HUMAN AND ANIMAL
ATHEROSCLEROTIC EFFECTS OF
APHERESIS, MTP INHIBITION, AND
ANTISENSE THERAPY IN
HYPERCHOLESTEROLEMIA (FH)

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Disclosures

• Merck- speaker, consultant
• Kowa-speaker
• Aegerion-speaker, consultant
• Genzyme-grant
Abstract-Outline

• Currently as of 2014 there are 3 approved therapies that have been utilized extensively in HoFH
  – These include: lomitapide, mipomersen, and LDL apheresis

• Review evidence in human and animal studies regarding the efficacy in reducing clinical events and regression of vascular lesions
  – In vivo data suggest mipomersen and lomitapide can cause regression; however, no human data is presently available. It remains unknown if their lipid effects (LDL, Lp(a), ApoCIII, ApoB-100, ApoB-48) will reduce CV events in humans
  – Apheresis demonstrated to regress atherosclerosis and reduce CV outcomes in humans
Selected references

Rosado, A et al. Does lipid apheresis in pts with isolated Lipoprotein(a) elevations reduce CV events. Artificial Organs 10;1111, 2013


Available therapies for FH over and above traditional treatments

- JUXTAPID (Lomitapide)
- KYNAMRO (Mipomersen)
- LDL apheresis
- PCSK9 Inhibitors (investigational)

These therapies are needed as most FH patients do not reach their LDL-C goal.
JUXTAPID (lomitapide)

Indication

• Lomitapide is a microsomal transfer protein inhibitor indicated
• Adjunct to low fat diet and other lipid-lowering treatments, including LDL apheresis where available
• Reduces LDL-C, TC, apo B, and non HDL-C in patients with homozygous familial hypercholesterolemia (HoFH)

Source: JUXTAPID (lomitapide) capsules full Prescribing Information. 12/2012
Lomitapide acts on both liver and intestine, and can inhibit apoB-100 and apoB-48 secretion.

MTP inhibition mimics abetalipoproteinemia.
Proof of Concept-MTP inhibition


2004  Implitapide suppressed atherosclerotic lesion area 83% compared to controls in Apo E knockout mouse fed a western diet after 8 weeks by lowering LDL and post prandial TG (chylomicrons) levels. Genetically induced

2011  MTP absence shows reversal of atherosclerosis “Reversa mice “

2013  Lomitapide a dose of 25 mg/kg in 16 weeks reduced inflammatory markers in lesions as well as reversing atherosclerosis plaques in LDL-receptor-deficient mice fed a western diet
LOMITAPIDE RAPIDLY REGRESSES ATHEROSCLEROSIS IN LDL RECEPTOR NEG MICE

Hewing, B et al Atherosclerosis 227;125,2013

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Efficacy of lomitapide in HoFH

Mean percent changes in LDL-C, TC and apoB from baseline to Week 26 (n=23)

LDL-C ↓ 50%, apoB ↓ 15%, TG ↓ 45%

Cuchel M et al. Lancet 2012:dx.doi.org/10.1016/S0140-6736(12)61731-0
Summary of Alteration of Apheresis and LDL goals

- 13 (57%) of the patients were receiving apheresis at the start of the safety phase
- 6 patients had changes to their apheresis regimen
- 55% reach LDL goal less than 100; 31% < 70

<table>
<thead>
<tr>
<th>Safety Phase (Week 26 – 78)</th>
<th>Patients Reducing Frequency of Apheresis Treatments</th>
<th>Patients Stopping Apheresis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3</td>
<td>3</td>
</tr>
</tbody>
</table>

KYNAMRO (mipomersen)

Indication

• Mipomersen is an oligonucleotide inhibitor of apolipoprotein B-100 synthesis
• An adjunct to lipid-lowering medications and diet
• Reduces LDL-C, TC, apo B, and non HDL-C in patients with homozygous familial hypercholesterolemia (HoFH)

Mipomersen: Apo B-100 as a Target

Mipomersen is a 2nd generation antisense oligonucleotide that inhibits synthesis of ApoB-100. Mimics hypobetalipoproteinemia.
ApoB Antisense Proof of Concept
ApoB Inhibition by Murine ApoB ASO Ameliorates Atherosclerotic Lesion Development in LDLr-/- Mice Fed HFC or HC Diet

Treatment

Diet

High-Cholesterol

Saline

ApoB ASO

High-Fat Cholesterol

Saline

ApoB ASO

Aortic Sinus Lesion Volume, mm³

- 80%
- 86%

(%Δ (vs saline)


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Mipomersen Reduces ApoC-III in Hypercholesterolemia

- Concentrations of apoCIII in VLDL AND LDL is highly and independently predictive of CAD. ApoCIII activates pro-inflammatory molecules.

