Lipodystrophy Syndromes: Diagnosis and Treatment

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Disclosures

◆ I will discuss use of METRELEPTIN for lipodystrophy (not approved for Partial LD)

◆ I am receiving drug and research support from Aegerion Pharmaceuticals and Akcea Therapeutics.

◆ Worked as a scientific advisor to Amylin, BMS, AZ and Aegerion over the years. Currently an advisor to Aegerion Pharmaceuticals, Regeneron, Ionis Pharmaceuticals and Akcea and Thera Therapeutics.

◆ Grant and other research support from Novo, BMS, GSK, BI and GI Dynamics in the past

◆ Grant support from Ionis Pharmaceuticals/Akcea Therapeutics/Gemphire Therapeutics currently.
Overview of My Talk

What are Lipodystrophy Syndromes?

How do we diagnose lipodystrophy?

Therapy
  Journey
    From high unmet medical need to an approved therapy

New therapies on the horizon
Lipodystrophy Syndromes

- Relative paucity of adipose tissue
- Metabolic abnormalities
  - Insulin resistance
  - Hypertriglyceridemia
  - Fatty infiltration of liver and other tissues
Classification of Lipodystrophy Syndromes

Inherited
Caused by genetic mutations
(known and unknown)

Acquired*
Often associated with autoimmune diseases
(also idiopathic, other etiologies*)

Generalized

Partial

Congenital Generalized Lipodystrophy

Fat loss apparent at birth
Metabolic manifestations early

Subtype  Gene
• CGL1  AGPAT2
• CGL2  BSCL2
• CGL3  CAV1
• CGL4  PTRF

New genetic markers:
PYCT1-A, LMNA, PPARG
AGPAT2 mutations in CGL, type 1
(TG biosynthetic pathway)
**BSCL2 Mutations in CGL, Type 2**

- *BSCL2* located on chromosome 11q13
- Encodes a 462 amino acid transmembrane ER protein, seipin
- Seipin has a CAAX motif at C-terminal and an N-glycosylation site
- Role in lipid droplet formation and adipocyte differentiation

- Szymanski et al. PNAS 2007; 104:20890-95
- Payne et al. Diabetes 2008;57:2055-60
Lipid Droplet Formation and CGL

Acquired Generalized Lipodystrophy (Lawrence syndrome)

- Very rare
- Onset in childhood or adolescence
- Female-to-male ratio: 3:1

Acquired Generalized Lipodystrophy

- Panniculitis Variety (Type 1)
- Autoimmune Disease Variety (Type 2)
- Juvenile Dermatomyositis
- Idiopathic Variety (Type 3)
- Paraneoplastic

Acquired Generalized Lipodystrophy

Panniculitis Variety

4 1/2 months

6 months

8 months

10 months

Familial Partial Lipodystrophy

- Typically autosomal dominant
- Normal fat distribution at birth or subtle loss from LE
- Changes around puberty
- Selective absence from extremities
- Hypertrophy of residual depots especially upon weight gain or positive caloric balance
Heterogeneity in Familial Partial Lipodystrophy

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Gene</th>
</tr>
</thead>
<tbody>
<tr>
<td>FPL1</td>
<td>Unknown or polygenic</td>
</tr>
<tr>
<td>FPL2</td>
<td>LMNA</td>
</tr>
<tr>
<td>FPL3</td>
<td>PPARG</td>
</tr>
<tr>
<td>FPL4</td>
<td>PLIN1</td>
</tr>
<tr>
<td>FPL5</td>
<td>CIDEC</td>
</tr>
<tr>
<td>FPL6</td>
<td>LIPE</td>
</tr>
</tbody>
</table>

Newer genes: AKT, ADR2A, Mitofusin 2, etc.
LMNA Mutations in FPLD

Cardiomyopathy
† Emery-Dreifuss Muscular Dystrophy
‡ Limb Girdle Muscular Dystrophy
§ Mild Myopathy
¶ Mild Lipodystrophy

Structure of Nuclear Lamina

Acquired Partial Lipodystrophy

- Caphalocaudal Variety (Barraquer Simmons type)
- Autoimmune Disease Variety
- Idiopathic Variety
- Juvenile Dermatomyositis
- Post childhood cancer: due to XRT or CTx

