LIPOPROTIEN APHERESIS

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Executive Medical Director
New York Blood Center
OUTLINE

• Familial Hypercholesterolemia (FH)
  – Diagnosis
  – Treatment options
• Lipoprotein apheresis
  – Procedures
  – Expected effects
  – Clinical Data
• Lp(a)
FAMILIAL HYPERCHOLESTEROLEMIA (FH)

- Autosomal dominant
- Mutation of the LDL-R
  - Many mutations
  - Loss or significant decrease in #/function
- Premature CAD
  - Also CVD and PVD
- Tendon xanthomas
FAMILIAL HYPERCHOLESTEROLEMIA (FH)

• Homozygous FH
  - 1 in 1,000,000 frequency
  - TC and LDL-C ↑ 3 – 6 fold

• Heterozygous FH
  - ~1 in 500 frequency
  - TC and LDL-C ↑ 2 – 3 fold
# NATIONAL CHOLESTEROL EDUCATION PANEL ATP III LDL-C GOALS

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>LDL-C Goal</th>
</tr>
</thead>
<tbody>
<tr>
<td>High Risk: Coronary Heart Disease (CHD)* or CHD Risk equivalents† (10-year risk &gt; 20%)</td>
<td>&lt; 100 mg/dL (Optional goal &lt; 70 mg/dL)‡</td>
</tr>
<tr>
<td>Moderate risk: 2+ risk factors (10-year risk &lt; 20%)</td>
<td>&lt; 130 mg/dL</td>
</tr>
<tr>
<td>Lower risk: 0-1 risk factor</td>
<td>&lt; 160 mg/dL</td>
</tr>
</tbody>
</table>

* CHD includes history of myocardial infarction, unstable angina, coronary artery procedures (angioplasty or bypass surgery), or evidence of clinically significant myocardial ischemia.
† CHD risk equivalents includes clinical manifestation of noncoronary forms of atherosclerotic disease (peripheral arterial disease, abdominal aortic aneurysm, and carotid artery disease [transient ischemic attacks or stroke of carotid origin or >50% obstruction of a carotid artery]), diabetes, and 2+ risk factors with 10-year risk for hard CHD >20%.
‡ Very high risk favors the optional LDL-C goal of < 70mg/dL, and in patients with high triglycerides, non-HDL-C<100mg/dL.

Adapted from Grundy et al, Circulation 2004; 110: 227-239
Treatment Goals

- At least 50% reduction in LDLC, better:
  - < 100 mg/dL, without CHD, major risks
  - < 70 mg/dL with CHD or major risks
  - Endorsed by National Lipid Association (NLA)
HOW TO TREAT?

- Diet
- Exercise
- Medication
  - Poly-pharmacy

NOT ENOUGH FOR MANY PATIENTS
ALTERNATIVE THERAPIES FOR SEVERE FH

- Partial ileal bypass
- Portacaval shunt
- Liver transplantation
- Gene therapy
- Plasma exchange
  - Removes all lipoproteins
  - Removes other plasma proteins
LIPOPROTEIN APHERESIS

• Separate plasma from the cellular elements of the blood
• Selectively remove LDL, vLDL, Lp(a)
• HDL minimally removed
INDICATIONS FOR LIPID-APHERESIS

• Functional FH, homozygote
  – LDL-C > 500 mg/dL
• Functional FH, heterozygote
  – LDL-C > 300 mg/dL
• Functional FH, heterozygote
  – LDL-C > 200 mg/dL
  – Documented coronary heart disease

• Lp(a) (with CAD)
• Medication intolerant (with CAD)
2013 ASFA GUIDELINES FOR LIPOPROTEIN APHERESIS

- Familial hypercholesterolemia
  - Homozygotes: Category I, Grade 1A
  - Heterozygotes: Category II, Grade 1A
- Lipoprotein (a) hyperlipoproteinemia
  - Category II, Grade 1B
- Peripheral vascular disease
  - Category III, Grade 2C
- Phytanic acid storage disease (Refsum’s disease)
  - Category II, Grade 2C
- Sudden sensorineural hearing loss
  - Category III, Grade 2A
US TECHNOLOGIES FOR SELECTIVE LIPOPROTEIN REMOVAL

