Discussant of Effect of Progenitor Cell Mobilization with Granulocyte Macrophage Colony Stimulating Factor (GM-CSF) in Patients with Peripheral Artery Disease and Claudication; GPAD-II: A Phase II Randomized Study

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Disclosures

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**Professional Society Roles:** Member AUC Task Force, Chair of Revascularization / Dx Cath AUC
Outline

• What do we know:
  • PAD patients as treatment group

• What did we learn?
  • Findings of GPAD-2 in context of Current therapy

• What do we need to know?
  • Way forward
What do we know?
PAD Patients as target for cell therapy
10-Year Natural History in Patients With Intermittent Claudication

Baseline Physical Activity and Mortality in Persons With PAD

<table>
<thead>
<tr>
<th>Physical Activity Quartile</th>
<th>Adjusted Hazards Ratio (95% Confidence Intervals)</th>
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</thead>
<tbody>
<tr>
<td>1st Quartile</td>
<td>P = 0.02</td>
</tr>
<tr>
<td>2nd Quartile</td>
<td>P = 0.07</td>
</tr>
<tr>
<td>3rd Quartile</td>
<td>P = 0.61</td>
</tr>
<tr>
<td>4th Quartile</td>
<td></td>
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P-trend = 0.003

**ACC/AHA Guideline for the Management of PAD: Treatment of Claudication**

**Confirmed PAD Diagnosis**
- **No significant functional disability**
  - No claudication treatment required.
  - Follow-up visits at least annually to monitor for development of leg, coronary, or cerebrovascular ischemic symptoms.

- **Lifestyle-limiting symptoms**
  - Supervised exercise program
    - Three-month trial
  - Preprogram and postprogram exercise testing for efficacy

- **Pharmacological therapy**
  - Cilostazol (Pentoxifylline)
    - Three-month trial

- **Lifestyle-limiting symptoms with evidence of inflow disease**
  - Further anatomic definition by more extensive noninvasive or angiographic diagnostic techniques
  - Endovascular therapy or surgical bypass per anatomy

**Clinical improvement**
- Follow-up visits at least annually

**Significant disability** despite medical therapy and/or inflow endovascular therapy, with documentation of outflow PAD, with favorable procedural anatomy and procedural risk-benefit ratio
- Evaluation for additional endovascular or surgical revascularization

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What do we know?
PAD Patients as target for cell therapy

- PAD patients are common
- PAD patients (CLI and IC) have a high rates of cardiovascular events
- Reduction in walking ability for intermittent claudication is associated with increased mortality
- Standard treatment (supervised exercise / cilostizol) is limited
What did we learn? What did the GPAD-2 Investigators Do and Find?

- Single Health System - Randomized 159 patients with IC to 500 ug GM-CSF vs. Placebo x week for 4 weeks

- Mobilized progenitor cells at 2 weeks

- Limited by some variation in use of cilostizol, possibly background exercise, degree of mobilization of PCs

- Trial found no improvement ABI, peak oxygen consumption, SF-36, and in claudication onset times (p=0.08) at 3 months (53 seconds)

- Secondary analyses found peak walking times 6-months (possibly driven by patients with more mobilization)
Pharmacotherapy of Claudication

Cilostazol (100 mg orally two times per day) is indicated as an effective therapy to improve symptoms and increase walking distance in patients with lower extremity PAD and intermittent claudication (in the absence of heart failure).

- Cilostizol increases peak walking distance by ~100 meters
- Ramipril in RCT (JAMA 2013 Feb 6;309(5):453-60) increased Pain free walking time 78 seconds and maximum walking time 255 seconds
What do we need to know?

• Are there cell based therapies for IC patients that improve functional status?
  • Larger studies
  • Control background therapy
  • Identify mechanisms for improvement (Perfusion – MRI)

• Do cell based therapies affect critical limb ischemia? (different disease state / studies)
• Can we standardize the definitions (PARC)