HIV related LD not shown.
Cephalacaudal Acquired Partial Lipodystrophy (Barraquer-Simmons type)

Age of Onset ~10 Years
Female to Male Ratio 4:1
Low Serum C3 72%
C3NeF Positive 83%
Autoimmune Diseases 11%
Membrano-proliferative Glomerulonephritis (MPGN) 19%

Misra et al. Medicine 2004;83:18-34.
MPGN and Drusen in APL
Localized Lipodystrophy

- Drug-induced
- Pressure-induced
- Panniculitis
- Centrifugal
- Idiopathic
Lipodystrophy Syndromes

- Heterogeneous in etiology and presentation
- Discovered as a metabolic disease, but common denominator is fat loss
- Rough clinical correlation between severity of metabolic abnormalities and fat loss

What is the link between fat loss and metabolic abnormalities?
Animal Models of Lipodystrophy

- Regardless of strategy used for fat ablation, the animals develop
  - Insulin resistance
  - Hypertriglyceridemia
  - Fatty infiltration of liver and other tissues
- Fat transplantation from littermates rescue metabolic abnormalities
- Adipocytokine profiles are abnormal, there is especially leptin deficiency.
  - When leptin is replaced, metabolic phenotype improves.
  - When leptin deficient fat is transplanted, improvement is attenuated.
Pathophysiology of Lipodystrophy

- Abnormal adipose tissue
- Leptin deficiency and abnormal adipokine profile

Etiologies
- Genetic (monogenic disorders)
- Autoimmune
- Unknown

Ectopic lipid deposition
Lipodystrophy Associated Severe Co-Morbidities

**Hyperphagia:** excessive food intake
Severely elevated triglycerides and glucose

**Progressive and multi-systemic complications:**

- **Pancreas**
  - Insulin resistance
  - Poorly controlled diabetes
  - Acute or chronic Pancreatitis

- **Liver**
  - Hepatic steatosis
  - Hepatomegaly
  - Steatohepatitis
  - Cirrhosis
  - Liver failure

- **Heart**
  - Cardiomyopathy
  - Atherosclerosis
  - Cardiac transplant

- **Reproductive**
  - Infertility
  - Hyperandrogenism

- **Kidney**
  - Accelerated renal disease related to diabetes
  - Glomerulonephritis
# Mortality in Lipodystrophy

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Life Expectancy (decade)</th>
<th>Causes of Mortality</th>
</tr>
</thead>
</table>
| Acquired Generalized LD       | Second or third          | Acute pancreatitis  
Sepsis  
End stage liver disease  
Malignancy: Lymphoma  
Diabetes related Cardiac |
| Acquired Partial LD           | Sixth                    | ESRD related complications                                                          |
| Congenital Generalized LD     | Second to fourth         | Acute pancreatitis  
Sepsis  
Diabetes Related Cardiac                                                            |
| Familial Partial LD           | Fourth to sixth          | Cardiac  
Diabetes related                                                               |
Lipodystrophy Syndromes

- Heterogeneous in etiology and presentation
- Discovered as a metabolic disease
- Multi-system involvement
- Significant comorbidity
- Potentially increased mortality
Overview of My Talk

What are Lipodystrophy Syndromes?

How do we diagnose lipodystrophy?

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  Journey
    From high unmet medical need to an approved therapy

New therapies on the horizon
How do we diagnose lipodystrophy?

Clinical Diagnosis
- Recognition of the pattern
- Synthesis of physical exam and labs

Major Criteria
- Selective absence of fat (but coupled with metabolic abnormalities)

Is physical exam sufficient?

How do we make diagnosis more objective?
Objective Fat Measurement
Using DEXA for Diagnosis of LD

% Fat trunk/% fat legs

Patients

Patients with familial partial lipodystrophy
Patient with acquired partial lipodystrophy
NHANES reference matched for age, gender and race

