (n = 3; 5%), CGL (n = 15; 27%), and FPL (n = 3; 5%). ALT levels improved by more than 50% after 4 months of metreleptin treatment, with a reduction of -67 ± 22 U/L (95% CI, -112 to -22) to 67 ± 12 U/L in the observed patient population (n = 21). The improvements in ALT levels were sustained throughout the 3-year metreleptin treatment period (-92 ± 35 U/L [95% CI, -174 to -11] to 35 ± 7 U/L [n = 9]) (Fig. 3 B).

The ITT population had a baseline AST of 71 ± 77 U/L (mean $\pm$ SD), which is also more than 2-fold above the upper limit of normal (34 U/L). AST concentrations declined by -24 ± 8 U/L (95% CI, -40 to -7) to 34 ± 5 U/L after 4 months of metreleptin treatment in the patient population with available data (n = 40). Improvements in AST were sustained throughout the 3-year metreleptin treatment period, with reductions from baseline of -33 ± 14 U/L (95% CI, -62 to -3) to 24 ± 1 U/L for the observed patient population (n = 19) (Fig. 4 A).

Patients (n = 29; 53%) with elevated baseline AST concentrations (> 34 U/L) (112 ± 87 U/L [mean $\pm$ SD]) had the following distribution of lipodystrophy subtypes: AGL (n = 10; 18%), APL (n = 3; 5%), CGL (n = 14; 25%), and FPL (n = 2; 4%). AST concentrations improved by approximately 50% with a reduction of -48 ± 15 U/L (95% CI, -80 to -16) to 47 ± 10 U/L after 4 months of metreleptin treatment (observed patient population, n = 19). The absolute change from baseline after 3 years of metreleptin treatment was -90 ± 27 U/L (95% CI, -156 to -23) to 21 ± 1 U/L for the observed patient population (n = 7) (Fig. 4 B).

Safety Assessments—Treatment-Emergent Adverse Events

Treatment-emergent adverse events assessed as related to metreleptin were reported in 17 patients (31%), and those occurring in 5% or more of the patients included fatigue (n = 6 [11%]), hypoglycemia (n = 6 [11%]), alopecia (n = 4 [7%]), and weight decrease (n = 3 [5%]). Injection-site adverse events (erythema, urticaria) assessed as related to metreleptin were observed in 2 patients (4%).

Notable adverse events of clinical interest included T-cell lymphoma, which was reported in 2 patients (4%) with acquired lipodystrophy, both of whom had immunodeficiency and severely abnormal bone marrow biopsy specimens at baseline. Other notable events were generally consistent with known comorbidities of lipodystrophy. Acute pancreatitis was reported in 5 patients (9%), all with a history of pancreatitis and severe hypertriglyceridemia. In most cases, pancreatitis was associated with abrupt discontinuation of or noncompliance with (or both) metreleptin treatment. Chronic renal adverse events were reported in 5 patients (9%) (all with a history of or evidence of renal disease at baseline) and

included proteinuria, membranoproliferative glomerulonephritis, focal segmental glomerulosclerosis, and chronic renal failure. Similarly, hepatic adverse events were reported in 4 patients (7%) (all with a history of or evidence of hepatic steatosis, steatohepatitis, or both) and included events of elevated liver function tests or events of liver disease (autoimmune hepatitis, chronic hepatitis, hepatic steatosis, and liver disorders). All these adverse events were deemed by the investigators as unrelated to study medication.

DISCUSSION

Lipodystrophies are rare disorders characterized by a generalized or partial loss of adipose tissue, resulting in low leptin levels and multiple, often severe metabolic disturbances (1,2). Because of the rarity of the condition, accurate numbers on the epidemiologic features of this condition are not available. According to a 2004 review, approximately 800 cases of lipodystrophy (CGL, FPL, AGL, and APL, excluding HIV-related lipodystrophy) have been reported in the literature (1).

Lipodystrophies can result from a spectrum of genetic mutations (for example, *AGPAT2*, *seipin*, *LMNA*, *PPAR γ* , *ZMPSTE24*, and *LMNB2*), which can follow autosomal recessive (*AGPAT2*, *seipin*) or autosomal dominant (*LMNA*) inheritance patterns, or can be autoimmune-associated (subtypes of acquired lipodystrophy) (1,2). Patients with CGL, AGL, and APL often present with metabolic abnormalities during childhood or adolescence, whereas those with FPL tend to present later in adolescence and adulthood (1,2).