• Heparin-induced Extracorporial LDL-cholesterol Precipiation (HELP)
  – Plasmat® Futurea System

• Dextran Sulfate Absorption
  – Liposorber®
PLASMAT® FUTUREA SYSTEM

The Process

Basic HELP treatment process to physically remove LDL-C

Reprinted with permission from B. Braun Medical Inc., Bethlehem, PA.
LIPOSORBER® SYSTEM
Figure 1-15. Comparative sizes of blood components. Note the large size difference between the largest plasma constituent and the smallest cellular elements. (Courtesy of Gambro BCT, Inc.)
LIPOSORBER® SYSTEM

Adsorption mechanism

Dextran sulfate

Cellulose beads

VLDL apo-B

LDL

HDL apo-A

Kanaka Pharma America Corporation
CHANGES IN LIPOPROTEIN LEVELS WITH LDL-APHERESIS
LDL APHERESIS

- **Baseline**
- **Diet & Drug Therapy**
- **LIPOSORBER® Treatment**
- **Pre**
- **Time Average**
- **Post**
TIME AVERAGE CONCENTRATIONS OF CHOLESTEROL

• \(^1\text{TAC} = C_{\text{min}} + 0.73(C_{\text{max}} - C_{\text{min}})\)

• Example:

  \[
  \begin{align*}
  C_{\text{max}} &= 370 \text{ mg/dL} \\
  C_{\text{min}} &= 80 \text{ mg/dL} \\
  \text{TAC} &= 90 + 0.73(350-90) \\
  \text{TAC} &= 292 \text{ mg/dL}
  \end{align*}
  \]

  TAC reveals a 22% reduction

• TAC is “Medication equivalent”

\(^1\text{Kroon et al, Atherosclerosis (2000)}\)
Sachais et al, J Clinical Apheresis (2005)
Sachais et al, unpublished
LDL-3

Sachais et al, unpublished
Sachais et al, J Clinical Apheresis (2005)
Sachais et al, J Clinical Apheresis (2005)
LONG TERM EFFICACY OF LDL-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 for LIPOSORBER Patients

<table>
<thead>
<tr>
<th>Clinical Characteristics</th>
<th>LDL-Apheresis (N=43)</th>
<th>Medication (N=87)</th>
<th>p-Value**</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (Years)</strong>*</td>
<td>57 ± 10</td>
<td>59 ± 12</td>
<td></td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td>1.000</td>
</tr>
<tr>
<td>Female/Male</td>
<td>11 (26%) / 32 (74%)</td>
<td>22 (25%) / 65 (75%)</td>
<td></td>
</tr>
<tr>
<td><strong>Risk Factors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>7 (16%)</td>
<td>15 (17%)</td>
<td>1.000</td>
</tr>
<tr>
<td>Diabetes</td>
<td>12 (28%)</td>
<td>18 (21%)</td>
<td>0.382</td>
</tr>
<tr>
<td>Smoking</td>
<td>4 (9%)</td>
<td>23 (26%)</td>
<td>0.024</td>
</tr>
<tr>
<td><strong>Cardiovascular Disease</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Angina Pectoris</td>
<td>26 (60%)</td>
<td>36 (41%)</td>
<td>0.061</td>
</tr>
<tr>
<td>CABG</td>
<td>11 (26%)</td>
<td>11 (13%)</td>
<td>0.082</td>
</tr>
<tr>
<td><strong>Achilles’ Tendon Thickness (mm)</strong>*</td>
<td>16.5 ± 6.6</td>
<td>12.2 ± 3.7</td>
<td>&lt;0.001***</td>
</tr>
<tr>
<td><strong>Lipid-Lowering Drug</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HMG-CoA Reductase Inhibitor</td>
<td>37 (86%)</td>
<td>67 (77%)</td>
<td>0.254</td>
</tr>
<tr>
<td>Probucol</td>
<td>25 (58%)</td>
<td>54 (62%)</td>
<td>0.705</td>
</tr>
<tr>
<td>Choleslyramine</td>
<td>11 (26%)</td>
<td>19 (22%)</td>
<td>0.662</td>
</tr>
<tr>
<td>Fibrate</td>
<td>2 (5%)</td>
<td>7 (8%)</td>
<td>0.717</td>
</tr>
<tr>
<td><strong>Treatment Period (Years)</strong>*</td>
<td>5.9 ± 3.4</td>
<td>6.1 ± 3.0</td>
<td>0.740***</td>
</tr>
</tbody>
</table>

