Important RCTs for Venous Wound Healing

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Bill Marston MD
Professor and Chief, Div of Vascular Surgery
University of North Carolina Hospitals

Disclosures

• Scientific Consultant
  – Veniti
  – Cardinal Healthcare
  – Tactile Medical
  – Volcano

• Clinical Trial Investigator
  – Tactile Medical, Veniti, Volcano

Selected Studies

• RCTs enrolling CEAP class 6 patients in last 2 years

• Outcome measures documenting comparative ulcer healing rates

Numerous recent failed Phase 3 clinical trials for VLU

• HP-802 (spray on skin)

Conservative vs surgical treatment of venous leg ulcers: 10-year follow up of a randomized, multicenter trial

• Van Gent, Catarinella, Lam, Wittens, et al
• Phlebology 2015;30:35-41

• Prospective randomized study of 196 limbs enrolled 1998-2001
• Surgical group: saphenous and perforator correction
• Conservative group: ambulatory compression

van Gent et al; results

• 80 of original legs returned for 10 year follow up

Ulcer recurrence
• Surgical group: 48.9%
• Conservative group: 94.3%  \( P = .007 \)

• Number of incompetent perforators correlated with increased ulcer recurrence
• Connexin 43—gap junction protein
  – Key role in control of small molecule signaling to and between cells
  – Regulator of inflammatory cytokine release
  – Mediates fibrosis pathway
  – Controls growth factor response at cellular level

• Concentrations upregulated at wound edge in chronic non-healing wounds

ACT1 peptide - competitive inhibition of Connexin 43

• ACT1 accelerated wound healing in multiple animal model studies
• Phase 2 study initiated Oct 2011
• 92 patients with VLU randomized to:
  – ACT1(topical) in addition to standard of care
  – SOC alone
• SOC included compression bandages, debridement, exudate control

ACT1 for VLU: Results

<table>
<thead>
<tr>
<th></th>
<th>ACT1 + SOC (n=46)</th>
<th>SOC alone (n=46)</th>
<th>P value</th>
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</thead>
<tbody>
<tr>
<td>100 % closure at week 12</td>
<td>57%</td>
<td>28%</td>
<td>0.01</td>
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<tr>
<td>Mean % area reduction at week 12</td>
<td>79%</td>
<td>36%</td>
<td>0.02</td>
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ACT1 VLU results

Future for Connexin-43 inhibitors

• Phase 3 studies underway with 2 separate competitive inhibitors studying benefit in accelerating venous leg ulcers
• Successful completion should support FDA approval and additional therapeutic option

Placental Membranes

• Described for decades as source of material to apply to wounds
• Proposed as rich source of stem/progenitor cells that might be useful in healing
• Numerous types of tissue products based on placental membranes recently entered market
• Studied growth factor cytokine profile of dHACM in vitro
• Demonstrated that extracts of dHACM resulted in increased proliferation of human dermal fibroblasts compared to control
• Mesenchymal stem cell migration significantly increased after exposure to dHACM

84 patients with VLUs randomized
- 53 to compression plus dHACM
- 31 to compression plus standard dressing

Primary outcome measure
– Percent wound closure at 4 weeks

dHACM VLU results
• Percent healed at 4 weeks
  – dHACM grp: 48.1%
  – Compression alone: 19.0%

• Percent closed at 12 weeks
  – dHACM

The pipeline: Interesting early work

Drop in TNF alpha levels correlates with ulcer healing

TNF-a inhibitor: results
• Biopsies taken at day 0 and 4 weeks later, TNF-a in tissue quantified

• 3 of 5 patients had significant decrease in TNF-a at 4 weeks compared to control
– These 3 patients all had wound reduction > 25% at 4 weeks
Supervised exercise training as an adjunctive therapy for venous leg ulcers: study protocol for a randomised controlled trial

Gary A. Tovey, Jonathan Michael, Helen Coakley, Geoff Middleton, and Mark Nancola

- Exercise training vs compression alone
- 3 60-minute exercise sessions per week
  - Treadmill walking
  - Upright cycling
  - Strength/ flexibility for lower extremities