± 2 SD
Fat Shadow
Increased neck and supraclavicular fat
No abdominal sc fat
Hypertrophy of mons pubis fat surrounded by lipoatrophy ("Dunnigan sign")
Muscle hypertrophy
Mons pubis hypertrophy may or may not be present
Increased neck and supraclavicular fat
Axillary fat
No abdominal sc fat
No sc fat in extremities
Hypertrophy of mons pubis fat surrounded by lipoatrophy ("Dunnigan sign")
Muscle hypertrophy
Increased neck and supraclavicular fat
Abdominal obesity & abundant sc fat
Mons pubis hypertrophy may or may not be present
Calf muscle hypertrophy may or may not be present
Congenital Generalized Lipodystrophy
Acquired Generalized Lipodystrophy
Familial Partial Lipodystrophy
Köbberling variety
Dunnigan variety
Female AGPAT2
Male BSCL2
Female LMNA p.R482L
Male LMNA p.R482Q
Acquired Partial Lipodystrophy
Köbberling variety
Dunnigan variety
Female
Male
Female
Male
Differential Diagnosis
(Generalized Lipodystrophy Syndromes)

- Neonatal Progeroid syndrome
- Starvation/Malnutrition/Cachexia/Anorexia
- Thyrotoxicosis/Adrenal insufficiency
- Uncontrolled diabetes
- Diencephalic syndrome
What to do if you suspect Generalized Lipodystrophy Syndromes

- Substantiate and prove evidence for decreased fat (physical exam is key)
  - Mid thigh skin folds is easy to obtain in clinic
  - DEXA scans may become clinically available
- Ruling out starvation and caloric deprivation is important
  - Adiponectin level may be of help to differentiate between hypercatabolic or starvation states (including poorly controlled Type 1 DM) and GL
- Document the time course of fat loss, do any of the syndromes apply with physical features?
  - Evaluate the patient for other physical features of progeria
- Document family history, many monogenic forms are AR
  - Can send a genetic lipodystrophy panel if you have medical genetics available at your institution.
- Evaluate for metabolic complications and comorbidities
Differential Diagnosis
(Partial Lipodystrophy Syndromes)

- Cushing’s syndrome
- Multiple symmetric lipomatosis
- Truncal obesity
- Progeroid disorders
What to do if you suspect Partial Lipodystrophy Syndromes

- Substantiate and prove evidence for decreased fat (physical exam is key)
  - Upper body versus peripheral fat loss
  - Mid thigh skin folds is easy for FPLD, DEXA may become available in the future, monogenic forms of disease have absolutely no fat in the LE
  - Do they have lipomatosisis, or other progeroid findings on exam?
- Ruling out Cushing’s syndrome
- Document family history, many monogenic forms are AD
  - Can send a genetic lipodystrophy panel if you have medical genetics available at your institution.
- Evaluate for metabolic complications and comorbidities
Overview of My Talk

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New therapies on the horizon
Severe Hypertriglyceridemia: Treatment with Plasmapheresis

- Signs and symptoms
  - Triglyceride levels >10,000 mg/dL
  - Painful, eruptive xanthomas
  - Severe hepatomegaly
- Plasmapheresis treatment
  - 1-3 sessions per week
  - > 24 months
- Results
  - Triglyceride levels decreased by 65-85% / session
  - Weekly average: 2,900-6,000 mg/dL
Leptin Levels in Lipodystrophy

Leptin ($\text{ng/mL}$) vs. Body fat (%) correlation: $r=0.86, p<0.001$
1997: Why not replace leptin in patients with severe lipodystrophy?

Analogy from Type 1 diabetes

Answer: Not affirmative
A Role of Leptin Therapy in Human Disease in 1997:

- Magic bullet for obesity (?)
Three Important Developments

**Leptin reverses insulin resistance and diabetes mellitus in mice with congenital lipodystrophy**

*Ichiro Shimomura*, Robert E. Hammer†, Shinji Ikemoto‡, Michael S. Brown‡ & Joseph L. Goldstein§

*Department of Molecular Genetics, †Department of Biochemistry and Biophysics, Howard Hughes Medical Institute, University of Texas Southwestern Medical Center, Dallas, Texas 75335-9046, USA*

Congenital generalized lipodystrophy (CGL) is a rare autosomal recessive disorder characterized by a paucity of adipose (fat) tissue which is evident at birth and is accompanied by a severe resistance to insulin, leading to hyperinsulinaemia, hyperglycaemia and enlarged fatty liver. We have developed a mouse model that mimics these features of CGL: the syndrome occurs in transgenic mice expressing a truncated version of a nuclear protein known as sREBP-1c (sterol regulatory element-binding protein-1c) under the control of the adipose-specific aP2 enhancer. Adipose tissue from these mice was markedly deficient in messenger RNAs encoding several fat-specific proteins, including leptin, a fat-derived hormone that regulates food intake and energy metabolism. Here we show that insulin resistance in our lipodystrophic mice can be overcome by a continuous systemic infusion of low doses of recombinant leptin, an effect that is not mimicked by chronic food restriction. Our results support the idea that leptin modulates insulin sensitivity and glucose disposal independently of its effect on food intake, and that leptin deficiency accounts for the insulin resistance found in CGL.

