Autologous CD34+ Cells for Treatment of Refractory Angina: Meta-Analysis of 3 Randomized, Double-Blinded Studies

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Disclosures

- Baxalta/Shire: research funding
- Pluristem: consulting
- Capricor: consulting
- Janssen: research funding
Introduction: Refractory Angina

• 10-12 million Americans have angina
• 50,000 – 100,000 new cases a year
• 10-15% of patients undergoing cardiac catheterization have CAD not amenable to revascularization
• Contemporary mortality is lower than expected (3-5%/yr) but
  – Quality of Life = Severe depression

Henry et al. Eur Heart J 2013;34:2683-2688
Povsic et al, JAHA, 2015;4:e001287.
Introduction: Refractory Angina

- 10-12 million Americans have angina
- 50,000 – 100,000 new cases a year
- 10-15% of patients undergoing cardiac catheterization have CAD not amenable to revascularization
- Contemporary mortality is lower than expected (3-5%/yr)
- Only two new therapies in the last 5 decades:
  - Ranexa: improves TET 24-45 s in stable angina
  - EECP: improves TET 16 s
Autologous CD34$^+$ Cell Therapy for Refractory Angina

- CD34$^+$ cells isolated
- Cultured on fibronectin
- Grew into colonies resembling embryonic blood islands

Asahara et al. Science 1997;275:964-7
Autologous CD34⁺ Cell Therapy for Refractory Angina

Similar effects on capillary density and fibrosis

PBS = Phosphate-buffered saline; MNC = mononuclear cells.
Phase I: Dosing Feasibility

Actual Auto-CD 34+ Cell Dose Delivered / kg
(n = 6 / dose group)

Auto-CD 34+ Cell Dose/kg x 10^4 (log scale)

- Control: No cells
- Group 1: 5 x 10^5 cells
- Group 2: 1 x 10^5 cells
- Group 3: 5 x 10^5 cells

ACT-34 CMI: Reduction in Angina

Anginal Episodes per Week
Change from baseline at 6 months

Placebo  Low  High
-8.6  -14.2  -13.7

P=0.04

Analysis of Variance (ANOVA)
Change in Exercise Capacity

Change in Exercise Duration - 6 months

Δ = 70s p = 0.014

Change in Exercise Duration - 12 months

Δ = 80s p = 0.017
Inclusion Criteria:
- 21-80 yrs
- CCS class III or IV Angina
- Attempted “best” medical therapy
- Non-candidate for Surgical/Perc. revasc.
- Ischemia w/stress
- 3-10 min. mod. Bruce protocol with angina or anginal equivalent at baseline
- ETT reproducible <20%
- 7 angina/wk

Exclusion Criteria:
- Recent hospitalization
- Other angiogenic trials
- Must forgo other txt x 2 years

Pre-Qual Committee Central Review

**RENEW Study Design**

**Screening and Baseline Visits**

**Randomization**

- 1 x 10^5 CD34+ cells/kg (n = 200)
- Active Control (n = 100)
- Unblinded Standard of Care (n = 100)

**Cell Mobilization (G-CSF 5 mg/kg/d x 4d)**

- Apheresis on Day 5

**Intramyocardial Mapping and Injection with NOGA**

- ISOLEX selected CD34+ cells / Placebo

**Efficacy Assessments during 12 month follow-up:** ETT, angina frequency, and QoL (SF-36)

**Safety Assessments during 24 month follow-up:** AEs, SAEs, MACE

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Statistics Plan

- **Sample Size**
  - 400 completed subjects
  - 90% power to detect 60 second difference in mean change from baseline in total exercise time
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Enrollment stopped December 2013
Goals: Combine patient level data from 3 trials of autologous-CD34\(^+\) stem cell therapy for refractory angina

- All trials:
  - Double-blind randomized design
  - Intra-myocardial injection of cells vs. placebo
  - Assessed exercise capacity (ETT) and angina frequency (diary) at 3-, 6- and 12- months
  - Collected AEs/MACE to 24 months
Methods

• Individual patient data meta-analysis of phase I, ACT-34, ACT-34 24 month extension, and RENEW

• Efficacy endpoints analyzed as randomized and as treated

• Change from baseline (TET and angina frequency) analyzed using repeated measures at 3, 6, and 12 months accounting for trial and baseline value
  – Placebo vs. Auto-CD34+

• Time to first MACE evaluated (K-M) using log-rank
  – Centrally adjudicated events for ACT-34 and RENEW
# Patient Composition

