Adjunctive Therapies: The Use of Skin Substitutes and Growth Factors in Venous Leg Ulceration (VLU)

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Disclosure

Sami Khan, M.D., FACS

I have no financial relationship(s) to disclose.
Chronic venous insufficiency (CVI) affects 10-35% US population

VLU prevalence: 0.5-1.0%; >65 yrs 4%

Financial burden/loss $1 billion
INTRODUCTION

• Recurrent ulceration after healing: 28-57% at 2 years

• In the majority of patients, if an ulceration recurs after initial healing the likelihood of multiple recurrences is significant

• Poor compliance with long term compression
RECURRENT VLU
RISK FACTORS FOR DELAYED HEALING OF VLU

• Initial large VLU (>20 cm²)
• Delay in treatment with compression after ulcer development ( >1 year)
• Concomitant arterial insufficiency
• Poor response to initial compression therapy after 4 weeks
• Age
• Venous refill time on plethysmography of < 20 seconds
PATHOPHYSIOLOGY

• Venous Microcirculation
  – Dermal functional derangement related to permeability
  – Primary inflammatory mechanism
  – Alterations in leukocyte activation

• Venous Macrocirculation
  – Abnormal pressure in the superficial or deep venous system leads to VENOUS HYPERTENSION
  – Valvular dysfunction
OTHER MODALITIES OF TREATMENT

• Pharmacological treatments

• Growth Factors

• Living Tissue substitutes

• Surgical Techniques
DRUGS

- Insufficient evidence about the benefit of systemic drugs
- Usually most effective when used in combination with compression
- MOA: Affect leukocyte metabolism
- Examples:
  - Daflon 500: Purified flavonoid fraction
  - Prostaglandin E1 analogue
PENTOXIFYLLINE

- Review of RCT, Jull identified 5 trials in which pentoxifylline added to compression compared with placebo and compression
- Data pooling concluded that more patients in the treatment group healed the VLU
- Falanga et al: median time to healing 71 days versus 100 days for placebo (800 mg/TID)
(ESCHAR): Randomised controlled trial

- 48 month ulcer recurrence rate
  - 51% in compression group
  - 27% in compression plus surgery grp
  $p < 0.01$

BMJ. 2007;335:83.
Macromolecules

RBC extravasation

RBC degradation fibrin+hemosiderin

EC activation ICAM-1 expressed

Leukocyte adhesion and margination

TGF-β1

Fibroblast

Collagen

Mast cells

Macrophages

MMPs

Plastic and Reconstructive Surgery

TGF-B PATHWAY

CYTOKINES IN VLU

• Analysis of VLU biopsy and fluid show upregulation of TNF-alpha, iL-1 and iL-6
• Fibroblasts from VLU display inhibition of proliferative phase of TGF-Beta 1 and cellular senescence
GROWTH FACTORS IN VLU

• Human epidermal growth factor: 17 pts versus 18 placebo pts ➔ No evidence of improvement @ 10 weeks

• Recombinant FGF (Repifermin): Double blind placebo controlled trial of 94 pts ➔ 75% treated group healed @ 12 weeks

• Prospective RCT of over 300 pts showed no difference in healing times from placebo
GROWTH FACTORS IN VLU

• Becaplermin (Regranex):
  – Recombinant platelet-derived growth factor
  – No evidence of benefit in limited studies

• Keratinocyte growth factor
  – No significant difference in trial of over 300 patients
GROWTH FACTORS IN VLU

No current growth factor therapy that is FDA approved for treatment of VLU
ADJUVANT THERAPIES

• Bioengineered dermal equivalents
  – Apligraf
  – Orcel
  – Dermagraft

• Non-living dermal substitutes
  – Oasis

• Growth factors
  • None currently

• Skin grafts

• Flaps
OASIS WOUND MATRIX

Contents

• Type I and III collagen
• Glycosaminoglycans
• Hyaluronic acid
• Other connective tissue components

• Growth factors?
OASIS VLU STUDY: Time to healing

34/62 = 55% SIS
20/58 = 34% Standard
p = .02
VLU RECURRENCE AFTER HEALING

• Follow-up data in 110 patients after ulcer healing

• Recurrent ulceration developed in:
  • 24% of limbs within 1 year
  • 33% of limbs within 2 years
  • 49% of limbs within 5 years
APLIGRAF

• Bilayered human skin equivalent
• Source neonatal foreskin
• Dermal layer composed of living fibroblasts interspersed within a bovine-derived collagen matrix
• Overlying epidermal layer composed of living human keratinocytes
DO YOU SUFFER FROM LEG AND FOOT SORES?