**Shimomura et al. Nature 1999; 401:73-6**

**Heymsfield, S. B. et al. JAMA 1999;282:1568-1575.**

![Image of children's body measurements](image-url)
2000: Why not replace leptin in patients with lipodystrophy?

Analogy from Type 1 diabetes

Answer: Affirmative
Study Design

- Prospective open study
- Inclusion criteria:
  - Clinical diagnosis of lipodystrophy
  - At least one metabolic abnormality
    - Presence of diabetes based on ADA criteria
    - Presence of hypertriglyceridemia (>200 mg/dL)
    - Elevated fasting insulin levels (>30 IU/mL)
## Metabolic Efficacy of Leptin

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>4-months</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HbA$_{1c}$ (%)</strong></td>
<td>9.1</td>
<td>7.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Triglycerides (mg/dL)</strong></td>
<td>1405</td>
<td>348</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>FFA (µmol/L)</strong></td>
<td>1540</td>
<td>790</td>
<td>0.045</td>
</tr>
</tbody>
</table>

*Oral EA, et.al, NEJM 346: 570-578, 2002*
Expansion of leptin treatment in lipodystrophy

Cutoff leptin level for treatment increased
- Males <3 → <8
- Females <4 → <12

Up to 75 patients
- 74% generalized;
- 16% partial
- Mean leptin 2.5 ng/dL

Distribution of metreleptin doses
- Usual treatment doses: 0.08-0.12 mg/kg/day
- Maximum dose: 0.24 mg/kg/day
Leptin effects on Hba1c in NIH Cohort

Generalized lipodystrophy: 8.4 → 6.4% (p<0.001)

Partial lipodystrophy: 8.1 → 7.3% (p=0.004)
Leptin Effects on Triglycerides in NIH Cohort

- **Generalized lipodystrophy**: Mean 1021 → 276; Median 396 → 169 ($p<0.001$)
- **Partial lipodystrophy**: Mean 971 → 524; Median 416 to 311 ($p=0.02$)
Additional Effects of Leptin

- Evaluate effects on multiple hormonal axes (n=7; all females)
  - Oral EA, et. al. JCEM 87:3110-7, 2002

- Evaluate effects of leptin therapy on immune system (n=10; 9 females)
  - Oral EA, et. al. JCEM 91:621-8, 2006
Decreased appetite and food intake

Leptin receptors in the hypothalamus

Food intake independent effects

HbA1c reduction

Improved insulin sensitivity

Improved hepatic steatosis and NASH

Reduction in triglycerides

Other shown benefits:
- Reduction in proteinuria and hyperfiltration
- Normalized gonadotropin secretion
- Improved fertility
- Clinical improvements in hyperandrogenemic women with PCOS
- Immunomodulatory effects, PBMC responsiveness

Other anticipated benefits (emerging data):
- Improvement in quality of life
- Improvement in mortality and cardiovascular risk reduction
- Prevention of diabetes and complications
Conclusions

- Leptin is a major contributor to the adipocytes’ regulation of whole body insulin sensitivity and lipid metabolism.

- Leptin has a role in the regulation of multiple endocrine axes and immune system in humans.
A Therapeutic After 20 Years

PRESS RELEASE
Feb. 25, 2014, 2:06 p.m. EST
U.S. FDA approves orphan drug MyaleptTM (metreleptin for injection)

WILMINGTON, Del., Feb 25, 2014 (BUSINESS WIRE) -- AstraZeneca AZN -0.03% today announced that the U.S. Food and Drug Administration (FDA) has approved Myalept™ (metreleptin for injection), which is indicated as an adjunct to diet as replacement therapy to treat the complications of leptin deficiency in patients with congenital or acquired generalized lipodystrophy. MYALEPT, a recombinant analog [laboratory-created form] of human leptin, is the first and only treatment approved by the FDA for these patients.
Novel Therapy: Leptin Replacement

- Metreleptin = recombinant human methionyl leptin
- Subcutaneous injection 1-2 times per day
Safety: Common Adverse Events

- Treatment-emergent adverse events occurred in 31% of patients.

