New and Emerging Drugs for Lipid Disorders

John Kane, MD, PhD

Conflict of Interest

• Research grant from Alexion, Inc.
Metabolism of VLDL and LDL

- Liver Parenchymal Cell
- Golgi apparatus
- Receptor
- Lysosome
- Capillary wall
- Lipoprotein Lipase
- Peripheral Cell
- Remnant
- Lysosome
- Receptor

New Agent for HoFH

- MTTP inhibitor (Lomitapide; REM status)
- MTTP is located on the endoplasmic reticulum of hepatocytes and enterocytes
  - Mediates transfer of CE and TG to apo B
  - Needed for formation of VLDL and chylos
- Diarrhea and hepatic steatosis – dose related side effects
- Average 50% reduction in LDL-C
New Agent for HoFH

- Apo B-100 mRNA antisense oligonucleotide
  - Mipomersin (REM status)
- Blocks translation of gene product, impairing lipoprotein assembly and reducing levels of VLDL, IDL, LDL (about 30%), and Lp(a)
- Subcutaneous injection site reactions and flu-like symptoms. 10% have a reversible increase in hepatic steatosis

Apo C-III ANTISENCE

- APO C-III inhibits LPL
- Possible role in gram negative sepsis
- LOF mutations reduce triglycerides
- Oligonucleotide therapy lowered triglycerides in a phase 3 trial

Gaudet D, et al. NEJM 2015; 373: 438-47
PCSK9 Inhibitor

- Proprotein convertase subtilisin/kexin 9 is secreted by hepatocytes; chaperones the LDL receptor from the cell surface into the cell for lysosomal degradation
- Loss of function mutations result in very low LDL-C (15 to 40 mg/dL) & very low risk of CVD
- Humanized monoclonal antibody inhibits effect on LDL receptor; useful in statin intolerance or if LDL-C goal not achieved

Recycling of LDLRs Enables Efficient Clearance of LDL-C Particles

LDL-C = low-density lipoprotein cholesterol

PCSK9 Regulates the Surface Expression of LDLRs by Targeting for Lysosomal Degradation

PCSK9 = proprotein convertase subtilisin/kexin type 9


Effect of Evolocumab or Ezetimibe Added to Moderate- or High-Intensity Statin Therapy on LDL-C Lowering in Patients With Hypercholesterolemia: The LAPLACE-2 Randomized Clinical Trial

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LAPLACE-2 = LDL-C assessment with PCSK9 monoclonal antibody inhibition combined with statin therapy. LDL-C = low-density lipoprotein cholesterol; PCSK9 = proprotein convertase subtilisin/kexin type 9

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AMP Kinase Activator

- Senses energy status via adenosine monoPO4 levels
- Decreases fatty acid synthesis [FCH, NASH, obesity]
- Decreases triglyceride synthesis [FCH, hyperTG]
- Increases oxidation of fatty acids [FCH, NASH, insulin resistance]
- Increases glucose oxidation in muscle via Glut4 [insulin resistance]
- Decreases cholesterol synthesis [Hyperbeta]
- Stimulates mitochondrial replication [DM, obesity]
Agents in Development That Reduce Triglycerides

- SCAP (SREBP cleavage activating protein) inhibitors
  - SCAP cleaves SREBP precursor; SREBP2 initiates cholesterol biosynthesis; SREBP1C – FA biosynthesis
- FXR (farnesoid X receptor) ligand
  - acts like a bile acid, causing feedback inhibition of bile acid synthesis and decreasing secretion of VLDL

Agents in Development That Reduce Triglycerides

- FGF21 (fibroblast growth factor 21)
  - improves insulin sensitivity & beta cell function, reduces TG
- ANGPTL3 (angiopoietin-like protein 3) inhibitor
  - reduces TG and LDL; increases half life of LPL
LAL DEFICIENCY

- Inability to hydrolyse cholesterol esters in liver
- Elevated LDL-C, low HDL-C
- Hepatomegaly, liver failure
- ASHD
- Recombinant LAL effective in phase 3 trial

Burton BK, et al. NEJM 2015; 373: 1010-20
LAL-D Is a Rapidly Progressive Disease Associated With Significant Morbidities and Premature Mortality

Kaplan-Meier Estimate: Survival in Infants With LAL-D


A retrospective chart review and data extraction of 36 patients diagnosed with LAL-D before age 2 (26 with growth failure before 6 months of age; 9 without). Growth failure is defined as either weight decrease across 2 major centiles or weight below 10th percentile with no weight gain for 2 weeks or loss of 5% of birth weight after 2 weeks of age within the first 6 months of life.

Devastating and with unpredictable consequences, LAL-D requires early diagnosis and active monitoring.


Hepatic Function Is Severely Compromised in LAL-D Patients in a Step-Wise Manner

86% of patients with LAL-D have liver manifestations

1. CE and TG accumulation in hepatocytes and Kupfer cells
   - Microvesicular steatosis
   - Fatty liver
   - Hepatomegaly
   - Elevated transaminases

2. Progression to fibrosis and micronodular cirrhosis

3. Portal hypertension
   - Esophageal varices
   - Ascites

* Based on an analysis of 56 genotyped LAL-D patients in a cohort of 135 cases
ANGIOPOIETIN-LIKE PROTEINS

- Eight member family
- Angiopoietin-like 3, 4, and 8 inhibit LPL
- Angiopoietin-like 4 directs triglyceride fatty acids to brown adipose tissue
- Angiopoietin-like 8 induces proliferation of pancreatic beta cells
- Many effects on cell proliferation, cancer, arteriosclerotic vascular disease (MI)
Large spherical (alpha) HDL

Preβ−1 HDL Metabolism

Preβ-1 HDL

CETP

Preβ-1 HDL

De novo synthesis of apo A-I

Liver and intestine

Abca1 Transporter

Free Cholesterol

LCAT

Removal and degradation

Peripheral Cell

Prebeta-1 HDL Metabolism

Preβ−1 HDL

CETP

Preβ-1 HDL

De novo synthesis of apo A-I

Liver and intestine
High levels of prebeta-1 HDL are associated with increased risk of CHD and MI

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<th>Myocardial infarction</th>
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Guery L et al. Am J Cardiol 2011 Aug 1;108:360-6