Many patients with lipodystrophy present with metabolic abnormalities, such as hypertriglyceridemia, insulin resistance, diabetes, or a combination of these disorders. These metabolic abnormalities are often quite severe and poorly controlled, even with use of high doses of currently available diabetes and lipid therapies. The loss of adipose tissue in lipodystrophy results in a state of relative leptin deficiency (3), akin to other hormone-deficient conditions that can be corrected with replacement of the deficient hormone. Thus, metreleptin is under investigation as a treatment approach in patients with lipodystrophy, in that it attempts to address a key endocrine pathophysiologic defect underlying the condition.

The data presented herein summarize the long-term (more than 3 years) effect of metreleptin on A1C, FPG, triglycerides and other lipids, and liver enzymes in the largest cohort of patients with lipodystrophy published to date. Long-term metreleptin treatment in this cohort of patients, including those with acquired and inherited forms of the disorder and with generalized and partial fat loss, led to substantial and sustained improvements in the key metabolic abnormalities of severe diabetes and hypertriglyceridemia. In addition, metreleptin treatment substantially improved hepatic enzymes (ALT and AST), which were increased severalfold above normal before treatment.

Magnitude of Reduction in A1C, FPG, Triglycerides, and Liver Enzymes

After the initiation of metreleptin treatment, marked improvements in metabolic abnormalities were evident by 4 months. These improvements are particularly notable because they occurred in some patients in the setting of substantial reductions or even discontinuation of the use of antidiabetic medications (insulin, orally administered agents, or both) (6,10).

Of note, the data presented herein are from an openlabel protocol without a placebo control. Using a placebocontrol study design in this patient population at risk for serious life-threatening metabolic complications was considered not justifiable because of the considerable improvements with metreleptin observed in the initial pilot study (6). The absence of a placebo-control design precluded the quantification of the true treatment effect

of metreleptin. The analysis of key efficacy measures in the entire ITT population, however, showed clinically meaningful improvements despite inclusion of some patients with relatively normal metabolic variables at baseline, who might not be expected to have improvements. In addition, on the basis of the degree and duration of the observed effects, it is unlikely that the improvements in A1C, FPG, triglycerides, ALT, and AST occurred solely as part of the natural history of the condition.

Although most patients with lipodystrophy have both lipid and glycemic abnormalities (65% in this cohort), it is important to note that some patients may present primarily with hypertriglyceridemia (without diabetes) or with diabetes (without hypertriglyceridemia). Thus, the assessment of metabolic variables conducted for the entire ITT population may be considered a conservative analysis, in light of the fact that all patients were included even though not all patients had abnormal A1C and triglyceride levels at baseline. For further characterization of the glucose- and lipid-lowering effects of metreleptin in lipodystrophy, we performed subgroup analyses in patients with abnormalities in A1C, triglycerides, or liver enzymes at baseline. These analyses indicated that the magnitude of the therapeutic response was even greater in patients presenting with baseline abnormalities than in the overall study population.

Durability of Reduction in A1C, FPG, Triglycerides, and Liver Enzymes

The long-term efficacy data presented herein demonstrated the durability of the effect of metreleptin on metabolic variables. After 3 years of metreleptin treatment, mean values for A1C, FPG, triglycerides, and liver enzymes were below currently recommended treatment targets or the upper limit of normal in the overall population and in the subgroups of patients with elevated baseline levels of A1C, triglycerides, and liver enzymes. Data within this analysis represent patients with up to 3 years of treatment exposure, but more than 30% of the patients have received metreleptin for longer than 6 years (in some patients, up to 9 years). Although individual treatment responses may show some fluctuation in variables over time, sustained efficacy with metreleptin treatment on key metabolic factors was generally observed. The progressively smaller number of patients with available data over a longer period, however, precluded robust analysis of data beyond 3 years; thus, such data were not presented herein.

Potential Mechanisms Underlying the Effect of Leptin in Lipodystrophy

The mechanisms by which leptin improves metabolic abnormalities in lipodystrophy have been studied in animal models of lipodystrophy as well as in a small mechanistic clinical study in patients with lipodystrophy (14,16). These studies indicated that leptin stimulates whole-body fatty acid oxidation and lowers plasma, hepatic, and myocellular lipid levels (especially triglycerides) (14,16). These antisteatotic effects are accompanied by increased insulin sensitivity (14). In addition, leptin has been shown to improve insulin suppression of glucose production by the liver and to increase insulin-stimulated peripheral glucose uptake in the muscle (14,17,18). Finally, a clinically important effect of leptin is correction of the hyperphagia that likely occurs as a result of leptin deficiency (13).

