Practical Use of Metreleptin in the Treatment of Lipodystrophy

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Disclosures

There are no relevant financial relationships to disclose.
Learning Objectives

• Review evidence that metreleptin therapy improves metabolic status (diabetes, insulin resistance, hypertriglyceridemia, fatty liver disease) in hypoleptinemic patients with congenital generalized, acquired or partial generalized, and familial partial lipodystrophy to appraise its role in clinical practice.
• Distinguish patients whose metabolic derangements at baseline are more likely to be significantly improved with metreleptin to determine how to tailor its use appropriately.
• Describe the formulation properties of leptin (dispensed as a dry powder plus diluent) and appropriate techniques for its reconstitution, storage, and administration to set a standard for best practice.
• Explain the importance of accurate subcutaneous injection of leptin and specify techniques for avoiding intramuscular injection to ensure safe administration in patients who lack subcutaneous adipose tissue.
Clinical Studies of Leptin in Lipodystrophy

• The largest cohort of lipodystrophy patients treated with metreleptin has been studied in the intramural research program of the National Institute of Diabetes and Digestive and Kidney Diseases of the National Institutes of Health (NIH).
• The first patient started leptin treatment in 2000 and has been continuously treated for 12 years.
• To date, 84 patients have been treated at the NIH.
• Smaller numbers of additional patients have been treated in Japan, Europe, and at other sites in the United States.
NIH Lipodystrophy Cohort

**Inclusion Criteria**
- Low serum leptin level:
  - <8 ng/mL in males
  - <12 ng/mL in females
- Age ≥6 months
- ≥1 metabolic abnormality, including:
  - Diabetes
  - Insulin resistance (fasting insulin ≥ 30 μU/mL)
  - Hypertriglyceridemia (fasting triglycerides >200 mg/dL)

**Patient Characteristics**
- 72 patients as of 2010 data cut
- 83% female
- 54% children (<18 years of age at enrollment)
- Lipodystrophy subtypes:
  - 44% congenital generalized
  - 25% familial partial
  - 22% acquired generalized
  - 6% acquired partial
Metreleptin:

- Metreleptin: recombinant human methionyl leptin
- Metreleptin is an analogue of human leptin, in which an additional methionine has been added at the amino terminus.
Metreleptin Dosing Principles

- Dosing was based on body weight in both children and adults.
- Starting dose depended on sensitivity to leptin, which in turn depended on:
  - Sex (males more sensitive than females)
  - Age (younger children more sensitive)
  - Lipodystrophy subtype
    - Generalized more sensitive than partial
    - Patients with AGPAT2 mutation more sensitive than those with BSCL2 (seipin) mutation
- Dose frequency was once or twice daily depending on patient convenience and severity of metabolic disease.
  - Doses >5 mg/day (1 mL) were typically divided into twice-daily doses.
Metreleptin Dosing Principles: Starting Dose

- Males (all ages and subtypes): 0.06 mg/kg/day
- Females:
  - <5 years of age: 0.06 mg/kg/day
  - >5 years of age:
    - 0.08-0.1 mg/kg/day for:
      - Congenital generalized lipodystrophy because of AGPAT2 mutation
      - Acquired generalized lipodystrophy
    - 0.1-0.12 mg/kg/day for:
      - Congenital generalized lipodystrophy because of BSCL2 (seipin) mutation
      - Familial partial lipodystrophy
      - Acquired partial lipodystrophy
Metreleptin Dosing Principles: Dose Adjustment

- Doses were increased after 6 months if metabolic control was inadequate:
  - Current dose 0.06: increased to 0.08 mg/kg/day
  - Current dose 0.08-0.1: increased to 0.12-0.18 mg/kg/day
  - Current dose 0.1-0.12: increased to 0.15-0.2 mg/kg/day
- If weight loss >5 kg occurred (less in young children):
  - Decreased dose by 0.01 mg/kg/day biweekly until weight stabilized

Distribution of metreleptin doses in 2008:
- Usual treatment doses: 0.08-0.12 mg/kg/day
- Maximum dose: 0.24 mg/kg/day

Clinical Effects of Metreleptin in Lipodystrophy

- Appetite and body weight
- Insulin resistance
- Diabetes
- Hypertriglyceridemia
- Steatohepatitis
- Reproduction
- Kidney disease
Appetite and Body Weight

Leptin reduced caloric intake by ~40%.
Mean weight loss after 1 year was ~4 kg.
Part of this weight loss was the result of reduction in ectopic lipid mass (e.g., liver weight).

