Metreleptin Treatment in Three Patients with Generalized Lipodystrophy

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Abstract:
Generalized lipodystrophy (GL) is a rare inherited or acquired disease characterized by widespread loss of subcutaneous fat, leading to leptin deficiency, ectopic fat deposition, and severe metabolic abnormalities. Previous studies have shown the benefit of leptin replacement (metreleptin) in ameliorating metabolic complications, but little is known about the experience of metreleptin treatment outside of a research setting. We report on post-marketing clinical experience with metreleptin therapy in three patients with GL and marked hypoleptinemia, uncontrolled diabetes, and hypertriglyceridemia. After metreleptin treatment for 12–168 weeks, the mean glycosylated hemoglobin decreased from 10.9% to 5.8%, and serum triglycerides were normalized (a mean decline of 90%). These benefits were observed within weeks of starting therapy, were durable, and were accompanied by subjective improvements in quality of life, decreased need for concomitant medications, and no significant adverse effects. Metreleptin was safe and effective in normalizing certain severe metabolic abnormalities in the clinic setting.

Keywords: diabetes, generalized lipodystrophy, hypertriglyceridemia, metreleptin

Introduction
Generalized lipodystrophy (GL) is categorized as a rare congenital generalized lipodystrophy (CGL) or acquired generalized lipodystrophy (AGL) disease characterized by widespread loss of adipocytes, leading to leptin deficiency, ectopic fat deposition, and severe metabolic abnormalities (insulin resistance, diabetes, and/or hypertriglyceridemia).1,2 In women with insulin resistance and hyperleptinemia, polycystic ovarian syndrome, hyperandrogenism, and amenorrhea are very common.3 Conventional glucose- and lipid-lowering medications do not address the underlying leptin deficiency and are often inadequate at addressing severe metabolic abnormalities.1

Metreleptin is a recombinant human leptin analog that binds to and activates the leptin receptor, and it is the only US Food and Drug Administration-approved treatment for patients with CGL or AGL as an adjunct to diet and as replacement therapy to treat complications of leptin deficiency.3 Metreleptin is not currently indicated for the treatment of partial lipodystrophy, liver disease, human immunodeficiency virus-related lipodystrophy, or diabetes and hypertriglyceridemia without evidence of concurrent CGL or AGL. The starting daily dose of metreleptin varies by weight and sex (Table 1), and daily dosing may be increased or decreased according to clinical response (changes in glycated hemoglobin [A1C], triglycerides, etc.). Per the US prescribing label, metreleptin should be administered once daily (QD) at the same time every day. In clinical trial experience, the most common adverse reactions (≥10% incidence) included headache, hypoglycemia, decreased weight, and abdominal pain.

There is limited experience using metreleptin to treat patients with GL in the clinic setting. Herein, we present the metreleptin treatment experience in three patients with GL inadequately managed with conventional medications. Patients or their guardians gave consent for the publication of this report.

Case Report 1
Patient 1 was a 19-year-old female of Arabic descent and consanguineous parentage diagnosed with CGL at early infancy.

Table 1. Metreleptin dosing per the US Package Insert.4

| Sex and Weight Range | Initial Daily Dose (Injection Volume) | Dose Adjustments (Injection Volume) | Maximum Daily Dose (Injection Volume) |
|----------------------|--------------------------------------|-------------------------------------|--------------------------------------|
| Males and females ≤40 kg | 0.06 mg/kg (0.012 mL/kg) | 0.02 mg/kg (0.004 mL/kg) | 0.13 mg/kg (0.026 mL/kg) |
| Males >40 kg | 2.5 mg (0.5 mL) | 1.25–2.5 mg (0.25–0.5 mL) | 10 mg (2 mL) |
| Females >40 kg | 5 mg (1 mL) | 1.25–2.5 mg (0.25–0.5 mL) | 10 mg (2 mL) |
(serum triglycerides >2000 mg/dL at two months) Table 2. Prior to metreleptin, she presented with generalized subcutaneous fat loss, muscular appearance, acanthosis nigricans, elevated alanine aminotransferase (ALT; 47 U/L), hepatomegaly (confirmed later by magnetic resonance imaging scan: moderate hepatomegaly with fatty infiltration), irregular menstrual cycles (three to four per year), increased abdominal girth, and elevated A1C and triglycerides (11.8% and 3675 mg/dL, respectively; Table 1). These metabolic abnormalities were noted despite ongoing therapy with metformin 500 mg three times daily (TID), pioglitazone 30 mg QD, insulin detemir 40 U twice daily (BID), insulin aspart 40 U TID, fenofibrate 145 mg QD, niacin 500 mg QD, omega-3 fatty acids 2 g TID, and orlistat 120 mg TID for four years.

