LDL Apheresis: Familial Hypercholesterolemia

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Disclosures

- **Speakers Bureau:**
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  - Amgen
  - Amarin
  - Kaneka America
  - KOWA

- **Consultant:**
  - Akcea Therapeutics
  - Kaneka America
  - Kastle Therapeutics
  - Kaneka America
What is FH?

- Familial hypercholesterolemia (FH) - inherited genetic disorder causing high cholesterol concentrations and increased risk of premature cardiovascular disease.

- This group of inherited genetic defects affects three separate areas:
  1. Low-density lipoprotein receptor - > 1600 LDL R mutations
  2. Apolipoprotein B (ApoB)
     - APOB mutations impair LDL receptor binding
  3. Alteration of proprotein convertase subtilisin/kexin type 9 (PCSK9) genes

  Resulting in high cholesterol concentrations in the blood and increased risk of premature coronary heart disease (CAD)
What is detrimental about familial hypercholesterolemia?

- Familial Hypercholesterolemia (FH) is one of the most common genetic disorders
- Lifetime exposure to high LDL levels, *essentially from birth*
  - Twice LDL cholesterol levels consistent by age 2
- Untreated, FH leads to substantial CVD risk in men and women, with early onset of cardiovascular disease
- Not rare but under diagnosed
- Treatable but undertreated
- Early diagnosis and treatment eliminate the excess CVD risk
“Statistically Speaking”

- Risk of premature CAD is elevated about 20-fold in untreated FH patients
- MIs as early as 20 to 30 years of age, often in 40s
- Only 20% of patients are diagnosed
- Of those diagnosed, ≤ 50% have treated cholesterol at target

## Two Forms of FH
Greater than 12 million worldwide

<table>
<thead>
<tr>
<th><strong>Heterozygote</strong></th>
<th><strong>Homozygote</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>• One defective LDL gene</td>
<td>• Both LDL receptors defective</td>
</tr>
<tr>
<td>• TC 350 – 550</td>
<td>• TC 650 -1000</td>
</tr>
<tr>
<td>• CHD onset 30 – 60 years</td>
<td>• 1 in 250,000 to 1 million people (more common in some groups)</td>
</tr>
<tr>
<td>1 in 250 1 in 100 in French Canadian, S. African, others</td>
<td>• CHD onset in childhood</td>
</tr>
<tr>
<td>• Most respond to pharmacologic therapy – but variable</td>
<td>• Poor response to drugs</td>
</tr>
</tbody>
</table>


McKenney, J. & Hawkins D. Handbook on the management of Lipid Disorders, 2nd edit, 2001
**Screening for FH**

- Universal screening for patients with elevated serum cholesterol is recommended.

- FH is suspected when untreated fasting LDL cholesterol is: LDL-C ≥ 190 mg/dL
  - For all patients with these levels, a family history of high cholesterol and heart disease in first-degree relatives should be evaluated
  - Rule out secondary causes: hypothyroidism, nephrotic syndrome

Measure Lipids in Children

- Universally at ages 9-11 years and 17-21 years
- Suspicious at ≥ 160 mg/dL
- Can measure total cholesterol and HDL-cholesterol or fasting lipid profile
- Measure at > 2 years of age as part of CVD risk assessment
  - e.g. positive family history, other CVD risk factor, high risk condition, obesity

Physical Findings

Although **not always present**, and **not necessary for a diagnosis** of FH, certain physical exam findings should prompt strong suspicion of FH and order lipid measurements if unknown:

- **Tendon xanthoma** at any age (most common in Achilles tendon and finger extensor tendons, but can also occur in patellar and triceps tendons)
- **Arcus corneae** in patients < 45 years of age
- **Tuberous xanthoma** or xanthelasma in a patient < 20-25

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Physical Characteristics of FH

