Therapy of Hypertriglyceridemia: What does the future hold?

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Severe Refractory HTG: High Unmet Medical Need

- 3-5000 with LPL or apoC-II deficiency (orphan indications)
- 30-50K with severe refractory HTG (orphan indication approved)
- 25% of patients with HTG have apoA-V polymorphisms

1. **Patient**
   TG 3700 mg/dL
   Ch 546 mg/dL

2. **Healthy**
   TG 100 mg/dL
   Ch 200 mg/dL

- xanthomas filled with foam cells

Yuan G et al. CMAJ 2007;176:1113-1120
Lipid metabolism with high and normal hepatic TG production

- **TG Production**
  - **Low**
  - **High**

- **Very Small VLDL**
  - ApoB
  - ApoE
  - Remnant Cholesterol
  - LPL

- **Large VLDL**
  - ApoB
  - ApoC-III
  - ApoE
  - Remnant Cholesterol
  - Non-HDL-C
  - LPL

- **Small LDL**
  - ApoB
  - ApoC-III
  - Non-HDL-C
  - LDL-C
  - CETP
  - HDL
  - HL
  - sHDL
  - Renal clearance

- **Remnant Cholesterol**
  - ApoB
  - ApoC-III
  - ApoE

- **Non-HDL-C**
  - CE
  - TG

- **LDL-C**
  - ApoC-III

- **Cholesterol**
  - Yellow

- **Triglycerides**
  - Pink
Targeted Therapies for Refractory Hypertriglyceridemia with Genotype based Patient Selection

Lipase enzyme activity is regulated by apolipoprotein

- ApoAV peptide
- ApoCII peptide

apoC3 ASO  LPL gene therapy

Cholesterol  Triglycerides
Glybera Gene Replacement Therapy for LPL Deficiency

- **AAV1-Capsid**
  - Containing the AAV2-LPL $^{s447x}$ cassette

- **In vivo intramuscular injection**

- **First Gene replacement therapy being authorized in the occidental world**

- **Designed for patients with FCS due to loss-of-function LPL gene mutations.**

- **Not for FCS caused by apoA-5, apoC-2, GPIHPB1, LMF-1 gene mutations.**

- **Requires genotyping (genetic test)**
Glybera Mechanism of Action
Fasting TG Decreased After 12 Weeks of Treatment but Returned to Baseline After 5 Months
Results shown are a mean ± SEM; n=5 (wk-2 and wk+14) or n=3 (wk+52)
p-values: t-test AUC24hrs; wk-2 versus wk +14 and wk +52

3H-Chylomicron Clearance 14 Weeks and One Year After Treatment (fasting TG values at week-52 were back to baseline values)
Risk Reduction of Definite, Probable Pancreatitis and Abdominal Pain Events

Consistent 56 - 67% risk reduction

- p-values 0.001 - 0.007
ApoC-III inhibits the conversion of VLDL to LDL and causes small dense LDL and low HDL.
Clinical Experience with 2nd Generation ASOs

- >4000 subjects treated by IV and/or SC administration
- >100 clinical studies
- Multiple therapeutic indications
- >100 patients dosed for >1 year
- Some patients dosed for > 4 years
- Doses as high as 1200 mg tolerated
Three patients in ApoCIII<sub>Rx</sub> Study in FCS
- Homozygotes or compound heterozygote for FCS-causing null LPL gene mutations
  - Have LPL mass but no or extremely low level (<5%) of LPL activity

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patient 1</th>
<th>Patient 2*</th>
<th>Patient 3*</th>
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<tbody>
<tr>
<td>Gender</td>
<td>Male</td>
<td>Female</td>
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<td>Age, yrs</td>
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<td>BMI, kg/m²</td>
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<td>29.0</td>
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<tr>
<td>Genotype</td>
<td>P207L/P207L</td>
<td>P207L/G188E</td>
<td>P207L/P207L</td>
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</table>