Metreleptin was initiated at 5 mg QD subcutaneously by self-injection. A1C and triglycerides were markedly improved at four weeks from 11.8% to 9.7% and 3675 to 2118 mg/dL, respectively (Fig. 1). At 12 weeks, while maintained at the same metreleptin dose, A1C and triglycerides dropped further to normal levels (5.7% and 121 mg/dL, respectively), and slightly elevated ALT at baseline was within normal limits (23 U/L). The normalization of laboratory values occurred while the patient discontinued insulin aspart, pioglitazone, niacin, and fenofibrate (insulin detemir was decreased from 40 to 30 U BID, and the dosing frequency of omega-3 fatty acids was reduced to QD). Weight remained stable, hepatomegaly and abdominal girth were reduced, and the patient reported resumption of regular menstrual cycles for the last two months. No adverse events (AEs) were noted.

**Case Report 2**

Patient 2 was a 10-year-old female with CGL diagnosed from birth with a history of pancreatitis (four episodes requiring hospitalization), lytic bone lesions, and mesangial proliferative glomerulonephritis (Table 2). Prior to metreleptin treatment, she presented with generalized subcutaneous fat loss, acanthosis nigricans, elevated liver enzymes (ALT: 132 U/L; aspartate aminotransferase [AST]: 80 U/L), prominent abdomen due to hepatosplenomegaly (abdominal ultrasound demonstrated enlarged liver, homogeneous parenchyma, and decreased echogenicity), decreased energy, proteinuria (2.5 g/24 hours), and elevated A1C and triglycerides (9.2% and 497 mg/dL, respectively; Table 1). Her metabolic abnormalities were managed with metformin 500 mg/day, regular U100 insulin 1000 U/day, fenofibrate 200 mg/day, and enalapril 20 mg/day for 21 months.

Metreleptin was initiated at 4.2 mg/day while the patient was enrolled in research protocol 02-DK-0022 at the National Institutes of Health. At 24 weeks, A1C and triglycerides were reduced from 9.2% to 8.0% and 497 to 302 mg/dL, respectively (Fig. 1), and the patient’s proteinuria was resolved (0 g/24 hours). As A1C was still elevated, the patient’s metreleptin and metformin doses were increased in a stepwise manner over consecutive visits to 10 mg/day and 2000 mg/day, respectively. At week 168, the patient’s metabolic parameters had improved (A1C: 6.6%; triglycerides: 84 mg/dL), and her total daily insulin requirement was reduced from 1000 to 75 U/day. ALT and AST were within normal limits (20 and 18 U/L, respectively). The patient’s weight increased by 10%, and she self-reported improved energy levels, a flat abdomen, and that she completed her pubertal development with her first menses. No AEs were noted.

**Case Report 3**

Patient 3 was a 19-year-old male with AGL manifesting between eight and nine years of age with panniculitis in the abdomen, legs, and face, followed later by generalized loss of subcutaneous fat (Table 2). He presented with acanthosis nigricans, prominent abdomen, acromegaloid features, hyperphagia, asthenia, elevated liver enzymes (ALT: 171 U/L; AST: 81 U/L), hyperinsulinemia (fasting: 228 µU/mL), and elevated A1C and triglycerides (11.0% and 861 mg/dL, respectively). The patient’s weight increased by 10% and that she completed her pubertal development with her first menses. No AEs were noted.

**Figure 1.** Changes in (A) A1C and (B) triglycerides in Patients 1–3. A1C, glycated hemoglobin.
A1C measurement before metreleptin treatment was 11.8%. He was also managed with fenofibrate 200 mg/day, vitamin K 5 mg/month (due to vitamin K deficiency related to steatohepatitis), ranitidine 150 mg/day, ursodiol 300 mg/day, and enalapril 5 mg/day.

Metreleptin was initiated at 3.5 mg/day. At six weeks, the patient’s A1C was reduced from 11.8% to 6.7% (Fig. 1). At 32 weeks, A1C was further reduced to 5.1% and triglycerides were reduced to 36 mg/dL. At 96 weeks, his A1C increased to 5.8%. It was noted that the patient gained 6 kg of weight during this time, so the metreleptin dose was increased to 4 mg/day. As of the last measurement (week 140), A1C was 5.1% and triglycerides were 80 mg/dL. During treatment with metreleptin, the patient was able to discontinue the use of insulin and fenofibrate, remaining only on ursodiol 300 mg/day and enalapril 10 mg/day. ALT levels were reduced from 171 to 120 U/L, while AST remained stable (from 81 to 79 U/L). Follow-up hepatic ultrasonography indicated increased spleen size with homogeneous structure and liver with rounded edges, enlarged, homogeneous-increased

