Optimizing Healing of Diabetic Foot Ulcers: An Updated Look at Growth Factors

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Ms. Seaman: Scientific advisor – Smith & Nephew, Inc; Promotional Speakers’ Bureau – Smith & Nephew, Inc

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Learning Objectives

• Review the physiology and pathophysiology of wound healing in diabetes
• Examine the role of growth factor therapy as an evidence-based biologic therapy for treating diabetic foot ulcers
• Translate the science of growth factor therapy into clinical relevance as an adjunct to proper wound care
• Summarize late-breaking safety data on adjunctive therapy based on PDGF to diabetic foot ulcer healing

PDGF = platelet-derived growth factor

Physiology and Pathophysiology of Wound Healing in Diabetes

The Role of Growth Factor Therapy as an Evidence-Based Biologic Therapy for Treating Diabetic Foot Ulcers

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**Acute Wound Healing vs Chronic Wound Healing**

**Acute Wound**
- Normal phases of wound healing
  - Hemostasis
  - Inflammation
  - Proliferation
  - Remodeling

**Chronic Wound**
- Repetitive trauma
  - Ischemia
  - Bacteria

**Acute Wounds**
- One-time injury
  - Bleeding/platelet activation/growth factor release
  - PMN influx ➔ secretion of pro-inflammatory cytokines ➔ bacterial killing/debridement ➔ PMNs recede ➔ macrophage/fibroblast influx ➔ inflammatory phase ends/proliferative phase begins

**Chronic Wounds**
- Repetitive trauma, ischemia, bacteria
  - Prolonged PMN influx and secretion of pro-inflammatory cytokines (TNFα, IL-1β, etc)
  - Macrophages fail to switch from pro-inflammatory phenotype to reparative phenotype
  - Increased MMP/decreased TIMP activity ➔ degradation of growth factors and target cell receptors ➔ degradation of ECM ➔ decreased cell proliferation and migration ➔ cellular senescence ➔ impaired healing

**Acute-Wound Fluid**
- High mitogenic activity
  - High levels of growth factors
  - Appropriate levels of pro-inflammatory cytokines (TNFα, IL-1β, etc)
  - Balance between MMPs and TIMPs

**Chronic-Wound Fluid**
- Low mitogenic activity
  - Decreased levels of growth factors
  - Increased levels of pro-inflammatory cytokines
  - Increased MMP/decreased TIMP levels

**Factors Interfering with DFU Healing**
- Altered microenvironment
  - Inflammation: Bacterial burden/infection, tissue necrosis
  - Tissue ischemia (PAD and/or impaired vasodilation)
  - Repetitive trauma (pressure)
  - Edema
  - Systemic conditions (eg, smoking, glycemic control, medications)

**ECM** = extracellular matrix
**MMP** = matrix metalloproteinase
**TIMP** = tissue inhibitors of metalloproteinase
**DFU** = diabetic foot ulcer
**PAD** = peripheral artery disease
**What Are Growth Factors?**

Complex proteins, released by cells, that stimulate:

- Cell migration (chemotaxis)
- Cell proliferation (mitosis)
- Angiogenesis
- Production and degradation of ECM
- Growth factor production by other cells

**PDGF Plays Key Roles in Each Phase of Wound Healing**

- Hemostasis
- Re-epithelialization
- Inflammation
- Chemokines for PMNs, monocytes, macrophages
- Proliferation
  - Chemotactic and mitogenic for fibroblasts, vascular smooth muscle cells, pericytes
  - Stimulates fibroblasts to synthesize collagen
  - Stimulates cell synthesis of angiogenic factors, VEGF and bFGF
  - Stimulates endothelial cells to form new blood vessels (angiogenesis)
  - Stimulates bone marrow-derived stem cells (progenitor progenitor cells) to wound
  - Stimulates transformation of fibroblasts to myofibroblasts
- Remodeling
  - Chemotactic, mitogenic; stimulation of fibroblasts in remodeled scar

**Growth Factors Are Key: They Mediate Many Biologic Steps in Wound Healing**

<table>
<thead>
<tr>
<th>Growth Factors</th>
<th>Cell Source</th>
<th>Biologic Actions</th>
</tr>
</thead>
<tbody>
<tr>
<td>PDGF-BB</td>
<td>Platelets, smooth muscle cells, fibroblasts, endothelial cells</td>
<td>Proliferation of fibroblasts, endothelial cells, and smooth muscle cells</td>
</tr>
<tr>
<td>TGF-β1</td>
<td>Platelets, monocytes, endothelial cells, fibroblasts, keratinocytes</td>
<td>Proliferation of fibroblasts, keratinocytes, and synthesis of ECM</td>
</tr>
<tr>
<td>EGF</td>
<td>Fibroblasts, keratinocytes, endothelial cells, platelets</td>
<td>Chemotactic and mitogenic for fibroblasts, endothelial cells, and keratinocytes</td>
</tr>
<tr>
<td>IGF-I, IGF-II</td>
<td>Fatigue, muscle cells, fibroblasts, chondrocytes, endothelial cells, keratinocytes</td>
<td>Proliferation of fibroblasts, endothelial cells, and keratinocytes</td>
</tr>
<tr>
<td>VEGF, bFGF</td>
<td>Platelets, smooth muscle cells, fibroblasts, endothelial cells, keratinocytes</td>
<td>Proangiogenic activity</td>
</tr>
</tbody>
</table>