- Events occurring in ≥4% 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 (4%; erythema, urticaria)

Safety and Tolerability

- Other notable serious adverse events
  - Pancreatitis: n=4 (6.3%)
  - Progression of liver disease: n=4 (6.3%)
  - Progression of kidney disease: n=3 (4.7%)
  - Lymphoma: n=3 (4.7%; all with acquired generalized lipodystrophy)
  - Neutralizing antibodies to leptin: n=3 (4.7%)
FDA Review of Metreleptin

- Approved for generalized lipodystrophy, with or without metabolic complications
- Not approved for partial lipodystrophy, regardless of metabolic disease

---

INDICATIONS AND USAGE

MYALEPT is a leptin analog indicated as an adjunct to diet as replacement therapy to treat the complications of leptin deficiency in patients with congenital or acquired generalized lipodystrophy. (1)

Limitations of Use

- The safety and effectiveness of MYALEPT for the treatment of complications of partial lipodystrophy have not been established. (1)
- The safety and effectiveness of MYALEPT for the treatment of liver disease, including nonalcoholic steatohepatitis (NASH), have not been established. (1)
- MYALEPT is not indicated for use in patients with HIV-related lipodystrophy. (1)
- MYALEPT is not indicated for use in patients with metabolic disease, without concurrent evidence of generalized lipodystrophy. (1)
Black Box Warnings

Neutralizing antibodies

T-cell lymphoma

WARNING: RISK OF ANTI-METRELEPTIN ANTIBODIES WITH NEUTRALIZING ACTIVITY AND RISK OF LYMPHOMA

Anti-metreleptin antibodies with neutralizing activity have been identified in patients treated with MYALEPT. The consequences are not well characterized but could include inhibition of endogenous leptin action and loss of MYALEPT efficacy. Worsening metabolic control and/or severe infection have been reported. Test for anti-metreleptin antibodies with neutralizing activity in patients with severe infections or loss of efficacy during MYALEPT treatment. Contact Bristol Myers-Squibb at 1-866-216-1526 for neutralizing antibody testing. (4.1, 5.1)

T-cell lymphoma has been reported in patients with acquired generalized lipodystrophy, both treated and not treated with MYALEPT. Carefully consider the benefits and risks of treatment with MYALEPT in patients with significant hematologic abnormalities and/or acquired generalized lipodystrophy. (5.2)

MYALEPT is available only through a restricted program called the MYALEPT REMS PROGRAM. (5.3)
Who is a candidate for Metreleptin therapy

- All patients with Congenital Generalized Lipodystrophy Syndromes regardless of metabolic state or age are eligible.
- Metreleptin is approved for both treatment and prevention of metabolic complications.
- For Acquired Generalized Lipodystrophy patients, decision may be more tricky and more close monitoring for treatment side effects may be warranted.
- All atypical generalized lipodystrophy patients deserve a careful work up in a specialty center before determining treatment course to evaluate risk for malignancy, etc.
Why was Metreleptin not approved for partial lipodystrophy?

Safety Concerns
- Neutralizing antibodies
- T-cell lymphoma

Disease Heterogeneity
What to do for the Partial Lipodystrophy Patients?

- Substantiate the diagnosis
- Diet and exercise (after cardiac risk considerations)
- Optimize diabetes and triglyceride therapies as tolerated, utilize the toolbox
- Obtain genetic diagnosis if possible
- Consider checking leptin levels, if low and significant metabolic burden, may consider compassionate use (cumbersome process)
- Consider cosmetic surgery if indicated
- Multidisciplinary care—patients are often very complex and there is multi-system involvement
FPLD is a Complicated Disease