Table 2. Baseline demographics, concomitant medications, and metabolic parameters prior to metreleptin treatment and at last measurement.

| PRIOR TO METRELEPTIN TREATMENT | LAST AVAILABLE MEASUREMENT |
|-------------------------------|----------------------------|
| **Patient 1: 19-year-old F with CGL (type 1 homozygous c.355 deletion mutation in AGPAT2); weight 49.8 kg; height 163 cm; baseline leptin ~0.6 ng/mL** | |
| Concomitant medications | Fenofibrate 145 mg QD  
Insulin aspart 40 U TID  
Insulin detemir 40 U BID  
Lisinopril 5 mg QD  
Metformin 500 mg TID  
Niacin 500 mg QD  
Omega-3 fatty acids 2 g QD  
Orlistat 120 mg TID  
Pioglitazone 30 mg QD | Insulin detemir 30 U BID  
Lisinopril 5 mg QD  
Metformin 500 mg TID  
Omega-3 fatty acids 2 g QD  
Orlistat 120 mg TID |
| A1C (%) | 11.8  
FPG (mg/dL) | 259  
TG (mg/dL) | 3675  
ALT (U/L) | 47  
AST (U/L) | 25 |
| **Patient 2: 10-year-old F with CGL (AGPAT mutation); weight 43.8 kg; height 149 cm; baseline leptin N/A** | |
| Concomitant medications | Enalapril 20 mg/day  
Fenofibrate 200 mg/day  
Metformin 500 mg/day  
Regular U100 insulin 1000 U/day | Enalapril 40 mg/day  
Fenofibrate 200 mg/day  
Metformin 2000 mg/day  
Regular U100 insulin 75 U/day |
| A1C (%) | 9.2  
FPG (mg/dL) | 315  
TG (mg/dL) | 497  
ALT (U/L) | 132  
AST (U/L) | 80 |
| **Patient 3: 19-year-old M with AGL; weight 60.8 kg; height 145 cm; baseline leptin 1.8 ng/mL** | |
| Concomitant medications | Enalapril 5 mg/day  
Fenofibrate 200 mg/day  
Metformin 2000 mg/day  
Ranitidine 150 mg QD  
Regular U100 insulin 600 U/day  
Regular U500 insulin 120 U/day  
Ursodiol 300 mg/day  
Vitamin K 5 mg/month | Enalapril 10 mg/day  
Ursodiol 300 mg/day |
| A1C (%) | 11.8  
FPG (mg/dL) | 298  
TG (mg/dL) | 861  
ALT (U/L) | 171  
AST (U/L) | 81 |

**Notes:** *Most recent value was at age 12 and was decreased from 32.9 ng/mL at age 11.*  
**Abbreviations:** A1C, glycated hemoglobin; AGL, acquired generalized lipodystrophy; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BID, twice daily; CGL, congenital generalized lipodystrophy; F, female; FPG, fasting plasma glucose; M, male; N/A, not available; QD, once daily; TG, triglycerides; TID, three times daily; U, units.
In addition to improved A1C and triglycerides, elevations of liver enzyme were numerically improved or normalized in all patients, with decreased size of hepatomegaly observed in Patient 1. At least one study group has described significant improvements in liver pathology from baseline with metreleptin treatment; however, improved liver enzymes do not always correlate with improved liver-related end points.

Patient 2 had proteinuria at baseline that resolved after metreleptin treatment. Metreleptin has been shown in a prior cohort of patients with GL to reduce urinary protein excretion in 11 of 15 patients treated for four months.

In the patients with GL presented here, metreleptin was effective at improving certain metabolic abnormalities in the clinic setting with no notable AEs. Subjective QoL improvements (increased energy, normalization of appetite/menstrual function, improved appearance, etc.) are equally important to the patient treatment experience, as are improvements in laboratory parameters.

**Acknowledgments**

Robert Schupp, PharmD, CMPP, of inScience Communications, Springer Healthcare (Philadelphia, PA, USA), provided medical writing support funded by Aegerion Pharmaceuticals, Inc.

CM would like to acknowledge Dr. Phillip Gorden and Elaine Cochran of the National Institutes of Health who helped to provide care for Patients 2 and 3 in this case series and for their collaboration.

**Author Contributions**

Provided care for Patient 1: VS. Provided care for Patients 2 and 3: CM, MLM, EA. All authors participated in manuscript development. They also reviewed and approved the final version prior to submission.

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