200 mg Mipomersen (SC, qw) Decreases LDL-C in HoFH Patients

LDL APHERESIS

INDICATED PATIENT POPULATION

LDL apheresis is indicated for the following patients for whom diet and maximum drug therapy has either been ineffective or not tolerated:

- LDL-C $\geq 200$ mg/dL (with CHD)
- LDL-C $\geq 300$ mg/dl
- Lp(a) > 50 - 60 (with CHD) new guidelines
SUMMARY OF EFFECTIVENESS

• Selective removal of LDL-C, VLDL, and Lp(a)
  – Acutely lowered Lp(a) 73-83%
  – LIPOSORBER, HELP system also lowers fibrinogen
• Little or no effect on other plasma components (Albumin, IgG) but does lower ApoE in HDL; Improves HDL function
• Time-averaged LDL-C and Lp(a) lowering of 50-58%
• Studies show significant reductions of cardiovascular event rate on therapy and stabilization or improvement of vascular lesions
EFFECT OF APHERESIS ON CORONARY HEART DISEASE IN FH

**Patients**
Heterozygous FH with CHD

**Treatment**
- LDL-Apheresis and Medication (n = 43)
  *(Average LDL-Apheresis Interval = 14 days)*
- Medication Only (n = 87)

**Follow-Up**
- 6 Year Observation of Coronary Events
  *(Non-Fatal MI, PTCA, CABG, CHD Death)*

**Results**
- 72% reduction in Coronary Events

Mabuchi et al. *American Journal of Cardiology* 1998;82:1489-1495
### CHANGES IN LIPIDS: BASELINE AND TREATMENT LEVELS

<table>
<thead>
<tr>
<th></th>
<th>LDL-Apheresis (n=43) (Mean ± SD)</th>
<th>Medication (n=87) (Mean ± SD)</th>
<th>p-Value**</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>On Treatment*</td>
<td></td>
</tr>
<tr>
<td>Total Cholesterol (mg/dl)</td>
<td>360 ± 67</td>
<td>305 ± 48</td>
<td>&lt;0.0001</td>
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<tr>
<td></td>
<td>171 ± 30</td>
<td>230 ± 61</td>
<td>&lt;0.0001</td>
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<tr>
<td></td>
<td>53</td>
<td>25</td>
<td></td>
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<tr>
<td></td>
<td><strong>% Reduction</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>60 ± 27</td>
<td>72 ± 43</td>
<td>0.058</td>
</tr>
<tr>
<td></td>
<td>28 ± 16</td>
<td>56 ± 31</td>
<td>&lt;0.0001</td>
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<tr>
<td></td>
<td>53</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>% Reduction</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDL-Cholesterol (mg/dl)</td>
<td>288 ± 67</td>
<td>234 ± 51</td>
<td>0.0002</td>
</tr>
<tr>
<td></td>
<td>122 ± 31</td>
<td>168 ± 59</td>
<td>&lt;0.0001</td>
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<tr>
<td></td>
<td>58</td>
<td>28</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>% Reduction</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HDL-Cholesterol (mg/dl)</td>
<td>40 ± 9</td>
<td>42 ± 12</td>
<td>0.375</td>
</tr>
<tr>
<td></td>
<td>31 ± 15</td>
<td>36 ± 13</td>
<td>0.036</td>
</tr>
<tr>
<td></td>
<td>22</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>% Reduction</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDL-C/HDL-C</td>
<td>7.17</td>
<td>5.54</td>
<td>0.0024</td>
</tr>
<tr>
<td></td>
<td>3.88</td>
<td>4.67</td>
<td>0.76</td>
</tr>
</tbody>
</table>

* Time-averaged levels in the LDL-Apheresis group were calculated based on the equation proposed by Dr. Kroon in *Circulation 93*, pp. 1826-35 (1996)
KAPLAN-MEIER CURVES SHOWING THE PROPORTION OF PATIENTS WITHOUT ANY CORONARY EVENTS:

Proportion of Patients Without Any Event

Years

LDL-Apheresis

Medication

p = 0.0088
Cardiovascular Events Reduction in Published Trials

Primary Prevention
- **CAPS**
  - Placebo: 37%

Secondary Prevention
- **CARE**
  - Placebo: 24%

Hypercholesterolemia
- **WOS**
  - Placebo: 31%
  - Lovastatin

- **4S**
  - Placebo: 34%
  - Simvastatin

Normocholesterolemia
- **CAPS**
  - Lovastatin

Familial Hypercholesterolemia
- **Hokuriku FH-LDL-A Study**
  - Medication: 66%
  - LDL-A

H. Mabuchi, Saishin-Igaku (Japan) 2001; 56: p1134
LONG-TERM EFFECTS OF LDL-APHERESIS ON CARDIAC EVENTS

Patients
64 Patients with Familial Hypercholesterolemia
10 Homozygotes, 54 Heterozygotes