* Figures are provided as mean ± S.D.
** By Fisher’s exact test
*** By Unpaired Student’s t test

## CHANGES IN LIPIDS

<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>Total Cholesterol (mg/dl)</td>
<td>Baseline</td>
<td>360 ± 67</td>
<td>305 ± 48</td>
</tr>
<tr>
<td></td>
<td>On Treatment*</td>
<td>171 ± 30</td>
<td>230 ± 61</td>
</tr>
<tr>
<td></td>
<td>% Reduction</td>
<td>53</td>
<td>25</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>Baseline</td>
<td>60 ± 27</td>
<td>72 ± 43</td>
</tr>
<tr>
<td></td>
<td>On Treatment*</td>
<td>28 ± 16</td>
<td>56 ± 31</td>
</tr>
<tr>
<td></td>
<td>% Reduction</td>
<td>53</td>
<td>22</td>
</tr>
<tr>
<td>LDL-Cholesterol (mg/dl)</td>
<td>Baseline</td>
<td>288 ± 67</td>
<td>234 ± 51</td>
</tr>
<tr>
<td></td>
<td>On Treatment*</td>
<td>122 ± 31</td>
<td>168 ± 59</td>
</tr>
<tr>
<td></td>
<td>% Reduction</td>
<td>58</td>
<td>28</td>
</tr>
<tr>
<td>HDL-Cholesterol (mg/dl)</td>
<td>Baseline</td>
<td>40 ± 9</td>
<td>42 ± 12</td>
</tr>
<tr>
<td></td>
<td>On Treatment*</td>
<td>31 ± 15</td>
<td>36 ± 13</td>
</tr>
<tr>
<td></td>
<td>% Reduction</td>
<td>22</td>
<td>12</td>
</tr>
<tr>
<td>LDL-C/HDL-C</td>
<td>Baseline</td>
<td>7.17</td>
<td>5.54</td>
</tr>
<tr>
<td></td>
<td>On Treatment*</td>
<td>3.88</td>
<td>4.67</td>
</tr>
</tbody>
</table>

Mabuchi et al. *American Journal of Cardiology* 1998;82:1489-1495

* 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)

** By Unpaired Student’s t-test
KAPLAN-METER CURVES SHOWING THE PROPORTION OF PATIENTS WITHOUT ANY CORONARY EVENTS

Mabuchi et al: Am J Cardiol 1998;82: 1489-1495
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 LDL Apheresis (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

UPENN EXPERIENCE 1996-2005

- Retrospective Study of 34 patients
- Biweekly Lipoprotein Apheresis (Liposorber®)
- Average 2.5 years of treatment
  - 3 months to 7 years
- ~3-fold reduction in cardiac events
  - (MI, stroke, TIA, ruptured AA)
- ~20-fold reduction in CV interventions
  - (CABG, Carotid endarterectomy, CA stents)

Sachais et al, Journal of Clinical Apheresis, 2005
THE LOW DENSITY LIPOPROTEIN-APHERESIS CORONARY MORPHOLOGY AND RESERVE TRIAL (LACMART)

Patients
Eighteen Patients with Heterozygous FH

Treatment
LDL-A group (n=11): bi-weekly LDL-A + medication
Medication group (n=7): medication only

Evaluation
Minimum Lumen Diameter (MLD) and Plaque Area (PA) were evaluated by Coronary Angiography (QCA) and IVUS, respectively, at Baseline and After One Year Follow-Up.