Appetite and Body Weight
Teaching Points

• Most patients with lipodystrophy are hyperphagic in the leptin-deficient state and experience appetite reduction with metreleptin.
• Mild weight loss is common in the first 6 months of metreleptin treatment and usually stabilizes by 1 year.
• In growing children (and occasionally in adults), the dose of metreleptin may need to be reduced if weight loss is excessive (>5 kg in older children and adults, less in younger children).
Insulin sensitivity gradually improves after starting metreleptin.

In insulin-treated patients, this may increase the risk for hypoglycemia, and reduction of insulin doses may be needed.


Insulin sensitivity measured by hyperinsulemic, euglycemic clamp studies in seven Japanese patients with generalized lipodystrophy before (baseline) and at various time points after metreleptin treatment.
Diabetes Control: Fasting Glucose

- Fasting glucose dropped rapidly after metreleptin initiation.

In patients with inadequate blood glucose control (A1C ≥7%) at baseline, A1C decreased by almost 2% after 4 months of metreleptin treatment, and mean A1C was <7% by 2 years.

Diabetes Control: Medication Requirements

Improvements in glycemia were seen with metreleptin despite reductions in insulin and oral hypoglycemic medications.

The median insulin dose decreased from 300 units/day at baseline to 75 units/day after 12 months of metreleptin treatment.

To date, at least 10 patients have been able to discontinue insulin altogether.

Diabetes Teaching Points

• Metreleptin was associated with substantial A1C lowering in lipodystrophic patients with diabetes (3% decrease in those with an initial A1C >7%).
• This improvement resulted, in part, from improvements in insulin sensitivity.
• Because of improved insulin sensitivity, patients taking insulin (and sulfonylureas) may be at increased risk for hypoglycemia after metreleptin initiation, and insulin doses usually need to be tapered.
Diabetes Teaching Points, cont.

- Some patients, even those requiring large doses of insulin, may be able to discontinue insulin entirely while taking metreleptin.
- Patients with type 1 diabetes (associated with acquired lipodystrophy) or with advanced β-cell failure will continue to require insulin (usually at lower doses) while taking metreleptin.
- Because of their severe insulin resistance, patients with lipodystrophy may require U-500 insulin both before and after metreleptin treatment.
Metreleptin was associated with a 60% decrease in triglycerides, with the most dramatic improvements seen in patients with extreme hypertriglyceridemia at baseline.

Metreleptin was associated with significant reductions in ALT and AST by 4 months of treatment.

These reductions were sustained over 3 years.

Liver Disease: Pathology

- 27 patients had paired liver biopsies before and after metreleptin treatment.
- 86% of patients met pathological criteria for nonalcoholic steatohepatitis (NASH) at baseline.
- Only 33% of patients met criteria for NASH after 26 ± 4 months of leptin treatment.
- Nonalcoholic fatty liver disease scores decreased by 44.2%.

Hematoxylin and eosin staining of liver biopsy specimens in a patient before (A) and after (B) leptin treatment.

Reproduction: Menstrual Cycles and Sex Hormones

Polycystic Ovarian Syndrome
- Free testosterone decreased from 40 to 19 ng/dL after 1 year of leptin in 10 women with generalized lipodystrophy.
- Polycystic ovaries were present in all 10 women and did not change after metreleptin.
- Eight of 10 women had amenorrhea before metreleptin, and all had normal menses after metreleptin.

Luteinizing Hormone (LH) Secretion
- LH secretion in response to LH-releasing hormone (LHRH) increased nonsignificantly after 4 months of metreleptin treatment.
- Significant increases in LH response to LHRH were seen in three adolescent girls.