Treatment
LDL-Apheresis and Medication

Follow-Up
2.5 Year Observation of Coronary Events Including:
Cardiac Death, Coronary Revascularization, Coronary Angioplasty, Atherectomy, CABG, MI or Cerebrovascular Event

Results
44% Reduction in Event Rate During 2.5 Year Observation Period When Compared to 5 Year Medication Only Period Prior to LDL-Apheresis Treatment

# CARDIOVASCULAR EVENT ANALYSIS

<table>
<thead>
<tr>
<th></th>
<th>Prior to Study (5 Years)</th>
<th>On APHERSIS® (2.5 Years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Patients</td>
<td>64</td>
<td>64</td>
</tr>
<tr>
<td>Total Duration (Months)</td>
<td>3,840</td>
<td>2,012</td>
</tr>
<tr>
<td>Mean Duration/Patient (Months)</td>
<td>60</td>
<td>31</td>
</tr>
<tr>
<td>Number of Events</td>
<td>24</td>
<td>7</td>
</tr>
<tr>
<td>Rate/1000 Months*</td>
<td>6.3</td>
<td>3.5</td>
</tr>
</tbody>
</table>

*44% reduction in event rates
Cardiovascular effects lowering Lipoprotein(a) in 120 treated pts over 5 years with mean LDL levels of 123 mg/dl with apheresis

<table>
<thead>
<tr>
<th>Measurements</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre Lp(a)</td>
<td>112 mg/dl</td>
</tr>
<tr>
<td>Post Lp(a)</td>
<td>31 mg/dl</td>
</tr>
<tr>
<td>MI rate</td>
<td>decreased 97%</td>
</tr>
<tr>
<td>MACE</td>
<td>decreased 89%</td>
</tr>
</tbody>
</table>

Mean levels after weekly Lp(a) Apheresis

<table>
<thead>
<tr>
<th></th>
<th>PRE</th>
<th>POST</th>
<th>TIME-AVERAGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL</td>
<td>84</td>
<td>34</td>
<td>71</td>
</tr>
<tr>
<td>Lp(a)</td>
<td>112</td>
<td>36</td>
<td>101</td>
</tr>
</tbody>
</table>

Rosada, A e al Artificial Organs 10;111,2013
Leebmann, el al Circulation 113 2432,2013 SIMILAR FININGS AS ABOVE

www.lipid.org
Survival in Pts undergoing Lp(a) Apheresis

Rosada, A et al Artificial Organs 10:1111, 2013
Long-term effect of LDL-apheresis on post CABG patients

A multi-center trial

Proportion of patients without coronary events

Changes in LDL-C (mg/dL)

Baseline | before LDL-A | after LDL-A
---------|--------------|-------------
261      | 177          | 60          

Post-CABG patients
- Hetero-FH (n=43)
- Homo-FH (n=5)
- Non-FH (n=13)

Coronary events: acute MI, PTCA, re-CABG, sudden death

ENDOTHELIAL FUNCTION BY SINGLE LDL-APHERESIS

**Patients:**
Seven Patients with Hypercholesterolemia
6 Men, 1 Woman

**Treatment:**
LDL-Apheresis

**Evaluation:**
Forearm Blood Flow (FBF) Before and After Single LDL-Apheresis While Infusing Acetylcholine (ACH) or Sodium Nitroprusside (SNP)

Tamai et al. *Circulation* 1997; 95:76-82
IMPROVEMENT OF PERIPHERAL ARTERY ENDOTHELIAL FUNCTION BY SINGLE LDL-APHERESIS

Responses of Forearm Blood Flow (FBF) to Intra-Arterially Infused Acetylcholine (ACh) or Sodium Nitroprusside (SNP)

![Graph showing responses of Forearm Blood Flow (FBF) to Intra-Arterially Infused Acetylcholine (ACh) or Sodium Nitroprusside (SNP).](image)

- ACh (g/min): 0, 4, 8, 16, 24
- FBF (mL/min/100 mL): 0, 10, 20, 30, 40, 50, 60
- SNP (g/min): 0, 0.2, 0.4, 0.8, 1.2
- Before Single LDL Apheresis
- After Single LDL Apheresis

- **p < .01**
- **p: NS**
Annual Rates of Progression of Mean Maximum IMT in the Common Carotid Artery

- FH Homozygote FH Heterozygote FH Heterozygote FH Pravastatin Group Placebo Group
- LDL Apheresis Group Control Group
- FH (total: n=11) (n=2) (n=9) (n=10)
- (PLAG-II data was reported Cardiol 1995;75:455)