## CHANGES IN SERUM LIPIDS

<table>
<thead>
<tr>
<th></th>
<th>LDL-A + Medication</th>
<th>Medication</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Follow-up</td>
</tr>
<tr>
<td><strong>TC (mg/dl)</strong></td>
<td>275±27</td>
<td>197±19*</td>
</tr>
<tr>
<td><strong>TG (mg/dl)</strong></td>
<td>143±74</td>
<td>139±93</td>
</tr>
<tr>
<td><strong>HDL-C (mg/dl)</strong></td>
<td>33±20</td>
<td>36±1</td>
</tr>
<tr>
<td><strong>LDL-C (mg/dl)</strong></td>
<td>213±25</td>
<td>140±27*</td>
</tr>
</tbody>
</table>

*: p=0.0001, vs follow-up on Medication

M. Matsuzaki et al., J Am Coll Cardiol 2002; 40: 220-227
CHANGE IN CAG AND IVUS PARAMETERS

- MLD: p=0.004
- Plaque Area: p=0.08
- Lumen Area: NS
- Vessel Area: NS

**BASELINE**

- **MLD** = 1.5 mm
- **Plaque Area** = 7.8 mm²
- **Lumen Area** = 3.3 mm²
- **Vessel Area** = 11.1 mm²

**FOLLOW UP**

- **MLD** = 2.2 mm
- **Plaque Area** = 7.0 mm²
- **Lumen Area** = 5.3 mm²
- **Vessel Area** = 12.3 mm²

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M. Matsuzaki et al., J Am Coll of Cardiol 2002; 40: 220-227
TREATMENT RELATED ADVERSE EVENTS
LIPOSORBER® SYSTEM

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>

Kanaka Pharma America Corporation
Data from Sachais et al, J Clinical Apheresis (2005)
Lp(a)

- Modified LDL in which apo(a) is covalently attached to apo-B
- apo(a)
  - Glycoprotein (400 – 700 kDa)
  - Variable repeats of kringle IV type
    - 2 donamains
      - 2 to 40 or more
  - Smaller size leads to higher levels
Lp(a) DISTRIBUTION IN NOT NORMAL

Figure from Nordestgaard et al, European Heart Journal (2010)
Lp(a) LEVELS AND RISK

Figure 2. Risk Ratios for Coronary Heart Disease, Ischemic Stroke, or Nonvascular Death by Quantile of Usual Lp(a) Level

Erqou et al, JAMA (2009)
LIPOPROTEIN APHERESIS IN PATIENTS WITH MAXIMALLY TOLERATED LIPID LOWERING THERAPY, LP(A) HYPERLIPIDEMIA AND PROGRESSIVE CARDIOVASCULAR DISEASE

• Prospective, observational, multicenter study
• 170 patients who began lipoprotein apheresis
  – Lp(a) hyperlipidemia
  – Progressive CVD
• Compared two years prior and first two years on lipoprotein apheresis
• Major Adverse Coronary Events (MACE)
  – CV death, non-fatal MI, CABG, PCI, stent

TECHNOLOGIES USED

• Double Filtration Plasmapheresis (DFPP)
• Heparin-Induced LDL precipitation (HELP)
• Destrans Sulfate Adsorption (DSA)
• ApoB100-immunoadsorption

### LIPOPROTEINS

**Table 2. Plasma Concentrations of Lipoproteins and Fibrinogen in 2 Years Before and in 2 Years During Steady State of Chronic LA**