Reproduction: Pregnancy

- Most women with partial lipodystrophy have normal fertility.
- Women with generalized lipodystrophy are rarely fertile without leptin replacement. (Only one woman with generalized lipodystrophy in the NIH study had a pregnancy before metreleptin.)
- Effective contraception was strongly encouraged during metreleptin treatment.
- Despite this, three women with generalized lipodystrophy had spontaneous pregnancies while taking metreleptin.
Kidney pathology in lipodystrophy includes diabetic nephropathy (A), membranoproliferative glomerulonephritis (B and C), and focal segmental glomerulosclerosis (D).

Effects of metreleptin on renal hyperfiltration and proteinuria in 15 patients with generalized lipodystrophy:

- Creatinine clearance was supranormal at baseline and declined to just above the normal range after 4-36 months of metreleptin treatment.
- Urine protein excretion was elevated at baseline and declined in 11 of 15 patients (individual patients shown as dotted lines).

## Summary of Metreleptin Effects in Lipodystrophy

<table>
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<tr>
<th>Clinical Parameter</th>
<th>Major Effects</th>
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<tr>
<td>Appetite and body weight</td>
<td>Decreased</td>
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<tr>
<td>Insulin resistance</td>
<td>Decreased</td>
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<td>Diabetes</td>
<td>Decreased A1C Decreased insulin doses</td>
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<td>Steatohepatitis</td>
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<td>Reproduction</td>
<td>Normalized menstrual cycles Increased fertility</td>
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<td>Kidney disease</td>
<td>Decreased hyperfiltration Decreased protein excretion</td>
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Safety: Common Adverse Events

- Treatment-emergent adverse events occurred in 31% of patients.
- Events occurring in ≥5% of patients included:
  - Hypoglycemia (11%)
    - Occurred only in insulin-treated patients, likely secondary to improved insulin sensitivity
  - Fatigue (11%)
  - Hair loss (7%)
  - Weight loss (6%)
  - Injection site reactions (erythema, urticaria) (4%)

Injection site reactions commonly consisted of erythema and swelling. These reactions may improve if the dose is lowered and gradually titrated back up to the target dose. Injection site reactions have not caused any patient with lipodystrophy to discontinue metreleptin.
Safety: Serious Adverse Events

• T-cell lymphoma occurred in three patients with acquired lipodystrophy, two of whom had pre-existing immunodeficiency.
  – Metreleptin initiation in patients with acquired lipodystrophy should be approached with caution and careful assessment of risk/benefit ratios.
• Other events likely related to underlying disease:
  – Pancreatitis
  – Worsening of kidney disease
  – Worsening of liver disease

Administration of Metreleptin

- Preparation of medication
- Storage of medication
- Injection technique
Teaching Patients to Give Leptin: Supplies

- Leptin is dispensed as 11.3 mg of dry powder in a vial.
- It must be reconstituted with 2.2 mL of bacteriostatic or sterile water to form a 5 mg/mL solution.
Teaching Patients to Give Leptin: Adding Diluent to Powder

**Transferring Liquid**

1a. Remove the needle guard from syringe 1. Pull the plunger back to the 2.2 mL mark.

1b. Clean the rubber stopper of the liquid vial with an alcohol wipe.

1c. Push the needle through the rubber stopper of the vial and press the plunger down completely, injecting air into the vial.

1d. Flip vial upside down. Slowly pull the plunger back to the 2.2 mL mark.

1e. Tap the syringe gently to move air bubbles toward the tip of the syringe. Note: It is normal for the bubbles to move slowly.

1f. Slowly push the plunger until most air bubbles are out of the syringe.

1g. Slowly pull the plunger back again until the syringe is filled with 2.2 mL of liquid.

1h. Insert the needle into the powder vial. Slowly push the plunger until it stops to transfer the liquid from the syringe into the powder vial.

1i. Remove the needle and syringe. Note: Pull the needle and syringe out of the vial. Set the liquid vial aside. Use care to not pull the plunger out of the syringe.
Teaching Patients to Give Leptin: Mixing Powder with Diluent and Drawing Up the Dose

Mixing the Powder and Diluent

Use care to not touch the top of the powder vial with your fingers.