Xanthelasma of the eyelid in hetero-FH

Arcus corneae and xanthelasma of the eyelid in hetero-FH

Achilles tendon xanthoma in hetero-FH

Xanthoma on extensor tendons of the hand in hetero-FH

Under supervision of Mabuchi (Kanazawa Uni., Japan)
Diagnosis

- Age of onset of family members with CAD is critical to document in the family history
- Any physical findings can be very specific in the diagnosis, although absence does not rule out for FH
- Clinical diagnosis is most likely when:
  - 2 or more first degree relatives are found to have elevated LDL cholesterol in ranges as previously noted
  - pediatric cases are identified in the family
  - patient or a close relative has a tendon xanthoma
- Patients with FH on occasion are noted to have elevated TGs, this should not exclude the diagnosis of FH

Rationale for Treatment

- Individuals with FH have a very high lifetime risk of CHD
- Those with FH are at very high risk of premature onset of CHD
- Early treatment is beneficial
- Adults as well as children with LDL cholesterol ≥190 mg/dL after lifestyle management will require pharmacologic therapy
- Long-term pharmacologic therapy of patients with FH significantly reduces or removes the excess lifetime risk of CHD, lowering the level of risk to that of the general population

Goldberg, A, MD et al. Familial Hypercholesterolemia: Screening, Diagnosis and Management of Pediatric And Adult Patients Clinical Guidance From The National Lipid Association Expert Panel on Familial Hypercholesterolemia
Management of FH

- Risk factors should be aggressively treated as in the general population, with special attention to smoking cessation.

- Pharmacologic treatment
  - For adults, initial treatment is moderate to high potency statins titrated to achieve LDL cholesterol reduction of $\geq 50\%$ from baseline.
  - Low potency statins generally inadequate for FH patients.
  - If initial statin is not tolerated, consider changing to an alternative statin.
  - Combination therapy cholesterol absorption inhibitors and/or PCSK9 Inhibitor is most often required to achieve LDL goals.

Traditional Lipid Lowering Therapies

Statins\(^1\)

- Inhibit HMG-CoA reductase, the rate limiting step in cholesterol synthesis

Ezetimibe\(^2\)

- Localizes at the brush border of the small intestine and inhibits the absorption of cholesterol

1. Lexicomp Drug information Handbook, 7\(^{th}\) Edition
PCSK9 Inhibition Background and Rationale

- Prevents the destruction of LDL Receptors

Mechanism of action:
- Prevents the destruction of LDL Receptors

In PCSK9 human population studies:
- Gain-of-function mutations result in hypercholesterolemia
- Loss-of-function mutations associated with low LDL-C and low prevalence of CHD events

*Stein EA, Mellis S, Yancopoulos GD et al. *NEJM* 2012; 366: 1108-1118
Familial Hypercholesterolemia (FH)

When do we consider treatment with LDL Apheresis?

- For patients for whom diet has been ineffective and **maximum drug therapy** has either been ineffective or not tolerated along with:
  - LDL-C $\geq 300\text{mg/dL}$ and/or
  - LDL-C $\geq 160\text{mg/dL}$ with documented CHD or PAD

- **What is LDL Apheresis?**
  - Mechanical means to remove LDL from the blood while preserving HDL and other plasma components
  - Extracorporeal
    - blood taken outside of the body
    - returned to the patient **without** need for albumin or other blood products
Miss R

- Father premature CAD – LDL > 400 mg off medication
  - HeFH = 1 defective gene

- Mother currently 65 y.o. but in her 30’s when first met No CAD but has off treatment LDL > 400 mg
  - HeFH = 1 defective gene

- Miss R was 7 years old when we first met, with homozygous FH – off treatment LDL in the 700 range, **1 defective gene contributed by each parent = 2 defective genes**
  - No cardiac symptoms, however angiographic changes noted in aorta, consistent myocardial perfusion defects in approximately 20% of youth ages 8 – 24
  - Illustrating the very early effects of high cholesterol on the blood flow to the heart

- Parents had a 4 year old before this child’s birth who died with MI
Evaluation and Diagnosis for this patient