Safety and Tolerability of Metreleptin in Lipodystrophy

The long-term data obtained in this cohort for several years (up to 9 years) provide important information about the overall safety profile of metreleptin in patients with lipodystrophy. Data on long-term safety are important because metreleptin is under investigation for prolonged treatment of patients with lipodystrophy. One notable adverse event identified during metreleptin treatment was T-cell lymphoma in 2 patients with acquired lipodystrophy who had immunodeficiency at baseline. Although there is currently no evidence that metreleptin treatment increases the risk of de novo development of T-cell

lymphoma, the use of metreleptin in patients with acquired lipodystrophy and hematologic or bone marrow abnormalities should be carefully considered and monitored. Other notable adverse events reported in this patient population were likely attributable to underlying coexisting medical conditions (pancreatitis, chronic renal disease, and chronic liver disease), which are often present in patients with lipodystrophy. In addition, there were 6 reports of adverse events of hypoglycemia, all in patients who were concomitantly treated with insulin. Therefore, it is likely that these hypoglycemic episodes were due to improved insulin sensitivity in patients receiving high doses of insulin at the initiation of metreleptin treatment. There were also 3 reported adverse events of weight loss, which might be expected to occur in leptin-sensitive patients (because of the known mechanism of action of leptin).

CONCLUSION

The metabolic complications of lipodystrophy (insulin resistance, diabetes, hypertriglyceridemia, and hepatic steatosis) are qualitatively the same as or similar to those observed in states of excess fat (obesity). Thus, lipodystrophy represents an intriguing human model of “metabolic syndrome.” Unlike the case in obesity-related metabolic syndrome, the pathophysiologic features of which remain complex and incompletely defined, the leptin deficiency in lipodystrophy provides a clearly defined mechanism that leads to the diverse metabolic disorder and, more importantly, provides a specific therapeutic target (19). Current treatment options (antidiabetic and lipid-lowering medications) for patients with lipodystrophy may address the metabolic abnormalities associated with lipodystrophy but not the underlying pathophysiologic abnormalities. These treatments, however, are often rendered marginally effective by the severity of the abnormalities observed in patients with lipodystrophy. Results from this long-term study suggest that metreleptin treatment is generally safe and demonstrate the clinical benefits of metreleptin on glycemic variables, triglycerides, and liver enzymes in patients with inherited or acquired lipodystrophy. These data support the continued development of this agent as a potential treatment for this condition.

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Abbreviations

A1C	hemoglobin A _{1c}
ADA	American Diabetes Association
AGL	acquired generalized lipodystrophy
ALT	alanine aminotransferase
APL	acquired partial lipodystrophy
AST	aspartate aminotransferase
CGL	congenital generalized lipodystrophy
CI	confidence interval

FPG	fasting plasma glucose
FPL	familial partial lipodystrophy
HDL	high-density lipoprotein
HIV	human immunodeficiency virus
ITT	intent-to-treat
LDL	low-density lipoprotein
NIH	National Institutes of Health
SD	standard deviation
SE	standard error

References

1. Garg A. Acquired and inherited lipodystrophies. *N Engl J Med*. 2004; 350:1220–1234. [PubMed: 15028826]
2. Chan JL, Oral EA. Clinical classification and treatment of congenital and acquired lipodystrophy. *Endocr Pract*. 2010; 16:310–323. [PubMed: 20061300]
3. Haque WA, Shimomura I, Matsuzawa Y, Garg A. Serum adiponectin and leptin levels in patients with lipodystrophies. *J Clin Endocrinol Metab*. 2002; 87:2395. [PubMed: 11994394]
4. Reitman ML, Arioglu E, Gavrilova O, Taylor SI. Lipodystrophy revisited. *Trends Endocrinol Metab*. 2000; 11:410–416. [PubMed: 11091118]
5. Shimomura I, Hammer RE, Ikemoto S, Brown MS, Goldstein JL. Leptin reverses insulin resistance and diabetes mellitus in mice with congenital lipodystrophy. *Nature*. 1999; 401:73–76. [PubMed: 10485707]
6. Oral EA, Simha V, Ruiz E, et al. Leptin-replacement therapy for lipodystrophy. *N Engl J Med*. 2002; 346:570–578. [PubMed: 11856796]
7. Javor ED, Cochran EK, Musso C, Young JR, DePaoli AM, Gorden P. Long-term efficacy of leptin replacement in patients with generalized lipodystrophy. *Diabetes*. 2005; 54:1994–2002. [PubMed: 15983199]
8. Musso C, Cochran E, Javor E, Young J, DePaoli AM, Gorden P. The long-term effect of recombinant methionyl human leptin therapy on hyperandrogenism and menstrual function in female and pituitary function in male and female hypoleptinemic lipodystrophic patients. *Metabolism*. 2005; 54:255–263. [PubMed: 15690321]
9. McDuffie JR, Riggs PA, Calis KA, et al. Effects of exogenous leptin on satiety and satiation in patients with lipodystrophy and leptin insufficiency. *J Clin Endocrinol Metab*. 2004; 89:4258–4263. [PubMed: 15356018]
10. Park JY, Javor ED, Cochran EK, DePaoli AM, Gorden P. Long-term efficacy of leptin replacement in patients with Dunnigan-type familial partial lipodystrophy. *Metabolism*. 2007; 56:508–516. [PubMed: 17379009]
11. Chong AY, Lupsa BC, Cochran EK, Gorden P. Efficacy of leptin therapy in the different forms of human lipodystrophy. *Diabetologia*. 2010; 53:27–35. [PubMed: 19727665]
12. Oral EA, Ruiz E, Andewelt A, et al. Effect of leptin replacement on pituitary hormone regulation in patients with severe lipodystrophy. *J Clin Endocrinol Metab*. 2002; 87:3110–3117. [PubMed: 12107209]
13. Moran SA, Patten N, Young JR, et al. Changes in body composition in patients with severe lipodystrophy after leptin replacement therapy. *Metabolism*. 2004; 53:513–519. [PubMed: 15045701]
14. Petersen KF, Oral EA, Dufour S, et al. Leptin reverses insulin resistance and hepatic steatosis in patients with severe lipodystrophy. *J Clin Invest*. 2002; 109:1345–1350. [PubMed: 12021250]