K. Koga Therapeutic Apheresis 5(4) 244-251 2001
Representative Example of CAG and IVUS

Baseline | Follow Up
---|---
MLD = 1.5 mm | MLD = 2.2 mm
Plaque Area = 7.8 mm² | Plaque Area = 7.0 mm²
Lumen Area = 3.3 mm² | Lumen Area = 5.3 mm²
Vessel Area = 11.1 mm² | Vessel Area = 12.3 mm²

M. Matsuzaki et al., *J Am Coll of Cardiol* 2002; 40: 220-227
Improvement of Myocardial Blood Flows (MBF) by Single LDL-Apheresis Assessed with PET

T. Sampietro, et al., Abstract from ISA 2000

<table>
<thead>
<tr>
<th>MBF (m l/m in/g)</th>
<th>Before LDL-A</th>
<th>After LDL-A</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenosine Stimulated</td>
<td>0.71</td>
<td>2.05</td>
</tr>
<tr>
<td>At Rest</td>
<td>0.86</td>
<td>1.31</td>
</tr>
</tbody>
</table>

(n=7) * p<0.05
CRP LEVELS IN PTS UNDERGOING APHERESIS
Otto C  Athero 2004 ;174:151

Acute Changes in Serum Lipid-Parameters, RLP-C, CRP and MDA-LDL by A Single LDL-Apheresis

<table>
<thead>
<tr>
<th>Changes in Lipid-Parameters</th>
<th>mean ± SD in mmol/L</th>
<th>Before</th>
<th>After</th>
<th>Reduction (%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TC</td>
<td>5.39 ± 0.81</td>
<td>2.79 ± 0.37</td>
<td>48</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>LDL-C</td>
<td>3.82 ± 1.03</td>
<td>1.63 ± 0.29</td>
<td>57</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>HDL-C</td>
<td>1.24 ± 0.29</td>
<td>1.18 ± 0.26</td>
<td>5</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>TG</td>
<td>0.92 ± 0.45</td>
<td>0.23 ± 0.11</td>
<td>75</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Changes in RLP-C, CRP and Oxidized-LDL</th>
<th></th>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>RLP-C (mg/dL)</td>
<td>6.52 ± 1.18</td>
<td>1.78 ± 0.27</td>
<td>73</td>
</tr>
<tr>
<td>CRP (mg/L)</td>
<td>0.79 ± 0.14</td>
<td>0.35 ± 0.04</td>
<td>56</td>
</tr>
<tr>
<td>MDA-LDL (U/L)</td>
<td>100 ± 13.6</td>
<td>38.6 ± 2.8</td>
<td>61</td>
</tr>
</tbody>
</table>


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# Comparison of Approved Aggressive Therapies for FH

<table>
<thead>
<tr>
<th></th>
<th>Apheresis</th>
<th>Mipomersen</th>
<th>Lomitapide</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL-C and ApoB Reduction</td>
<td>~70-80% PCSK9 52% decrease</td>
<td>~25-38% (higher in Women)</td>
<td>50-60%</td>
</tr>
<tr>
<td>Lp(a) Reduction ApoC-III</td>
<td>~70-80%, ? (lowers ApoE)</td>
<td><del>20-30</del>40%</td>
<td>~1-19% ?</td>
</tr>
<tr>
<td>Short Term Safety</td>
<td>Good</td>
<td>Hepatic Fat (5%)</td>
<td>Hepatic Fat (8-9%)</td>
</tr>
<tr>
<td>Compliance</td>
<td>Good</td>
<td>90%</td>
<td>90%</td>
</tr>
<tr>
<td>Long Term Safety</td>
<td>37 yrs</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
<tr>
<td>Availability</td>
<td>Limited</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Cost</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Cardiac Benefit</td>
<td>Yes</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
<tr>
<td>Quality of Life</td>
<td>Yes</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
<tr>
<td>Vascular Lesions</td>
<td>Yes</td>
<td>Animal models</td>
<td>Animal models</td>
</tr>
</tbody>
</table>

References:
- Fazio S Circ Res 2013;113:1290
- Falko JM Clin Lipidol 2011;6:523
- Previous citations and my experience
## Summary and take home message of Approved Aggressive Therapies for FH

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apheresis</td>
<td>Improves CV events, symptoms, regresses atherosclerosis. Lowsers LDL-C and Lp(a) the most. Approved for all forms of FH and Lp(a) lowering.</td>
</tr>
<tr>
<td>Mipomersen</td>
<td>No CV outcomes, injection, approved for HoFH only in US, hepatic fat increases, no drug-drug interactions, large safety database; flu like symptoms, long t½ life</td>
</tr>
<tr>
<td>Lomitapide</td>
<td>No CV outcomes, oral, approved for HoFH only, hepatic fat increases, drug-drug interactions, diarrhea, supplemental vitamins and essential fatty acids required, smaller safety database, studied in apheresis pts</td>
</tr>
</tbody>
</table>