HDL Therapy Via Plasmapheresis
A First-In-Man, Randomized, Placebo-Controlled Study to Evaluate the Safety and Feasibility of Autologous Delipidated HDL Plasma Infusions in Patients with Acute Coronary Syndrome

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How Does HDL Therapy Work?
Delipidated HDL Enhances Reverse Cholesterol Transport

The major pathway for cholesterol efflux from macrophages to HDL is by interaction of HDL with the ABCA1 transporter.

α HDL transports Excess Cholesterol to the liver

HDL Therapy Infusion of Delipidated HDL.
HDL Selective Delipidation
“Energized HDL”

PLASMA BAG 1
(Upon Collection From Patient)

Selectivity Delipidation
(Device + Disposable Kit)

PLASMA BAG 2
(After Delipidation)

HDL Selective Delipidation
“Energized HDL”

Pre-β HDL
α HDL
Pre-β HDL
Objectives

- The primary aim of this study was to test the safety and feasibility of autologous delipidated HDL infusions in acute coronary syndrome (ACS) patients.

- An exploratory aim of this study was to assess the impact on plaque volume assessed by IVUS measurements.
Patients with ACS scheduled for cardiac cath with non obstructive atheroma were randomized to HDL delipidation or control and subjected to apheresis/ reinfusion. Patients had 7 sessions each 1 week apart. IVUS performed up to 14 days from last procedure to assess atheroma volume indices.
Schematic Overview of the Methodology for the Selective Delipidation of HDL in Plasma

**HDL Delipidation Process**

- NOT Patient connected
- Uses patient’s own HDL
- Cholesterol removed from $\alpha$-HDL to yield pre-$\beta$-HDL
- Delipidated plasma is reinfused into patient
Study Design

- FDA Approval: 01/27/06
- Trial Launch: 05/31/06
- Trial Conclusion: 01/29/08

Patient presents with ACS with non-obstructive atheroma in ≥ 1 native coronary artery

Undergo IVUS of target non-obstructive atheroma native coronary artery (n=28)

Control n=14
7 apheresis/reinfusion (1 week apart)

HDL delipidation n=14
7 apheresis/reinfusion (1 week apart)

Randomized (1:1) Single-Blind

Undergo repeat IVUS of target atheroma (n=26)
Within 14 days after final reinfusion

2 control subjects discontinued after sessions 1 & 6
## Major Adverse Cardiac Events

<table>
<thead>
<tr>
<th>Variable, n (%) - ITT</th>
<th>Delipidation Group n=14</th>
<th>Control Group n=14</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Re-infarction</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Target Lesion Revascularization</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Non-Target Lesion Revascularization</td>
<td>1 (7.2)</td>
<td>2 (11.8)</td>
</tr>
<tr>
<td>Unanticipated Adverse Device Effects</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
Quantitative 2-D Gel Electrophoresis & Pre-β HDL (ELISA) Following Delipidation

<table>
<thead>
<tr>
<th>HDL Subfraction</th>
<th>Undelipidated</th>
<th>Delipidated</th>
</tr>
</thead>
<tbody>
<tr>
<td>preβ HDL</td>
<td>5.6%</td>
<td>79.1%</td>
</tr>
<tr>
<td>αHDL</td>
<td>92.8%</td>
<td>20.9%</td>
</tr>
</tbody>
</table>

Preβ HDL in post-delipidated plasma increases an average of 28X vs. preβ HDL in pre-delipidated plasma.
## Change in IVUS parameters, post delipidation treatments minus baseline ACS presentation

<table>
<thead>
<tr>
<th>Variable</th>
<th>Delipidated Group n=14</th>
<th>Control Group n=12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in Total Atheroma Volume (mm³)</td>
<td>-12.18 ± 36.75</td>
<td>2.80 ± 21.25</td>
</tr>
<tr>
<td>Change in Plaque Burden (%)</td>
<td>-1.0 ± 4.0</td>
<td>0.0 ± 4.0</td>
</tr>
<tr>
<td>Change in 10 mm Most Diseased Subsegment – Atheroma Volume (mm³)</td>
<td>-6.24 ± 17.94</td>
<td>-1.73 ± 11.21</td>
</tr>
<tr>
<td>Change in 10 mm Least Diseased Subsegment – Atheroma Volume (mm³)</td>
<td>-1.10 ± 11.35</td>
<td>1.53 ± 11.70</td>
</tr>
</tbody>
</table>
IVUS Data

Change in atheroma volume (mm$^3$)

- Change in Total Atheroma Volume
- Change in 10 mm Most Diseased Subsegment
- Change in 10 mm Least Diseased Subsegment

- Delipidated Group
- Control Group
Rapid Regression of Human Coronary Plaque after 5 Weekly Intravenous Injections of Recombinant rApo A-I Milano (ETC-216)

N=47 patients with ACS

Overall rApo A-I Milano (ETC-216) produced 4.5% net regression of coronary atheroma volume in 6 Weeks

Nissen et al.: JAMA, 2003
### Comparison of the Changes in IVUS Parameters in Lipid Sciences Selective Delipidation Trial and ApoA-I Milano Trial

<table>
<thead>
<tr>
<th>Variable (mean ± SD)</th>
<th>LS-001 Trial N=14</th>
<th>ApoA-I Milano Trial N=36*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in Total Atheroma Volume (mm³)</td>
<td>-12.18 ± 36.75</td>
<td>-14.10 ± 39.50</td>
</tr>
<tr>
<td>Change in % Atheroma Volume (Plaque Burden)</td>
<td>-1.0% ± 4.0%</td>
<td>-1.1% ± 3.2%</td>
</tr>
<tr>
<td>Change in Most Diseased 10 mm Subsegment, Atheroma Volume (mm³)</td>
<td>-6.24 ± 17.94</td>
<td>-7.20 ± 12.60</td>
</tr>
</tbody>
</table>

*Nissen et al JAMA 2003: 290, 2292-300
Summary

- Pre-clinical studies have demonstrated that pre-\(\beta\) HDL is a key component in reverse cholesterol transport
- Safety and feasibility of delipidation were demonstrated
- Infusions are well tolerated by patients
- Patient compliance is excellent
- The PDS-2 consistently, reliably, and dramatically converts \(\alpha\)HDL to pre-\(\beta\) HDL
- IVUS data demonstrates a numeric trend towards reduction in atheroma volumes
Conclusions

- In patients with ACS, serial autologous infusions of HDL delipidated plasma are well tolerated by patients, and are clinically feasible and safe.

- This therapy may offer a novel adjunct treatment for patients presenting with ACS, and may ultimately stabilize and regress atherosclerotic plaques.

Thank You