Comorbidities and Medication Usage in PLD

A

- any glucose lowering agent: 82.6%
  - metformin: 52.2%
  - insulin: 52.2%
  - insulin >100 u/day: 13.0%
  - insulin <100 u/day: 17.4%
  - GLP1 agonist: 8.7%
  - sulfonylurea: 8.7%
  - pioglitazone: 4.3%
  - sitagliptin: 4.3%
  - any anti-hypertensive: 73.9%
    - ACE inhibitor: 21.7%
    - beta blocker: 17.4%
    - angiotensin receptor blocker: 17.4%
    - thiazide: 13.0%
    - other diuretic: 13.0%
    - calcium channel blocker: 13.0%
    - nitrate: 4.3%
  - any lipid lowering agent: 73.9%
    - fish oil: 56.5%
    - statin: 47.8%
    - fibrate: 39.1%
    - niacin: 4.3%
  - any psychiatric medication: 52.2%
    - benzodiazepine: 26.1%
    - SSRi: 21.7%
    - SNRI: 17.4%
    - tricyclic antidepressant: 4.3%
    - atypical antipsychotic: 4.3%
    - other psychiatric: 17.4%
    - any analgesic: 43.5%
      - opioid analgesic: 34.8%
      - gabapentin: 21.7%
      - other analgesic: 17.4%

B

- NASH: 55.7%
- hypertriglyceridemia: 56.5%
- diabetes: 62.6%
- hypertension: 52.2%
- peripheral neuropathy: 43.5%
- OA/back pain: 47.8%
- depression: 43.5%
- proteinuria/microalbuminuria: 43.5%
- PCOS: 39.1%
- myopathy: 39.1%
- gallbladder disease: 34.8%
- pancreatitis: 30.4%
- GERD requiring treatment: 30.4%
- OSA: 30.4%
- diabetic retinopathy: 26.1%
- anxiety: 26.1%
- fibromyalgia: 21.7%
- Pre-diabetes: 17.4%
- CAD/MI: 17.4%
- asthma/emphysema: 13.0%
- kidney stones: 13.0%
- cardiomyopathy: 8.7%
- DVT: 8.7%
- pancreatic cyst(s): 8.7%
- hypothyroidism: 8.7%
- gastroparesis: 4.3%
## Partial Lipodystrophy: Without a Treatment in the US

<table>
<thead>
<tr>
<th></th>
<th>Familial Partial Lipodystrophy (FPL)</th>
<th>Generalized Lipodystrophy (GL)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Appearance of clinical features</strong></td>
<td>Mostly post-puberty</td>
<td>Infancy/childhood</td>
</tr>
<tr>
<td><strong>Leptin level</strong></td>
<td>Variable, overlap with general population; significantly higher than patients with GL</td>
<td>Very low; significantly lower than patients with FPL</td>
</tr>
<tr>
<td><strong>Underlying genetic mutations</strong></td>
<td>LMNA, PPARG, AKT2, PLIN1, CAV1, ZMPSTE24, POLD1, others</td>
<td>LMNA, AGPAT2, BSCL2, CAV1, PTRF</td>
</tr>
<tr>
<td><strong>Approved treatment</strong></td>
<td>No</td>
<td>Yes (Metreleptin: leptin replacement therapy)</td>
</tr>
</tbody>
</table>

There are other biomarkers that associate with metabolic risk.
Role of ApoC-III in Lipid Metabolism

- ApoC-III is a 79 aminoacid glycoprotein synthesized principally in the liver
  - Multiple apoc-III proteins on VLDL and HDL particles
- Plays a key role in determining serum triglyceride (TG) levels
  - Potent inhibitor of LPL
  - Inhibits hepatic uptake of TRLs
ApoC3 as a Target for CHD Risk Reduction

**Loss-of-Function Mutations in APOC3, Triglycerides, and Coronary Disease**

The TG and HDL Working Group of the Exome Sequencing Project, National Heart, Lung, and Blood Institute*

**Loss-of-Function Mutations in APOC3 and Risk of Ischemic Vascular Disease**


40% Reduction in apoC3

40% Reduction in TG

40% Reduction in CHD Risk
Volanesorsen is an Antisense Oligonucleotide (ASO) Against ApoC-III

apoC3 gene  Volanesorsen  apoC-III Protein

Transcription  mRNA
ISIS 304801 (volanesorsen) Treatment Significantly Reduced TG (Monotherapy) in Previous Phase 2 Study

**Mean % Change in Fasting Triglycerides**

- Placebo
- ISIS-ApoCIII_Rx 100 mg
- ISIS-ApoCIII_Rx 200 mg
- ISIS-ApoCIII_Rx 300 mg

Study Day:
- 1
- 8
- 15
- 29
- 43
- 57
- 71
- 85
- 92
- 99
- 127
- 176

**p-value**
- ***p-value ≤0.001
- **p-value ≤0.01
- *p-value ≤0.05

Gaudet D. et.al. NEJM 2015. 373:438-447
IONIS 304801 (volanesorsen) Improves Whole-Body Insulin Sensitivity on Clamp

Andres Digenio et.al. Diabetes Care 2016. May; dc160126.
doi.org/10.2337/dc16-0126
**RATIONALE for the BROADEN STUDY:**
Why should a drug targeting ApoC3 be effective in treating FPLD?