<table>
<thead>
<tr>
<th></th>
<th>y-2</th>
<th>y-1</th>
<th>1st LA</th>
<th>y+1, 6 mo</th>
<th>y+1, 12 mo</th>
<th>y+2, 6 mo</th>
<th>y+2, 12 mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lp(a)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean or interval</td>
<td>3.94±1.77</td>
<td>3.95±1.61</td>
<td>3.16±1.35</td>
<td>2.57±1.05</td>
<td>2.54±0.99</td>
<td>2.54±0.99</td>
<td>2.53±0.96</td>
</tr>
<tr>
<td>mean level, µmol·L⁻¹ [mg·dL⁻¹]</td>
<td>[110.4±49.6]</td>
<td>[110.6±45.1]</td>
<td>[88.6±37.8]</td>
<td>[72.0±29.4]</td>
<td>[71.2±28.1]</td>
<td>[71.2±27.6]</td>
<td>[70.9±26.8]</td>
</tr>
<tr>
<td>Cₘₐₓ before LA, µmol·L⁻¹ [mg·dL⁻¹]</td>
<td>ND</td>
<td>ND</td>
<td>3.74±1.63</td>
<td>3.12±1.30</td>
<td>3.09±1.26</td>
<td>3.10±1.23</td>
<td>3.10±1.20</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>[104.9±45.7]</td>
<td>[87.4±36.4]</td>
<td>[86.6±35.2]</td>
<td>[86.8±34.5]</td>
<td>[86.8±33.5]</td>
</tr>
<tr>
<td>Cₘᵟᵢ after LA, µmol·L⁻¹ [mg·dL⁻¹]</td>
<td>ND</td>
<td>ND</td>
<td>1.51±0.83</td>
<td>1.04±0.50</td>
<td>0.97±0.42</td>
<td>0.97±0.40</td>
<td>0.94±0.44</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>[42.2±23.3]</td>
<td>[29.2±14.4]</td>
<td>[27.3±11.7]</td>
<td>[27.1±11.1]</td>
<td>[26.4±12.4]</td>
</tr>
<tr>
<td>Reduction, %</td>
<td>ND</td>
<td>ND</td>
<td>59.8±14.1</td>
<td>66.6±11.5</td>
<td>68.5±9.4</td>
<td>68.8±9.5</td>
<td>69.6±9.8</td>
</tr>
<tr>
<td>LDL-C</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean or interval</td>
<td>2.56±0.98</td>
<td>2.57±1.02</td>
<td>2.17±0.88</td>
<td>2.13±0.79</td>
<td>2.09±0.75</td>
<td>2.15±0.79</td>
<td>2.10±0.83</td>
</tr>
<tr>
<td>mean level, mmol·L⁻¹ [mg·dL⁻¹]</td>
<td>[98.7±37.8]</td>
<td>[99.2±39.4]</td>
<td>[83.7±34.1]</td>
<td>[82.3±30.4]</td>
<td>[80.6±29.0]</td>
<td>[83.0±30.4]</td>
<td>[81.1±31.9]</td>
</tr>
<tr>
<td>Cₘₐₓ before LA, mmol·L⁻¹ [mg·dL⁻¹]</td>
<td>ND</td>
<td>ND</td>
<td>2.56±1.04</td>
<td>2.54±0.92</td>
<td>2.55±0.93</td>
<td>2.64±0.96</td>
<td>2.59±1.05</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>[99.0±40.1]</td>
<td>[98.1±35.5]</td>
<td>[98.3±35.9]</td>
<td>[101.8±36.9]</td>
<td>[100.0±40.6]</td>
</tr>
<tr>
<td>Cₘᵟᵢ after LA, mmol·L⁻¹ [mg·dL⁻¹]</td>
<td>ND</td>
<td>ND</td>
<td>1.10±0.54</td>
<td>0.93±0.51</td>
<td>0.87±0.42</td>
<td>0.87±0.40</td>
<td>0.85±0.47</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>[42.4±20.9]</td>
<td>[36.1±19.5]</td>
<td>[33.4±16.2]</td>
<td>[33.4±15.6]</td>
<td>[32.7±18.0]</td>
</tr>
<tr>
<td>Reduction, %</td>
<td>ND</td>
<td>ND</td>
<td>57.2±13.2</td>
<td>63.2±12.2</td>
<td>66.0±12.2</td>
<td>67.2±10.2</td>
<td>67.3±9.8</td>
</tr>
</tbody>
</table>

MACE

- 78% decrease in MACE after initiation of lipoprotein apheresis

- ACVE: Adverse Cardiac and Vascular Events – MACE and Cerebrovascular events

SUMMARY

• Lipoprotein apheresis represents a viable treatment option for FH and other hypercholesterolemic patients with non-optimal responses to medical therapy

• Regular treatment with lipoprotein apheresis reduced cardiovascular morbidity in our patients with FH and Lp(a) hyperlipidemia

• Treatment related AEs are rare, and are often related to use of ACE-inhibitors