Patients with Intermittent Claudication Injected with ALDH Bright Cells

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PAD affects 8-12% of Americans over 65 and is associated with significant morbidity and mortality

Claudication affects 1-3 million Americans; treatments include supervised exercise, claudication pharmacotherapy (cilostazol) and revascularization

Cell therapy has the potential to promote arteriogenesis, angiogenesis and direct effects on skeletal muscle

Ideal cell type, dose, timing of dose, local physiologic mechanisms and treatment effect of potential cell types are unknown
PACE was designed as a Phase 2 investigation to evaluate:

1. Co-primary endpoints: to provide point estimates of possible treatment effects
2. A pre hoc-defined set of physiological relationships that could inform PAD claudication research.


**PAD**
Intermittent Claudication

**Cell Therapy**
ALDHbr

**MR Imaging**
Anatomy
Flow
Perfusion

**PWT**

**PAD Anatomy**
PAD Physiology
Mechanism of Treatment effect
Why ALDHbr Cells?

- Express high levels of the cytosolic enzyme aldehyde dehydrogenase
- Enriched for hematopoietic, endothelial progenitors and multipotent mesenchymal colony forming cells
- Increased co-expression of primitive cell surface markers, CD 34, CD 117 (c-kit) and CD 133, myeloid progenitors and monocytes (CD 33, CD 14). High PECAM-1 expression
- Capable of ischemic repair in preclinical models
- Safety and feasibility Phase I trials in CHF and CLI

1. Balber et al, Stem Cells 2011;29(4):570  
2. Capoccia et al, Blood 2009;113:5340  
3. Perin et al, Cath Cardiov Int 2011;78:1060  
Inclusion Criteria:

- Patients with atherosclerotic PAD with claudication, with one predominantly symptom-limiting leg
- Age ≥40 years
- Baseline pre-exercise ABI <0.90 or a pre-exercise TBI <0.70
- Presence of significant stenosis (≥ 50%) or occlusion of infrainguinal arteries by advanced imaging with no inflow disease

Site Selection Criteria:

- CCTRN network interdisciplinary sites
- 1.5-3 T MR scanner and MR leadership
- Site MR anatomy and perfusion data acquisition training
- Site MR thigh occlusion and peak hyperemic flow training
- Calibrated ABI and treadmill function data acquisition certification
Primary Endpoints

PAD Limb Function (treadmill)

1. Peak Walking Time (PWT)

PAD Anatomy and Physiology (MRI)

2. Collateral artery count
3. Peak hyperemic popliteal flow
4. Capillary perfusion

Outcome Assessment:
Change from baseline to 6 months between groups
Time-resolved MR angiography for observing arterial, tissue, and venous phases of contrast inflow (8-12 s per dynamic)

**Contrast**
Thigh - 0.1 mmol/kg
Lower leg - 0.05 mmol/kg

**Resolution**
Thigh – 1.3 mm X 1 mm X 1.3 mm
Lower leg - 1mm X 1mm X 1mm
Peak Hyperemic Popliteal Flow and Capillary Perfusion

- **Resting Flow**
- **Flow (mL/sec)**
- **Cuff Inflation**
- **Peak Hyperemic Flow**
- **Time to Peak Flow**

**Popliteal Artery**
- **Ant Tibial**
- **Arterial Input**
- **Soleus**
- **Gastroc**

**Graph**
- **X-axis:** Time (sec)
- **Y-axis:** CA Concentration (mM/L)
- **Legend:**
  - Gastronem
  - Soleus
  - Ant Tibialis
- Total of 10 injections
  1 ml / injection