• Findings and evaluation:
  – Bilateral achilles tendon xanthomas
  – Multiple extensor tendon xanthomas
  – Ping-Pong ball size xanthomas noted bilaterally at elbows

• Diagnosis
  – Homozygous familial hypercholesterolemia with early findings of atherosclerosis
  – Severe liver receptor deficit with poor response to statin therapy
Continuous flow system MA03

Disposable tubing set, a plasma separator, two adsorption columns
LIPOSORBER® System

Blood Pump

Heparin Pump

Blood Withdrawal

Blood Pump

Plasma Separator

Blood Return

Plasma Pump

Plasma Line

Regeneration Solution

Regeneration Pump

LIPOSORB ER® Column

Waste Line
Plasma Exchange (TPE) vs Liposorber LDL Apheresis

<table>
<thead>
<tr>
<th></th>
<th>TPE</th>
<th>LIPOSORBER</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL reduction (%)</td>
<td>45 - 65</td>
<td>73 - 83</td>
</tr>
<tr>
<td>HDL reduction (%)</td>
<td>45 - 65</td>
<td>3 - 14</td>
</tr>
<tr>
<td>Immunoglobulin reduction (%)</td>
<td>45 - 65</td>
<td>&lt;15</td>
</tr>
<tr>
<td>Plasma Volume (ml)</td>
<td>3,000 - 4,000</td>
<td>4,000 - 5,000</td>
</tr>
<tr>
<td>Cost ( $)</td>
<td>1,400 – 2,000</td>
<td>1,500 – 2,000</td>
</tr>
<tr>
<td>Treatment Time (hours)</td>
<td>1 - 3</td>
<td>2 - 4</td>
</tr>
<tr>
<td>Anticoagulation</td>
<td>ACD-A (250-750 ml)</td>
<td>Heparin (5,000-10,000 USP Units)</td>
</tr>
</tbody>
</table>
## Liposorber vs Futura (H.E.L.P.)

<table>
<thead>
<tr>
<th>Product Features</th>
<th>LIPOSORBER /MA-03</th>
<th>H.E.L.P. (Futura)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LDL-C Reduction Rate</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDL-C 250 mg/dl, 60kg</td>
<td>73-83%</td>
<td>60-64% (US labeling)</td>
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<td>LDL-C 300 mg/dl, 60kg</td>
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</tr>
<tr>
<td>LDL-C 500 mg/dl, 60kg</td>
<td>73-83%</td>
<td>60%??</td>
</tr>
<tr>
<td>LDL-C 250 mg/dl, 90kg</td>
<td>73-83%</td>
<td>60-64% (US labeling)</td>
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<tr>
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<tr>
<td>LDL-C 500 mg/dl, 90kg</td>
<td>73-83%</td>
<td>60%??</td>
</tr>
<tr>
<td><strong>Treatable Plasma Volume</strong></td>
<td>9,990 ml</td>
<td>Approx. 3,000 ml</td>
</tr>
<tr>
<td><strong>Minimum Body Weight</strong></td>
<td>15 kg</td>
<td>37 kg</td>
</tr>
<tr>
<td><strong>Extra Corporeal Volume</strong></td>
<td>404 ml (160 whole blood +244 plasma)</td>
<td>590 ml (whole blood 200 ml, plasma 390 ml)</td>
</tr>
<tr>
<td><strong>ACE-I Contraindicated?</strong></td>
<td>Yes (but ARB is OK)</td>
<td>No</td>
</tr>
<tr>
<td><strong>Preparation Time</strong></td>
<td>Approx. 50 minutes?</td>
<td>Approx. 50-60 minutes</td>
</tr>
<tr>
<td><strong>Treatment Time</strong></td>
<td>2 – 3 hours (depends on plasma volume treated)</td>
<td>2 – 3 hours (depends on plasma Volume treated)</td>
</tr>
</tbody>
</table>
## Patient Reactions