**Becaplermin Gel**

- rhPDGF-BB in CMC topical gel
- Biologic activity similar to endogenous PDGF-BB
- The only approved prescription drug indicated for treatment of full-thickness lower-extremity diabetic neuropathic ulcers with adequate blood supply
Phase 3 Trial of Becaplermin Gel in the Treatment of DFUs

Objective
- Study the efficacy and safety of becaplermin gel

Design
- Multicenter, double-blind, placebo-controlled trial
- Healing rates including complete wound closure over a maximum duration of 20 weeks were assessed

Patient population
- 382 patients with type 1 or type 2 diabetes mellitus with at least 1 full-thickness neuropathic ulcer of the lower extremity ≥ 8 weeks’ duration
- Ulcer size 1 cm² to 40 cm² post-debridement
- TcPO₂ ≥ 30 mm Hg on affected limb

Treatment regimen
- After sharp debridement of the ulcer, patients were randomized to receive:
  - Becaplermin gel + good ulcer care
  - Placebo gel + good ulcer care

Results: Wound Closure at 20 Weeks

Compared to placebo gel, becaplermin gel significantly increased the incidence of complete wound closure by 43% (P=0.007)


Results: Wound Closure Rates

Becaplermin gel, along with good ulcer care, reduced healing time by 32%, nearly 6 weeks faster, compared with patients receiving placebo gel (86 vs 127 days, P=0.013)


Summary
- Chronic wounds, including DFUs, do not follow expected sequence of repair
- Recognize and address issues leading to impaired healing
- Growth factors are crucial in wound-healing process
- Becaplermin gel (PDGF) has been shown to speed healing in patients with DFUs

Translating the Science of Growth Factor Therapy into Clinical Relevance

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Every 30 Seconds

5-Year Mortality Rates


Healing of DFUs after 4 Weeks

- Percentage of Patients in Whom the Ulcer Healed during the 12-Week Period

- Wounds achieving >53% area reduction at week 4 have minimal chance of healing with conventional therapy

Good Ulcer Care

- Instituting a structured diabetic foot program can yield a major reduction in amputation rates and a large reduction in in-patient mortality

Good Ulcer Care: Debridement

Good Ulcer Care: Infection Control

Good Ulcer Care: Moisture Balance
Good Ulcer Care: Offloading

- Early adoption of advanced or appropriate care may be more cost-effective than traditional standard practices for decreasing the incidence of lower-extremity amputation and may speed healing


Advanced Wound Healing

- Case Study: Left Lateral Foot

  Patient description
  - 60-year-old woman with:
    - Uncontrolled type 2 diabetes mellitus (HbA1c, 12%)
    - Peripheral neuropathy
    - Peripheral artery disease
  - Left foot ulcer that she thought developed as “insect bite”
  - Fully ambulatory in postoperative shoe
  - Intermittent sharp pain in left foot

HbA1c = hemoglobin A1c

Case Study: Left Lateral Foot

Wound Presentation

- 3.2 cm x 3.2 cm x 1.7 cm
- Vascular examination showed left femoral bruit
- Non-palpable pedal pulses
- Angiogram showed:
  - 40% focal stenosis of left popliteal artery
  - Left anterior tibial artery occluded
  - Left dorsalis pedis filled via collaterals
  - Extensive plaque and diffuse narrowing in left peroneal artery and left posterior tibial artery


Wound Presentation (cont)

- Day 16: Revascularization
- Day 23: NPWT
- Day 58: Split-thickness skin graft

Day 75

Day 110: Start PDGF

After 2 Weeks of PDGF

After 4 Weeks of PDGF

After 6 Weeks of PDGF

After 8 Weeks of PDGF

After 10 Weeks of PDGF

Objectives

- To discuss Boxed Warning Label for PDGF
- To discuss animal research and the risk of cancer
- To discuss epidemiologic studies

Becaplermin Boxed Warning Label 2008

- FDA has received information regarding a study that was performed to investigate the possibility of an increased risk of cancer in patients with diabetes mellitus.
- This study was done using a health insurance plan database.
- Following the report of the study completed in 2001, an additional study was performed using a health insurance database that covered the period from January 1998 through June 2003.
- Deaths from all types of cancer combined were observed.