- 2 injections to target semimembranosus and biceps femoris

- 8 injections distributed into the gastrocnemius.
## Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>ALDHbr [n=38]</th>
<th>Placebo [n=40]</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD)</td>
<td>66 (9)</td>
<td>66 (9)</td>
<td>0.989</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>12 (32)</td>
<td>9 (23)</td>
<td>0.447</td>
</tr>
<tr>
<td>Race (nonwhite), n (%)</td>
<td>4 (11)</td>
<td>6 (15)</td>
<td>0.738</td>
</tr>
<tr>
<td>Weight (lbs), mean (SD)</td>
<td>167 (40)</td>
<td>193 (43)</td>
<td>0.007</td>
</tr>
<tr>
<td>Diabetes</td>
<td>14 (37)</td>
<td>16 (40)</td>
<td>0.819</td>
</tr>
<tr>
<td>Current Smoker</td>
<td>12 (32)</td>
<td>14 (35)</td>
<td>0.813</td>
</tr>
<tr>
<td>Pre-exercise ABI*, mean (SD)</td>
<td>0.60 (0.14)</td>
<td>0.63 (0.11)</td>
<td>0.646</td>
</tr>
<tr>
<td>Cilostazol use</td>
<td>7 (18)</td>
<td>5 (13)</td>
<td>0.540</td>
</tr>
</tbody>
</table>

*ALDHbr group = 37
Primary Functional Endpoint: PWT

Change between Baseline and 6 months

- Placebo
- ALDHbr

P = 0.238
# Primary MRI Endpoints

<table>
<thead>
<tr>
<th></th>
<th>Placebo mean ± SD [n]</th>
<th>ALDHbr mean ± SD [n]</th>
<th>Mean Diff ± SE (CI)</th>
<th>T-Test P-value</th>
<th>Weight Adj P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Collateral Count</td>
<td>0.6 ± 2.2 [38]</td>
<td>1.5 ± 2.7 [37]</td>
<td>0.9 ± 0.6 (-0.2 – 2.1)</td>
<td>0.116</td>
<td>0.081</td>
</tr>
<tr>
<td>Peak Hyperemic Flow</td>
<td>0.2 ± 1.9 [36]</td>
<td>0.2 ± 1.5 [35]</td>
<td>0.0 ± 0.4 (-0.8 – 0.8)</td>
<td>0.978</td>
<td>0.835</td>
</tr>
<tr>
<td>Capillary Perfusion</td>
<td>-0.25 ± 2.36 [38]</td>
<td>-0.42 ± 2.40 [38]</td>
<td>-0.17 ± 0.55 (-1.26 – 0.91)</td>
<td>0.752</td>
<td>0.937</td>
</tr>
</tbody>
</table>

Table displays the change from baseline to 6 months
Secondary endpoints were not changed by ALDHbr cell administration

- Resting and post-exercise ABI at 3 and 6 mos
- PWT at 3 mos; COT at 3 and 6 months
- Walking Impairment and PAD Questionnaire at 1,3, and 6 months
- Relationship between PWT and the 3 MRI based primary endpoints

- The pre-specified subgroup of baseline pre-exercise ABI \( \leq 0.6 \) showed significant change in collateral count with ALDHbr cell administration (n=28)

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<tr>
<td>Collateral Count</td>
<td>0.5 ± 1.7 [14]</td>
<td>2.4 ± 3.0 [14]</td>
<td>1.9 ± 0.9 (-0.1 – 3.8)</td>
<td>0.058</td>
<td>0.021</td>
</tr>
</tbody>
</table>

Table displays the change from baseline to 6 months
Patients with **occluded femoral arteries** at baseline had significantly more collaterals than those with patent femoral arteries ($p=0.015$)

<table>
<thead>
<tr>
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<th>Occluded</th>
<th>Patent</th>
</tr>
</thead>
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<tr>
<td></td>
<td>[n=54]</td>
<td>[n=21]</td>
</tr>
<tr>
<td>Baseline Collateral Count</td>
<td>5.1 ± 4.4</td>
<td>2.9 ± 3.1</td>
</tr>
</tbody>
</table>

Patients with **occluded femoral arteries**:

<table>
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<tr>
<td>Collateral Count</td>
<td>0.3 ± 2.4 [28]</td>
<td>1.5 ± 2.4 [26]</td>
<td>1.3 ± 0.7 (-0.1 – 2.6)</td>
<td>0.063</td>
<td>0.047</td>
</tr>
</tbody>
</table>

Table displays the change from baseline to 6 months
Conclusions

- Administration of ALDHbr cells was feasible and safe

- Administration of ALDHbr cells – at this dose & in this PAD cohort – did not change PWT, or MRI-based anatomic and perfusion endpoints

- The MRI techniques, now developed and applied for the first time in a multicenter PAD clinical trial, are now available for application in future PAD clinical research to determine if a clinically relevant therapeutic benefit might be achieved (from cells or any promising intervention)