15. Javor ED, Ghany MG, Cochran EK, et al. Leptin reverses nonalcoholic steatohepatitis in patients with severe lipodystrophy. *Hepatology*. 2005; 41:753–760. [PubMed: 15791619]
16. Asilmaz E, Cohen P, Miyazaki M, et al. Site and mechanism of leptin action in a rodent form of congenital lipodystrophy. *J Clin Invest*. 2004; 113:414–424. [PubMed: 14755338]
17. Unger RH, Zhou YT, Orci L. Regulation of fatty acid homeostasis in cells: novel role of leptin. *Proc Natl Acad Sci U S A*. 1999; 96:2327–2332. [PubMed: 10051641]
18. Minokoshi Y, Kim YB, Peroni OD, et al. Leptin stimulates fatty-acid oxidation by activating AMP-activated protein kinase. *Nature*. 2002; 415:339–343. [PubMed: 11797013]
19. Gorden P, Lupsa BC, Chong AY, Lungu AO. Is there a human model for the “metabolic syndrome” with a defined aetiology? *Diabetologia*. 2010; 53:1534–1536. [PubMed: 20401463]

Fig. 1.

Effect of metreleptin treatment on hemoglobin A_{1c} (A1C) during a 3-year treatment period. *A*, Effect of metreleptin on A1C over time (observed population). A decline in A1C was observed 4 months after the initiation of metreleptin treatment, and A1C continued to decrease during the 3-year treatment period. *B*, In patients with elevated baseline A1C, metreleptin treatment substantially lowered A1C throughout the treatment period, achieving a mean A1C of $6.3\% \pm 0.3\%$ at the end of the 3-year treatment period. The *dashed line* in both figures denotes a common treatment goal for glucose control (A1C 7%). *SE* = standard error.

Fig. 2. Effect of metreleptin treatment on triglycerides during a 3-year treatment period. *A*, Metreleptin treatment substantially improved geometric mean triglyceride concentrations during the 3-year treatment period in the observed population, achieving a geometric mean $\pm$ standard error (*SE*) concentration of 164 ± 26 mg/dL. *B*, In patients with elevated triglyceride levels at baseline ($n = 41$), metreleptin treatment substantially lowered triglyceride concentrations throughout the treatment period, achieving a geometric mean $\pm$ SE concentration of 197 ± 35 mg/dL at the end of the 3-year treatment period. The *dashed line* in both figures denotes a common criterion for hypertriglyceridemia of 200 mg/dL.

Fig. 3.

Effect of metreleptin treatment on alanine aminotransferase (*ALT*) during a 3-year treatment period. *A*, A rapid decline in *ALT* concentrations was observed after 4 months of metreleptin treatment, after which the *ALT* concentrations were sustained during the 3-year study period. *B*, In patients with elevated *ALT* concentrations at baseline, an initial reduction at 4 months of metreleptin treatment was observed, and patients achieved further reductions after 3 years of treatment. The *dashed line* in both figures denotes the upper limit of normal for *ALT* of 41 U/L in this assay. *SE* = standard error.

Fig. 4.