2a. Mix the powder and liquid by gently rolling the powder vial containing the mixture on a hard surface for approximately 30 seconds until the powder is well mixed. The mixture should be clear, colorless, and have no visible clumps.

2b. Examine the vial, especially the bottom edge, for unmixed powder and visible clumps. If unmixed powder or clumps are observed, repeat step @a.

2c. Write the date of mixing on the mixed vial.

Filling a New Syringe with the Mixture

3a. Allow the mixed vial to reach room temperature prior to use.

3b. Remove the needle guard from syringe 2.

3c. Insert syringe 2 into the mixed vial.

3d. Draw out the volume specified by your doctor following the procedure outlined in steps 1b to 1g.

NOTE: If the mixed vial sits for more than 5 minutes, gently shake the vial to remix before proceeding.
Storage of Metreleptin

- Powered metreleptin vials should be stored in the refrigerator—NOT the freezer.
- Metreleptin reconstituted with BACTERIOSTATIC water may be stored in the refrigerator and used for a maximum of 3 days.
- Metreleptin reconstituted with STERILE water should be used for a single injection, and any remainder should be discarded.
**Injection Technique**

- The basic principles of leptin injection are identical to those of insulin or other subcutaneous injection.
- In patients with partial lipodystrophy who have adequate subcutaneous tissue in parts of their bodies, standard injection technique such as that shown on the right may be used.

4a. Select one of the upper two quadrants of the abdominal region injection. Rotate between quadrants 1 and 2 for each dose. Clean the selected area using an alcohol wipe.

4b. Using the technique recommended by hospital staff (skin fold lift with the needle entering at a 90 degree angle), insert the needle into your skin and push in the plunger slowly as far as it will go.

4c. Wait for 5 seconds before withdrawing the needle.

4d. Press a cotton ball over the injection site and massage gently for several seconds.

4e. Discard needle and syringe.

4f. Put the mixed vial back into the kit and return the kit to the refrigerator, NOT FREEZER.

DO NOT attempt to administer intravenously.
Injection Technique in Patients Lacking Subcutaneous Fat

- In patients with generalized lipodystrophy, the lack of subcutaneous fat makes accurate subcutaneous injection challenging.
- Subcutaneous injections in patients with lipodystrophy may be better termed “injections under the skin.”
- The needle hub needs to be placed past the epidermal and dermal layers of the skin, but not into the muscle tissue.
- Accidental intramuscular injection not only is more painful, but also may alter absorption kinetics of the medication, leading to more rapid absorption.
Injection Technique in Patients Lacking Subcutaneous Fat

- In certain regions of the body at boundaries between muscle groups (shown in subsequent slides), the skin is less taut, and patients can more easily pinch up the skin.
- We describe the pinched skin as a “tent” and advise patients to angle the needle so that it enters the “door” of the tent. Thus, the needle is inserted at a 45° angle to avoid intramuscular injection.
In the arm, a good site to use in patients lacking subcutaneous fat is the juncture between the deltoid and triceps muscle (arrows). Using sites at the borders between muscle groups allows patients to pinch up relatively loose skin and minimize the chance of accidental intramuscular injection.
Injection Sites: Abdomen

Optimal injection sites in the abdomen include the lateral border of the rectus abdominus muscle (right arrow), and the inferior border of the external oblique muscle (left arrow). Note that identification of these muscles is easy in patients lacking subcutaneous adipose tissue.

In the picture above, a mother demonstrates inserting the needle at an approximately 45° angle into her child’s abdominal subcutaneous tissue.
In the thigh, injections may be optimally given at the medial border of the gracilis (right arrow) or the lateral border of the rectus femoris (left arrow).
Summary of Metreleptin Preparation and Administration

- Patients must be taught how to mix, store, and inject metreleptin.
- Subcutaneous injections are challenging in patients with lipodystrophy because of their lack of subcutaneous fat.
- Accidental intramuscular injection can be avoided by appropriately selecting injection sites and angling the needle.