*participated in post-heparin LPL activity measurements

**Phase 2 Open Label Cohort in FCS**

**Treatment Period**
- 300 mg ApoCIII<sub>Rx</sub>
- Once a week for 13 Weeks

**Post-Treatment f/u Period**
- 13 weeks
**ISIS-APOCIII<sub>Rx</sub> Treatment Reduced Fasting Plasma ApoC-III and Triglyceride Levels in FCS Patients**

### Fasting ApoC-III Levels

<table>
<thead>
<tr>
<th>Parameter (mg/dL)</th>
<th>Patient No.</th>
<th>Baseline&lt;sup&gt;*&lt;/sup&gt;</th>
<th>Primary Endpoint&lt;sup&gt;†&lt;/sup&gt;</th>
<th>Change from Baseline</th>
<th>% Change from Baseline</th>
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<tbody>
<tr>
<td>Triglyceride</td>
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<td>1406</td>
<td>616.5</td>
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<td>-1795.5</td>
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<td>3</td>
<td>2043</td>
<td>734.5</td>
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<td>-64.0</td>
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<tr>
<td>ApoC-III</td>
<td>1</td>
<td>18.9</td>
<td>5.5</td>
<td>-13.4</td>
<td>-70.9</td>
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<td></td>
<td>2</td>
<td>35.1</td>
<td>3.4</td>
<td>-31.7</td>
<td>-90.4</td>
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<td>3</td>
<td>19.8</td>
<td>3.5</td>
<td>-16.3</td>
<td>-82.5</td>
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</tbody>
</table>
**ISIS-APOCIII<sub>Rx</sub> Treatment Reduced Fasting Plasma Chylomicron-TG and ApoB-48 Levels in FCS Patients**

**Fasting Chylomicron-TG Levels**

**Fasting ApoB-48 Levels**

<table>
<thead>
<tr>
<th>Parameter (mg/dL)</th>
<th>Patient No.</th>
<th>Baseline&lt;sup&gt;*&lt;/sup&gt;</th>
<th>Primary Endpoint&lt;sup&gt;*&lt;/sup&gt;</th>
<th>Change from Baseline</th>
<th>% Change from Baseline</th>
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<td>Chylomicron-TG</td>
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<td>ApoB-48</td>
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<td>2</td>
<td>1.54</td>
<td>0.27</td>
<td>-1.27</td>
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<td></td>
<td>3</td>
<td>0.72</td>
<td>0.53</td>
<td>-0.19</td>
<td>-26.3</td>
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Non-HDL Cholesterol was also Reduced in Parallel with Triglyceride Levels
High Correlation Between ApoC-III and Triglycerides and Between Chylomicron-TG and Triglycerides
ISIS-APOCIII\textsubscript{Rx} Safety and Tolerability

- **Drug-related adverse events**
  - No elevations of liver enzymes $>3\times$ ULN
  - No abnormalities in renal function
  - No clinically meaningful changes in other laboratory values

- **Tolerability**
  - Generally well tolerated
  - No flu-like symptoms
  - Low incidence of injection site reactions (primarily mild erythema)
Postulated extracellular effects of apoA-V on TG-rich lipoprotein metabolism.

Forte T M et al. J. Lipid Res. 2009;50:S150-S155
**Hereditary Defects in apoA-V Cause HTG**

- Impaired synthesis of apoA-V (1131T>C variant) linked to HTG in 25% of patients
- 50K participants in 27 studies

![APOA1/C3/A4/A5 “gene cluster” & dyslipidemia](image)

Sarwar et al., Lancet 2010
APOA5 Causal for both Hypertriglyceridemia and Premature Cardiovascular Disease

**APOA5 Association with Lipid levels in Patients with HTG**

- Triglyceride (n=45730)
- HDL cholesterol (n=38266)

**APOA5 Association in Patients with Coronary Heart Disease**

- Genetically-raised triglyceride† (20842 cases/35206 controls)

50K participants in 27 studies

21K cases, 35K controls in 39 studies
Apo-A5 has a High Impact at Low Concentrations

- Attractive template for anti-HTG peptidomimetics
- Apo-A5 physiologically active at low concentrations