Effect of metreleptin treatment on aspartate aminotransferase (*AST*) during a 3-year treatment period. *A*, A robust decline in *AST* concentration was observed after 4 months of treatment. The reduction was sustained throughout 3 years. *B*, In patients with elevated *AST* concentrations at baseline, an initial reduction at 4 months of metreleptin treatment was observed, and patients achieved further reductions after 3 years of treatment. The *dashed line* in both figures denotes the upper limit of normal for *AST* of 34 U/L in this assay. *SE* = standard error.

Table 1 Demographics and Baseline Characteristics (Intent-to-Treat Population)^a

Demographics and baseline characteristics	All patients (N = 55)
Sex, male:female (%)	20:80
Race (%) ^b	
White	67
Hispanic	11
Black	9
Native American	4
Asian	4
Other	6
Mean age (y)	25 (53% pediatric)
Age-group (y), no. (%)	
12	10 (18)
>12 to <18	19 (35)
18 to 65	25 (45)
>65	1 (2)
Lipodystrophy type (%)	
Congenital generalized	42
Familial partial	25
Acquired generalized	24
Acquired partial	9
Body weight (kg)	59.0 ± 14.2
Body mass index (kg/m ²)	22.2 ± 3.4
Hemoglobin A _{1c} (%)	8.5 ± 2.1
Fasting plasma glucose (mg/dL)	184 ± 91
Fasting serum triglycerides (mg/dL), geometric mean ± SE	479 ± 80
Alanine aminotransferase (U/L)	100 ± 120
Aspartate aminotransferase (U/L)	71 ± 77
Leptin (ng/mL)	2.8 ± 2.8
<i>Baseline measurements for patients with elevated hemoglobin A_{1c}, triglycerides, alanine aminotransferase, or aspartate aminotransferase^c</i>	
Hemoglobin A _{1c} (7%)	9.4 ± 1.5
Fasting serum triglycerides (200 mg/dL), geometric mean ± SE	743 ± 123
Alanine aminotransferase (41 U/L)	149.8 ± 134.5
Aspartate aminotransferase (34 U/L)	112.3 ± 87.2

Abbreviation: SE = standard error.

^aValues are reported as mean ± standard deviation unless indicated otherwise.^bBecause of rounding, percentages do not total 100.^cSubpopulations of patients with lipodystrophy who had elevated hemoglobin A_{1c} (n = 41 [75%]), elevated triglycerides (n = 41 [75%]), elevated alanine aminotransferase (n = 33 [60%]), and elevated aspartate aminotransferase (n = 29 [53%]) at baseline.

Table 2**Patient Disposition and Exposure to Metreleptin Treatment (Intent-to-Treat Population)**

Factor	n (%)
<i>Patient disposition</i>	
Intent-to-treat population	55 (100)
Currently ongoing	42 (76)
Withdrew from study ^a	13 (24)
Primary reason for withdrawal	
Noncompliance	5 (9)
Ineligibility determined	2 (4)
Adverse events	2 (4)
Death	1 (2)
Other	3 (5)
<i>Extent of exposure to metreleptin (mo)^b</i>	
6	4 (7)
>6 to 12	9 (16)
>12 to 24	11 (20)
>24 to 36	6 (11)
>36 to 48	5 (9)
>48 to 60	3 (5)
>60 to 72	0 (0)
>72	17 (31)

^a Although 13 patients withdrew from the study, 5 (9% of the 55) subsequently reentered the study. The data for these patients on reentry are not included in the analysis presented here.

^b Because of rounding, percentages do not total 100.

Table 3

Effect of Metreleptin on Lipids After a 3-Year Treatment Period (Intent-to Treat Population, N = 55)

Lipid	Baseline (mean $\pm$ SD) (n)	Year 3
Low-density lipoprotein cholesterol (mg/dL)	117.7 $\pm$ 47.7 (35)	75.2 $\pm$ 9.8 (12) ^a
Change from baseline (mean $\pm$ SE)		-64.3 $\pm$ 18.6
95% Confidence interval		-105.8 to -22.8
High-density lipoprotein cholesterol (mg/dL)	31.5 $\pm$ 8.8 (54)	34.4 $\pm$ 1.9 (19) ^a
Change from baseline (mean $\pm$ SE)		0.05 $\pm$ 2.1
95% Confidence interval		-4.4 to 4.5
Total cholesterol (mg/dL)	244.4 $\pm$ 148.2 (55)	141.7 $\pm$ 8.6 (19) ^a
Change from baseline (mean $\pm$ SE)		-105.8 $\pm$ 35.7
95% Confidence interval		-180.9 to -30.7

Abbreviations: n = number of patients for whom data were available at the indicated time point; SD = standard deviation; SE = standard error.

^aData are presented as mean $\pm$ SE (N).