What a foot or leg sore begins for weeks, months or even years without healing, it's named to feel hopeless. Perhaps you've used other basic treatments, but they're ineffective in healing your wound.

Now there's Apligraf®, an advanced wound care therapy offering real hope for healing your wound: the fastest in biotechnology. Like human skin, Apligraf® consists of living cells, protein and skin-healing advances. Apligraf® isn't another treatment or dressing. It's designed as a living "skin patch" to replace the function of healthy human skin by helping the skin "heal itself."

Hope for healing even the most persistent sores.

April 8-9, 2011
New York LaGuardia Marriott
APLIGRAF
APLIGRAF
<table>
<thead>
<tr>
<th></th>
<th>Human Keratinocytes</th>
<th>Human Dermal Fibroblasts</th>
<th>Apligraf</th>
<th>Human Skin</th>
</tr>
</thead>
<tbody>
<tr>
<td>FGF-1</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>FGF-2</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>FGF-7</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>ECGF</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>IGF-1</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>IGF-2</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>PDGF-AB</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>TGF-α</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>+</td>
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<tr>
<td>IL-1α</td>
<td>+</td>
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<td>IL-6</td>
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<td>IL-8</td>
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<td>IL-11</td>
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<td>+</td>
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<tr>
<td>TGF-β1</td>
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<td>+</td>
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<td>+</td>
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<tr>
<td>TGF-β3</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>VEGF</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

FGF = fibroblast growth factor; ECGF = endothelial cell growth factor; IGF = insulin-like growth factor; PDGF = platelet-derived growth factor; TGF = transforming growth factor; IL = interleukin; VEGF = vascular endothelial growth factor.
APLIGRAF: APPLICATION

• Adequate wound bed preparation
  – good granulation
  – edema control
  – bacterial balance
• Debride wound to healthy, bleeding base
APLIGRAF

• Must use compression if treating VLU
  – Multi-layered elastic compression
• Management of wound drainage critical
  – Foam dressings optimal for exudate
• Do not debride wound for 2-3 weeks after application
  – Avoid temptation to remove yellow slough
APLIGRAF: VLU TRIAL

- 240 patients
- Ulcers present > 1 month
- Average 3.3 applications
- Applied with compression
- Percent closed at 24 weeks compared to compression alone

0 10 20 30 40 50 60
24 weeks

57%
40%

p=0.02
### Table 1. General Summary of Some Bioengineered Skin Products and Representative Properties

<table>
<thead>
<tr>
<th>Product</th>
<th>Company</th>
<th>Structure/Characteristics</th>
<th>Uses</th>
<th>Advantages/Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epiderm</td>
<td>BioTime Technologies, Freiberg, Germany (<a href="http://www.biotime-technologies.com">www.biotime-technologies.com</a>)</td>
<td>Analogous keratinocytes suspended in a fibrin glue</td>
<td>Venous leg ulcers</td>
<td>Single injection: the gel-like construct is applied to the wound with a syringe.</td>
</tr>
<tr>
<td>CriScler</td>
<td>Groton Science LLC, Boston, Mass. (<a href="http://www.grontonscience.com">www.grontonscience.com</a>)</td>
<td>Living dermal-derived allogenic keratinocytes</td>
<td>Partial and full-thickness burns, venous ulcers</td>
<td>Partial-thickness and full-thickness wounds</td>
</tr>
<tr>
<td>GelStry</td>
<td>Asia Medical, Boston, Mass. (<a href="http://www.asiamedical.com">www.asiamedical.com</a>)</td>
<td>Synthetic vascular scaffold composed of a silicone support with a vascular lumen</td>
<td>Partial-thickness burns, deep dermal and full-thickness burns</td>
<td>Non-invasive treatment of deep dermal and full-thickness burns</td>
</tr>
<tr>
<td>Epiderm</td>
<td>Groton Science LLC, Boston, Mass. (<a href="http://www.grontonscience.com">www.grontonscience.com</a>)</td>
<td>Colloidal silica-aluminometer</td>
<td>Deep dermal and full-thickness burns, grafting after partial-thickness wound healing</td>
<td>Non-invasive treatment of deep dermal and full-thickness burns</td>
</tr>
<tr>
<td>AWKAT</td>
<td>Atlanta, Inc., Carlsbad, Calif. (<a href="http://www.awkatan.com">www.awkatan.com</a>)</td>
<td>Patient-matched acellular dermal matrix</td>
<td>Venous and arterial reconstructions</td>
<td>Non-invasive treatment of venous and arterial reconstructions</td>
</tr>
</tbody>
</table>