<table>
<thead>
<tr>
<th>Apolipoprotein</th>
<th>Effect on TG levels</th>
<th>Plasma concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>apoC-III</td>
<td>↑</td>
<td>3.4 μM</td>
</tr>
<tr>
<td>apoC-II</td>
<td>↓</td>
<td>34.7 μM</td>
</tr>
<tr>
<td>apoA-V</td>
<td>↓</td>
<td>0.0038 μM</td>
</tr>
</tbody>
</table>

- Apo-a5 knockout mice have 4x higher TG (*Science*, 2001)
- Apo-A5 gene expression lowers TG in normal mice by ~ 66%
- Plasma concentration is 10,000-fold less than apo-C2 or Apo-Al
Technology: AV-peptide to Stimulate Lipase Activity

- AV-peptides binds to VLDL, lipase & heparan sulfate (acts as a “reservoir”)

- lead-peptide (AV-H/K) can boosts lipase activity 8x

**2D Graph 4**

**Rate of TG Hydrolysis**

- LDL, VLDL & Chylomicrons

- C-II, A-V, C-III, B48, 100, C-III

- AV-peptide

- heparan sulfate proteoglycan

- Cells, tissues

- LpL

- FA

Graph showing the rate of triglyceride (TG) hydrolysis over time (min) with different peptides and VLDL.
Apo-CII Peptidomimetic Structure

- Apo-C2 peptidomimetic is 2 alpha helices joined together – 36 aa
- Helix1 is a high affinity peptide for lipoproteins - previously described, 18A
- Helix2 derived from apo-CII LPL activating domain
- More effective than full length Apo C2
- Increased ABCA1 cholesterol efflux
Effective in both Apo-C2 Deficient and General HTG Patients

- Addition of Apo-C2 ex vivo was highly efficacious in Apo-C2 deficient patients
- Was also efficacious in HTG population – over 50 subjects tested
- Data suggest an enhanced efficacy in the presence of LPL
Apo-C2 modulates TG and Cholesterol Levels in Apo-E Knockout Mice

- Apo-E Knockout mice were given Apo-C2 bolus and followed for 4 hours
- Consistent with in vitro activities, there was a decrease in both TG and Cholesterol
DGAT Catalyzes TG Synthesis
Role of Acyl CoA: diacylglycerol acyltransferase 1 (DGAT1) in the Absorption of Fat

- DGAT1 catalyzes final step in triglyceride synthesis
- DGAT1 is expressed in gut > adipose, liver, skeletal muscle, heart
Inhibition of DGAT2 Decreases Hepatic Triglyceride (TG) Accretion and Secretion

4 hrs with 0.4 mM [3H]oleate

Li et al, ATVB 2015
DGAT Inhibition as a Treatment for Obesity

- Pharmaceutical companies have DGAT inhibitor programs
- Some data from clinical trials with DGAT1 inhibitor are available but it does not look all that good: diarrhea
- Why so different from mice?:
- A rare DGAT1 mutation in human is associated with congenital diarrheal disorder (very severe): kids die within 6 months
- DGAT2 inhibitor has been developed

Harris et al. JCI 2012
• HDL declines reflect upregulation of reverse cholesterol transport
• TG declines from SREBP-1c downregulation
• LDL increase from CETP block? Increased LPL activity?
Improvement in NAS components

Steatosis

- Placebo: 38%
- OCA: 61%

Inflammation

- Placebo: 35%
- OCA: 53%

Ballooning

- Placebo: 31%
- OCA: 46%

Serum lipids

A Treasure Trove of Information for Lipoprotein Biology

Omics and Emerging TG-Lowering Therapies

Potential targets for gene replacement therapy:
- LPL, apoC2, ApoA-5, GPIHBP1

Potential targets for anti-sense therapy:
- apoB, apoC-III, DGAT2,
  MicroRNAs
  Aptamers

Cell Pathways:
- Peptide linker technologies

metabolic pathways:
- DGAT-2inh, MTPI, FXR agonism

Peptide-based mimetics:
- ApoC2, apoE, ApoC5
- Monoclonal Ab-ANGLPT 3