Becaplermin Boxed Warning Label 2008 (cont)

- Following publication of an abstract suggesting use of multiple tubes (3+) associated with cancer mortality, but not increased cancer incidence.
- Resulted in decline in use.
- Restricted-use guidance in certain institutions.
- FDA required another postmarketing study.

Becaplermin and Safety

- Long-standing theoretical concern for growth factor and cancer promotion.
  - PDGF is overexpressed by some tumor cells.
  - Some types of cancer exhibit upregulated PDGF signaling.
  - Very limited clinical evidence of any association with therapy.
  - Stimulates tumor-infiltrating fibroblasts in melanoma.
  - Activation of PDGF signaling is growth promoting in certain gliomas, sarcomas, and leukemias.

Cancer Studies: J&J Study

- Premarket follow-up of two European trials of sterile becaplermin gel vs placebo gel
- Follow-up for 20 months with cancer monitoring
  - 291 exposed → 9 cases (2.7%)
  - 201 placebo → 2 cases (1.0%)
  - Rate ratio = 2.8 (0.6-12.8); not statistically significant
- Various types of cancer; no skin cancer; no cancer deaths

J&J = Johnson & Johnson.

Solchaga LA, et al.

- TCP combination products β using rhPDGF-BB/becaplermin
- Approved in 2009 for foot and ankle fusions
- Augment
- Reported adverse events and cancers in clinical trials
- Follow-up for 20 months with cancer monitoring
- Premarketing follow-up of two European trials of sterile becaplermin gel vs placebo gel
- Various types of cancer; no skin cancer; no cancer deaths

Nonclinical Safety Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharmacokinetics rat</td>
<td>Pharmacokinetics of rhPDGF-BB in Sprague-Dawley rats following intravenous administration &lt;br&gt; Cmax: 61.4 ng/mL &lt;br&gt; T1/2: 1.5 min &lt;br&gt; CL: 17.5 mL/kg &lt;br&gt; T1/2: 1.4 min &lt;br&gt; CL: 423.3 mL/min/kg</td>
</tr>
<tr>
<td>Pharmacokinetics Dog</td>
<td>Pharmacokinetics study of male beagle dogs following single intravenous administration &lt;br&gt; Cmax: 10.0 ng/mL &lt;br&gt; T1/2: 2 min &lt;br&gt; CL: 6161.2 ng/mL</td>
</tr>
<tr>
<td>Reproduction and developmental toxicity</td>
<td>rhPDGF-BB: an intravenous injection teratology study in the rat &lt;br&gt; No maternal toxicity &lt;br&gt; No fetal toxicity</td>
</tr>
<tr>
<td>Contingency and chronic toxicity</td>
<td>No carcinogenicity &lt;br&gt; No maternal toxicity &lt;br&gt; No fetal toxicity</td>
</tr>
</tbody>
</table>

Safety of PDGF-Based Therapies

- Because of its biologic activity, altered expression of PDGF-BB has been associated with concerns of potential tumor promotion
- Emerging data appear to provide reassurance about the safety of rhPDGF-BB
  - Animal data
  - Bone grafts with rhPDGF-BB
  - DFU epidermiologic studies

Safety of PDGF-Based Therapies

- Reported adverse events and cancers in clinical trials using rhPDGF-BB/β-TCP combination products
- Augment® Bone Graft
  - Resorbable synthetic bone substitute made of pure beta-tricalcium phosphate (β-TCP) (1000-2000 µm) and rhPDGF-BB solution (0.3 mg/mL)
- rhPDGF-BB solution (0.3 mg/mL)
- Approved in 2009 for foot and ankle fusions

Reported Adverse Events and Cancers in Clinical Trials Using rhPDGF-BB/β-TCP Combination Products

<table>
<thead>
<tr>
<th>Indication</th>
<th>No. of Subjects</th>
<th>Country</th>
<th>Patients with Cancers</th>
<th>Total Cancers</th>
<th>Cancers at Any Site</th>
<th>Cancers at Specific Sites</th>
</tr>
</thead>
<tbody>
<tr>
<td>Periarticular arthritis</td>
<td>58 (23/35)</td>
<td>USA</td>
<td>0 (0%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hand/wrist fusion</td>
<td>40 (21/19)</td>
<td>Sweden</td>
<td>2 (5.0%)</td>
<td>4</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Foot and ankle arthrodesis</td>
<td>39 (21/18)</td>
<td>Canada</td>
<td>2 (5.1%)</td>
<td>3</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>137 (75/62)</td>
<td>3 (2.2%)</td>
<td>6</td>
<td>9</td>
<td>9</td>
<td>0</td>
</tr>
</tbody>
</table>