(During Clinical Study
74 Patients/4,936 Treatments)

<table>
<thead>
<tr>
<th>Events</th>
<th>Episodes</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypotension</td>
<td>41</td>
<td>0.8%</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>27</td>
<td>0.5%</td>
</tr>
<tr>
<td>Flushing</td>
<td>20</td>
<td>0.4%</td>
</tr>
<tr>
<td>Angina</td>
<td>10</td>
<td>0.2%</td>
</tr>
<tr>
<td>Fainting</td>
<td>9</td>
<td>0.2%</td>
</tr>
</tbody>
</table>
Liposorber Standard Treatment

Recommended Treatment Schedule:

- LDL-C ≥160 mg/dL with known CHD
- LDL-C ≥300 mg/dL without CHD

- Blood flow: 50 ~ 100 mL/min
- Plasma flow rate: 15 ~ 30 mL/min
- Treated plasma volume: 3 ~ 5 L
- Treatment time: 2 ~ 4 hours
- Blood Access: Antecubital Veins, Fistula’s, PermaCath’s or Ports

Once every other week
Once a week
Involved in trials with gene therapy, still not state of the art

Needed to have:
- plasma exchange until LDL apheresis was approved as modality by the FDA
- weekly treatment taking about 3-4 hours each treatment, inherent issues with school, socialization

Although not really effective for LDL lowering, still took statin therapy for ongoing “other” benefits, not just LDL number

Has participated in multiple trials for newer medications

Even with all the newest modalities still needs to have LDL apheresis related to the absence of LDL receptors in HoFH

Xanthomas were greatly reduced with LDL Apheresis over time

Now in her 30’s, college graduate, married and living a “fairly normal life”
Summary of Liposorber for FH

- Selective removal of LDL-C, VLDL, Lp(a) (Acutely lowered 73%-83%)
- Little or no effect on other plasma components (HDL, Albumin, IgG)
- Studies showed significant reductions of cardiovascular event rate on LIPOSORBER® therapy
Investigational Agent: Anacetrapib

- Cholesteryl ester transfer protein (CEPT) inhibitor\(^1\)
- Phase 3 DEFINE trial (2-year extension of 76-week base study):\(^1\)
  - Anacetrapib reduced LDL-C by 39.9% and increased HDL-C by 153.3% vs placebo
  - Study is still ongoing\(^2\)
- Phase 3 REVEAL trial ongoing\(^2\)
  - Goal is to determine whether lipid modification with anacetrapib 100 mg daily reduces the risk of major coronary events in patients with circulatory problems receiving statin therapy for LDL-C levels

Investigational Agents: TA-8995
CEPT inhibitor evaluated in patients with mild dyslipidemia in the phase 2 TULIP trial

 adapté by Lillian McVey from Hovingh GK, et al. 
Lancet. 2015;386(9992):452-460. 
Used with permission.
Investigational Agents: ETC-1002

- Dual adenosine triphosphate citrate lyase inhibitor/adenosine monophosphate-activated protein kinase activator
- Oral, once-daily small molecule in phase 2 development
- May have a modest beneficial effect on LDL-C as well as other cardiometabolic risk factors

Take Home Messages

- FH is a treatable condition
- Under diagnosed and undertreated
- Screen earlier and screen family members
- Earlier recognition and appropriate treatment can decrease the risk of developing CHD
- Those with FH will require lifestyle management and medication in the form of statin or other therapies to reduce the atherogenic LDL cholesterol
- LDL apheresis for patients with inadequate response to therapy
- In patients with FH, early identification and long term treatment to targeted LDL goals:
  - significantly reduces or removes the excess lifetime risk of CHD
  - lowering the level of risk to that of the general population
Resources

- National Lipid Association:  www.lipid.org
- Patient information web site:  www.learnyourlipids.com
- The FH Foundation:  www.theFHfoundation.org
- Preventive Cardiovascular Nurses Association
Thank You