ApoC3 levels are elevated in FPLD.

<table>
<thead>
<tr>
<th>Abnormality</th>
<th>Can apoC3 Inhibition Help?</th>
<th>Probability Of Success</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertriglyceridemia with possible associated pancreatitis</td>
<td>By reducing TG levels can reduce risk of pancreatitis</td>
<td>High</td>
</tr>
<tr>
<td>Presence of diabetes with evidence of severe insulin resistance</td>
<td>May improve insulin sensitivity</td>
<td>Moderate to High</td>
</tr>
<tr>
<td>Hepatic steatosis</td>
<td>May reduce liver fat by reducing TG levels and improving insulin sensitivity</td>
<td>Moderate</td>
</tr>
<tr>
<td>Loss or absence of subcutaneous body fat in a partial fashion</td>
<td>It is unknown what improving insulin sensitivity can do to ectopic fat stores</td>
<td>Low</td>
</tr>
</tbody>
</table>
BROADEN STUDY UNIQUE FEATURES

• First global randomized placebo controlled study in the FPLD population.
• Objective inclusion criteria that combines genetic and morphometric criteria for the first time.
12 sites enrolled 40 FPLD patients in 7 countries
Randomized, double blind, placebo-controlled, parallel arm, multicenter, global study with open label extension (OLE)

- **6 wk diet run in:**
  - Fasting TG ≥ 500 mg/dL at screening and qualification*
  - Fasting TG levels ≥ 200 to < 500 mg/dL at both Screening and Qualification who meet genetic or family history criteria

- **12 months**
  - 300 mg qw
  - Placebo qw

- **1:1 Randomization** (N=40)

- **Primary Efficacy Endpoint**
  - % change in TG from Baseline to Wk13
  - 300 mg vs placebo

- **12 months placebo-controlled**
  - Safety
  - Durability of response

- **1 YR OLE**
- **2 YR OLE**
What else is going on

Three Novel Studies

• 2 new drugs for the same target
  • A new proof-of-concept study
  • A global study, but not launched
• Two older drugs repurposed
  • Proof-of-concept study at UM (Gemcabene)
  • Proof-of-concept study at UTSW (obethicholic acid)

Other possibilities in development
Lessons Applied to the New Trials

• Some of the new studies have randomization as part of the study design
• Inclusion and exclusion criteria are well thought out and incorporate morphometric documentation with skin fold measurements
• Treatment time specified
• Patient reported outcomes
What does the future promise?

- Targets involving hepatokines that regulate metabolic dyslipidemia or liver lipid trafficking and oxidation
- Other endocrine targets
- Therapies involving the bone marrow:
  - Tight link of the communication between bone marrow and adipocytes.
  - If there is increased food flux, there is a demand to make new MSCs to take up extra energy storage capacity.
  - Massive lipolysis and energy deficit also signals back to the bone marrow.
  - Internal control of MSCs from various sources.
  - In lipodystrophy, the control of MSCs may be perturbed to may favor apoptosis.
  - Full mapping of the connections may lead to the potential to prevent apoptosis or use the pluripotent nature of one of the pools of MSCs.
What is Next for Lipodystrophy Research?

It is very important for the community to form an Global Research Network

SOLID (Study of Lipodystrophy Syndromes).

The mission of this research collaboration will be to define the various lipodystrophy syndromes precisely, uncover disease mechanisms related to lipodystrophy, and develop new therapeutics; therefore, improve the lives of patients afflicted with these disorders.