Cancer Studies: i3 Study

- Postmarketing follow-up (cohort) study
  - Followed for an average of 20 months with cases confirmed by medical charts and cancer deaths from National Death Index
  - 1622 PDGF group: 28 confirmed cancers and 9 cancer deaths
  - 2809 control group: 43 confirmed cancers and 16 cancer deaths

Cancer Studies: i3 Study (cont)

- Postmarketing follow-up (cohort) study
  - 1622 becaplermin users and 2809 nonusers in yearly propensity score matches from Ingenix (Omni360° Data Mart (1998-2003))
  - Followed for an average of 20 months with cases confirmed by medical charts and cancer deaths from National Death Index

<table>
<thead>
<tr>
<th>Beacaplermin</th>
<th>Comparators</th>
<th>Adjusted RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>Cases</td>
<td>No.</td>
</tr>
<tr>
<td>All cancers</td>
<td>26</td>
<td>10.5</td>
</tr>
<tr>
<td>NMS cancer</td>
<td>19</td>
<td>7.1</td>
</tr>
<tr>
<td>Cancer deaths</td>
<td>8</td>
<td>3.0</td>
</tr>
</tbody>
</table>

No increased risk of incident cancer or cancer death overall

VA Study: Beacaplermin and Cancer

- Study sample consisted of 6429 becaplermin users and an equal number of matched unexposed control subjects (N=12,858)
- This sample was used for evaluating the risk of cancer death

<table>
<thead>
<tr>
<th>Cancer</th>
<th>Beacaplermin Users</th>
<th>Comparators</th>
<th>Adjusted RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>Cases</td>
<td>No.</td>
<td>Cases</td>
</tr>
<tr>
<td>Any</td>
<td>9</td>
<td>1.0</td>
<td>16</td>
</tr>
<tr>
<td>3+ tubes dispensed</td>
<td>4</td>
<td>2.0</td>
<td>16</td>
</tr>
</tbody>
</table>

Risk estimate for cancer death decreased and was no longer statistically significant


Extension of i3 Study

- Continued follow-up of original study sample for cancer deaths for up to 8 years

VA Study Design

- Follow-up study of veterans in VA care from 1996-2007
  - Limited to those with foot ulcers and no prior cancer
  - Followed through 2009 (up to 11 years)
- Beacaplermin initiators compared with matched comparators
  - Random sample of other patients in VA care on initiation day, matched on survey participation, sex, age, prior amputation, treatment of diabetes mellitus, and frequency of VA and Medicare visits
- Identified in follow-up
  - Incident cancer: Confirmed in reviews of charts and pathology reports by trained nurse abstractors
  - Cancer deaths: Identified in National Death Index searches

VA Study: Incident Cancer Risks

- Multivariable Cox regression with adjustment for demographics, healthcare use, cancer screening, physical examination and laboratory tests, comorbidities, medications, other foot ulcer treatment, as well as survey data on the duration of diabetes mellitus, tobacco and alcohol use, diet, physical activity, military exposures, education, and employment

Risk estimates are close to 1.0 with narrow CIs for risk of incident skin cancer and other cancers


Per personal correspondence with Donald Miller.
No increased risk of incident cancer at any specific site

VA Study: Incident Cancer Risks

Per personal correspondence with Donald Miller.

Results: Incident Cancers Malignancies Other Than NMS Cancer

VA Study: Study Sample

No significant difference in cancer incidence between groups

VA Study: Study Sample

Per personal correspondence with Donald Miller.

Results: Cancer Deaths

VA Study: Total Sample

No significant difference in cancer incidence between groups

VA Study: Study Sample

Per personal correspondence with Donald Miller.

Results: Cancer Risks

VA Study: Total Sample

No increased risk for cancer death, overall, and at any specific site

VA Study: Study Sample

Per personal correspondence with Donald Miller.

Results: Incident Cancers NMS Cancer (Basal Cell, Squamous Cell)

VA Study: Study Sample

No significant difference in cancer incidence between groups

VA Study: Study Sample

Per personal correspondence with Donald Miller.

Results: Incident Cancers Malignancies Other Than NMS Cancer

VA Study: Study Sample

No significant difference in cancer incidence between groups

VA Study: Study Sample

Per personal correspondence with Donald Miller.

Results: Incident Cancers (Comparison)

VA Study: Study Sample

No significant difference in cancer incidence between groups

VA Study: Study Sample

Per personal correspondence with Donald Miller.

No evidence for increased risk in any prespecified subgroup or with higher becaplermin dose

VA Study: Cancer Death Risks by Dose

Per personal correspondence with Donald Miller.

No increased risk for cancer death, overall, and at any specific site

VA Study: Total Sample

No significant difference in cancer incidence between groups

VA Study: Study Sample

Per personal correspondence with Donald Miller.
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