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=89)</th>
<th>CD34+ (n=186)</th>
<th>SOC (n=28)</th>
<th>Total (n=303)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase I</td>
<td>6 (7%)</td>
<td>18 (10%)</td>
<td>-</td>
<td>24 (8%)</td>
</tr>
<tr>
<td>ACT-34</td>
<td>56 (63%)</td>
<td>112 (60%)</td>
<td>-</td>
<td>168 (55%)</td>
</tr>
<tr>
<td>RENEW</td>
<td>27 (30%)</td>
<td>57 (31%)</td>
<td>28 (100%)</td>
<td>112 (37%)</td>
</tr>
</tbody>
</table>
## Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=89)</th>
<th>CD34+ (n=186)</th>
<th>SOC (n=28)</th>
<th>Total (n=303)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (median)</strong></td>
<td>64 (56,69)</td>
<td>62 (56,68)</td>
<td>63 (55,69)</td>
<td>63 (56,69)</td>
</tr>
<tr>
<td><strong>Female</strong></td>
<td>11 (12%)</td>
<td>30 (16%)</td>
<td>4 (4%)</td>
<td>45 (15%)</td>
</tr>
<tr>
<td><strong>Caucasian</strong></td>
<td>80 (90%)</td>
<td>171 (91%)</td>
<td>27 (96%)</td>
<td>278 (91%)</td>
</tr>
<tr>
<td><strong>Diabetes</strong></td>
<td>50 (56%)</td>
<td>95 (51%)</td>
<td>16 (57%)</td>
<td>161 (53%)</td>
</tr>
<tr>
<td><strong>Hypertension</strong></td>
<td>77 (87%)</td>
<td>163 (87%)</td>
<td>24 (86%)</td>
<td>264 (87%)</td>
</tr>
<tr>
<td><strong>Hyperlipidemia</strong></td>
<td>74 (83%)</td>
<td>154 (82%)</td>
<td>27 (96%)</td>
<td>255 (84%)</td>
</tr>
<tr>
<td><strong>CHF</strong></td>
<td>31 (35%)</td>
<td>50 (27%)</td>
<td>8 (29%)</td>
<td>89 (29%)</td>
</tr>
<tr>
<td><strong>PVD</strong></td>
<td>24 (27%)</td>
<td>44 (24%)</td>
<td>4 (14%)</td>
<td>72 (24%)</td>
</tr>
<tr>
<td>h/o PCI</td>
<td>78 (88%)</td>
<td>162 (87%)</td>
<td>26 (93%)</td>
<td>206 (88%)</td>
</tr>
</tbody>
</table>
## Results: Total Exercise Time

<table>
<thead>
<tr>
<th></th>
<th>Placebo (s)</th>
<th>CD34+ (s)</th>
<th>Treatment Effect (95% CI) (s)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ITT</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Month 3</td>
<td>31.4 (16.0)</td>
<td>78.0 (12.1)</td>
<td>46.6 (13.0, 80.3)</td>
<td>0.007</td>
</tr>
<tr>
<td>Month 6</td>
<td>50.2 (18.5)</td>
<td>100.2 (13.6)</td>
<td>49.9 (10.0, 89.8)</td>
<td>0.014</td>
</tr>
<tr>
<td><strong>As Txt</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Month 3</td>
<td>28.1 (15.7)</td>
<td>80.5 (12.1)</td>
<td>52.5 (19.2, 85.7)</td>
<td>0.002</td>
</tr>
<tr>
<td>Month 6</td>
<td>48.8 (18.2)</td>
<td>101.8 (13.7)</td>
<td>52.9 (13.5, 92.4)</td>
<td>0.009</td>
</tr>
<tr>
<td>Month 12</td>
<td>39.5 (20.3)</td>
<td>90.5 (14.7)</td>
<td>50.9 (6.0, 95.9)</td>
<td>0.027</td>
</tr>
</tbody>
</table>
Results: Angina Frequency

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=89)</th>
<th>CD34+ (n=186)</th>
<th>Total (n=275)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median (Q1, Q3)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline Angina/wk</td>
<td>17 (9,25)</td>
<td>18 (11,30)</td>
<td>18 (11,28)</td>
</tr>
<tr>
<td>Month 3</td>
<td>7 (1,13)</td>
<td>5 (2,12)</td>
<td>5 (1,12)</td>
</tr>
<tr>
<td>Month 6</td>
<td>5 (1,12)</td>
<td>4 (1,13)</td>
<td>4 (1,12)</td>
</tr>
<tr>
<td>Month 12</td>
<td>3 (0,10)</td>
<td>3 (1,9)</td>
<td>3 (1,9)</td>
</tr>
<tr>
<td><strong>Δ from Baseline</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Month 3</td>
<td>-8 (-16, -4)</td>
<td>-10 (-19, -6)</td>
<td>-9 (-18, -6)</td>
</tr>
<tr>
<td>Month 6</td>
<td>-8 (-15, -5)</td>
<td>-12 (-20, -7)</td>
<td>-11 (-18, -6)</td>
</tr>
<tr>
<td>Month 12</td>
<td>-9 (-15, -6)</td>
<td>-13 (-21, -7)</td>
<td>-11 (-19, -7)</td>
</tr>
</tbody>
</table>
## Results: Relative Risk of Angina

<table>
<thead>
<tr>
<th>ITT</th>
<th>Relative Risk Ratio of Angina (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Month 3</td>
<td>0.90 (0.69, 1.17)</td>
<td>0.48</td>
</tr>
<tr>
<td>Month 6</td>
<td>0.81 (0.62, 1.06)</td>
<td>0.12</td>
</tr>
<tr>
<td>Month 12</td>
<td>0.79 (0.57, 1.12)</td>
<td>0.19</td>
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<tr>
<td>Month 3</td>
<td>0.90 (0.69, 1.16)</td>
<td>0.40</td>
</tr>
<tr>
<td>Month 6</td>
<td>0.81 (0.62, 1.07)</td>
<td>0.14</td>
</tr>
<tr>
<td>Month 12</td>
<td>0.79 (0.57, 1.10)</td>
<td>0.16</td>
</tr>
</tbody>
</table>
Kaplan-Meier Analysis

Death
Comparison of Placebo vs. CD34+:
p = 0.003

MACE
Comparison of Placebo vs. CD34+:
p = 0.08
Conclusions

• CD34\(^+\) cells, compared with placebo injections, result in:
  - Clinically and statistically significant durable improvements in exercise capacity
  - No safety issues, all MACE events favor cell therapy
  - Statistically significant improvement in mortality with cell therapy
  - Compared with both active control and CD34\(^+\) therapy, SOC arm faired poorly
Conclusions

• We believe that this type of cell therapy for refractory angina is particularly promising and may improve both functional status and mortality

• It is imperative to explore methods to bring this therapy to patients