Collectively work towards increased understanding

Standardized disease definitions

Improved treatments
Grant Support

- NIDDK-5RO1-DK-088114A1
- NIDDK- RO3-DK-074488
- MDRTC DK020572 P&F
- Peptide Research Center P&F
- MICH-R—UL 1RR 024986
Earlier NIH Studies

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Endocrinology
Genetics
Radiology
Nephrology
Neurology
Cardiology
Pathology
Histology
DEU
Biogenome

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Marmara University, Istanbul
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Pamukkale University, Denizli
Osmangazi University, Eskisehir
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Inonu University, Malatya
Cumhuriyet University, Sivas
Mersin University, Mersin
Diyarbakir Training Hospital, Diyarbakir
Koc University, School of Medicine, Istanbul
Kecioren Training Hospital, Ankara
Karabuk State Hospital, Karabuk
Urfa State Hospital, Urfa
Kocaeli Training Hospital, Kocaeli
Uludag University, Bursa
Dr. Behcet Uz Children's Hospital, Izmir

Dr. Sami Ulus Obstetrics and Gynecology, Children's Training Hospital, Ankara
Ataturk University, Erzurum
Study of AKCEA-ANGPTL3-LRX (ISIS 703802) in Patients With Familial Partial Lipodystrophy (FPL)

The safety and scientific validity of this study is the responsibility of the study sponsor and investigators. Listing a study does not mean it has been evaluated by the U.S. Federal Government. Know the risks and potential benefits of clinical studies and talk to your health care provider before participating. Read our disclaimer for details.

ClinicalTrials.gov Identifier: NCT03514420

Recruitment Status: Not yet recruiting
First Posted: May 2, 2018
Last Update Posted: May 2, 2018

See Contacts and Locations
One More Drug for the Same Target
Evinacumab for Extreme Hypertriglyceridemia

The safety and scientific validity of this study is the responsibility of the study sponsor and investigators. Listing a study does not mean it has been evaluated by the U.S. Federal Government. Know the risks and potential benefits of clinical studies and talk to your health care provider before participating. Read our disclaimer for details.

Sponsor:
Regeneron Pharmaceuticals

ClinicalTrials.gov Identifier:
NCT03452228

Recruitment Status : Not yet recruiting
First Posted : March 2, 2018
Last Update Posted : May 30, 2018

See Contacts and Locations

Safer and more effective
"folllowing 12 weeks of repeated..."
**Gemcabene’s Mechanism of Action**

**REDUCES PRODUCTION**
- Inhibits de novo synthesis of TGs and cholesterol in the liver
- TG effects due to inhibition of acetyl CoA carboxylase 1
- ↓VLDL-C particles leaves fewer apolipoproteins for catabolism to LDL-C

**IMPROVES CLEARANCE**
- Reduces ApoC-III gene expression and plasma ApoC-III protein levels
- Enhances VLDL-C clearance through increased affinity for the hepatic remnant receptor

Gemcabene calcium is the monocalcium salt of a dialkyl ether dicarboxylic acid having 2 terminal gem dimethyl carboxylate moieties.
Gemcabene Overview

SAFETY
- Nearly 1,100 subjects treated with gemcabene
- No muscle or liver toxicities in patients treated
- No drug interactions with statins or metformin

ATHEROGENIC PROFILE
- Significant LDL-C reduction as monotherapy and on top of statins
- Significant atherogenic burden with reductions in non-HDL-C, apoB and apoE

TRIGLYCERIDES
- Significant triglyceride reductions in hypertriglyceridemic patients

INFLAMMATION
- Gemcabene has demonstrated over 40% reductions in hsCRP in patients
- Significant TNF-α and IL-6 reduction in preclinical STAM™ Model

INSULIN SENSITIVITY
- Gemcabene demonstrated a doubling of the glucose disposal rate suggesting potential effects on insulin sensitivity
**Adult FPLD/NASH Phase 2a Trial Design**

**Familial Partial Lipodystrophy (FPL) Patients, Open-Label**

**Principal Investigator**
- Elif Oral, MD, University of Michigan

**Primary Endpoint:**
- % change in triglycerides (TG) from baseline to 12 weeks

**Secondary Endpoints:**
- Change in hepatic steatosis as measured by MRI-PDFF at 12 and 24 weeks
- Change in NAS (histology) at 24 weeks
- Change in ALT, insulin sensitivity, serum lipids (including TG), apolipoproteins, and inflammatory markers (including hsCRP)
- Safety and tolerability