### Table 1. Continued

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</tr>
</thead>
<tbody>
<tr>
<td>Ongel</td>
<td>Owens International, N.C. (<a href="http://www.owensinternational.com">www.owensinternational.com</a>)</td>
<td>Alloderm consists of dermal, epithelial, and keratinocytes, which are cultured on an acellular scaffold</td>
<td>Venous and arterial reconstructions</td>
<td>Non-invasive treatment of venous and arterial reconstructions</td>
</tr>
<tr>
<td>Acraflex</td>
<td>Plastic and Reconstructive Surgeons</td>
<td>Acraflex consists of acellular dermal matrix</td>
<td>Venous and arterial reconstructions</td>
<td>Non-invasive treatment of venous and arterial reconstructions</td>
</tr>
</tbody>
</table>
CLINICAL TRIALS

• 2nd generation living dermal equivalents
  – Dermagraft
  – HP-802

• Dermal matrix implants
  – Integra

• Stem cell delivery
  – Early phase results promising

• Protease inhibitors

• Anti-inflammatory agents
INTEGRA
INTEGRA
STEM CELL THERAPIES
STEM CELL THERAPIES

Inductive “Smart” Scaffolds

Composite Dressings

MEM/Microfluidic Technology

Biomaterial Delivery Systems

Plastic and Reconstructive Surgery

Longaker, MT. PRS. 127:10S-20S, January 2011
## STEM CELL THERAPIES

### Table 1. Human Clinical Trials on Stem Cell-Based Therapy for Wound Healing

<table>
<thead>
<tr>
<th>Model</th>
<th>Cell Type</th>
<th>Delivery Method</th>
<th>Results</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute ((n = 5)) and chronic wounds ((n = 8))</td>
<td>Autologous BM-MSCs</td>
<td>Spray cells with a mixture of fibrin and thrombin</td>
<td>Instant pain relief to acute wound patients; accelerated wound closure; reduction in wound size or complete closure by 16–20 wk</td>
<td>Falanga et al., 2007[6]</td>
</tr>
<tr>
<td>Three patients with chronic ulcer ((&gt;1\text{ yr})) unresponsive to previous therapy</td>
<td>Autologous culture-expanded BM-MSCs Hair follicle micrograft</td>
<td>Topical</td>
<td>Complete wound closure</td>
<td>Badiavas and Falanga, 2003[5]</td>
</tr>
<tr>
<td>Single patient with 12% full-thickness burn of scalp</td>
<td></td>
<td>Integra (Integra LifeSciences Corp., Plainsboro, N.J.) dermal regeneration template</td>
<td>Complete reepithelialization and hair-bearing scalp</td>
<td>Navsaria et al., 2004[7]</td>
</tr>
<tr>
<td>Full-thickness skin defects ((n = 15)) caused by burn or trauma</td>
<td>Neonatal immortalized keratinocytes Biological skin substitute (StrataGraft; Stratatech Corp., Madison, Wis.)</td>
<td>Maintained healthy wound bed suitable for autograft, comparable to cadaver allograft</td>
<td>Schurr et al., 2009[8]</td>
<td></td>
</tr>
</tbody>
</table>

BM-MSC, bone marrow-derived mesenchymal stem cells.
COMMON DENOMINATOR FOR SUCCESSFUL HEALING

Compression of the limb to eliminate edema