Novel therapies for the treatment of persistent corneal epithelial defects

Bennie H. Jeng, M.D.
Associate Professor of Ophthalmology
Co-Director, Cornea Service, UCSF
Chief of Ophthalmology, SFGH
December 4, 2010

Corneal Epithelium

- Composed of non-keratinized stratified squamous epithelial cells
- Is essential to the normal functioning of the eye
- Provides a transparent and optically regular conduit for visual stimuli to pass to the retina and visual system

Disclosures

- I have no financial interests in any of the techniques or products discussed.

Corneal Epithelium

- Provides one of the first lines of biodefense for the eye
  - Connected by hemidesmosomes and gap junctions
  - Prevents infectious agents from penetrating into the eye under normal circumstances
Corneal Epithelium

- In the event that a breach in the integrity of the corneal epithelium occurs, a wound healing response occurs
- Corneal epithelium typically resurfaces an epithelial defect quickly and uneventfully

Corneal Epithelium

- In certain conditions, the epithelial defect may be slow to heal, or it may not heal at all:
  - Non-healing corneal epithelial defects
  - Persistent epithelial defects

Persistent Epithelial Defect

- Defined in numerous ways
  - When epithelial cells fail to show the expected rate of healing for the time course involved
  - Two weeks

Etiologies

- Neurotrophic states:
  - Diabetic keratopathy
  - Post-PK
  - HSV
- Limbal stem cell deficiency
- Dry eye conditions
- Exposure
Complications

- Infection
- Inflammation
- Corneal thinning
- Perforation
- Graft rejection

Therapeutic Modalities

- Medical
  - Lubrication
  - Punctal occlusion
  - Eyelid patching
  - Bandage soft contact lens
  - Discontinuation of toxic medications

- Surgical
  - Tarsorrhaphy
  - Limbal stem cell transplantation
  - Amniotic membrane graft
  - Conjunctival flaps

- Other Medical
  - Gas permeable scleral lens (PROSE)
  - Fibronectin
  - Growth factors
  - Insulin
  - Umbilical cord serum
  - Autologous serum
  - Other compounds
    - Thymosin β4
    - Nexagon®
Autologous serum eyedrops

- Many indications for its use:
  - Persistent epithelial defects
  - Dry eye syndrome
  - Neurotrophic keratopathy
  - Recurrent erosion syndrome
  - Superior limbic keratoconjunctivitis

Commonly believed that it was first described by Fox et al in 1984 to be used as a tear substitute.
- Ralph, Doane, and Dohlman described the use of a mobile ocular perfusion pump in 1975.
- Used autologous serum in alkali burn patients
Autologous serum eyedrops

- Proposed by Tsubota et al (1999) to be beneficial because of presence of growth factors and vitamins.
- Most studies from abroad.
- Used in U.S. but seldom reported.
Serum for PED

<table>
<thead>
<tr>
<th>Healed within</th>
<th>Jeng et al (n=25)</th>
<th>Tsubota et al (n=16)</th>
<th>Schrader et al (n=6)</th>
<th>Young et al (n=10)</th>
<th>Toon et al (n=15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 weeks</td>
<td>13 (52.0%)</td>
<td>7 (43.8%)</td>
<td>2 (33.3%)</td>
<td>6 (60.0%)</td>
<td>3 (20.0%)</td>
</tr>
<tr>
<td>4 weeks (cumulative)</td>
<td>17 (68.0%)</td>
<td>10 (62.5%)</td>
<td>3 (50.0%)</td>
<td>6 (60.0%)</td>
<td>8 (53.3%)</td>
</tr>
<tr>
<td>&gt;4 weeks or not healed</td>
<td>8 (32.0%)</td>
<td>6 (37.5%)</td>
<td>1 (16.7%)</td>
<td>2 (20.0%)</td>
<td>8 (53.3%)</td>
</tr>
<tr>
<td>Lost to follow-up</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>2 (20.0%)</td>
<td>0 (0.0%)</td>
</tr>
</tbody>
</table>

Defect present for mean of 97.3 days
Defects healed in 23 of 25 eyes in mean of 22.4 days
- 13 eyes (52.0%) within 2 weeks
- 17 eyes (68.0%) within 4 weeks
- 22 eyes (88.0%) within 8 weeks
- In one eye, defect healed after 126 days
- 2 eyes did not heal
No cases of serum-related complications


Serum for PED

Days to healing = 9.5 + 0.085 * (duration of defect prior to serum therapy)
r = 0.73
p < 0.001

50% autologous serum appears to be safe and efficacious in the treatment of PED
Consider a lower threshold for declaring an epithelial defect as non-healing by conventional methods
- consider the use of autologous serum earlier in the course of the disease process so as to minimize the chances of:
  - infection
  - subepithelial haze

Serum for PED

Challenges for Serum Use

- The ability to attain the production of serum in an efficient and feasible manner that satisfies governmental regulations
  - Protocol at UCSF
  - Patient inconvenience
    - Needle stick/blood draw
  - Patient cost
    - Insurance payment

Thymosin β4

- Synthetically produced copy of a naturally-occurring 43 amino acid peptide
- Found in high concentrations in the majority of tissue types, highest in:
  - Platelets
  - White blood cells
- One of a family of at least 16 highly conserved peptides (beta-thymosins)

Thymosin β4

- Wound healing and anti-inflammatory properties
- Therapeutic effect though:
  - promotion of keratinocyte and endothelial cell migration
  - increased collagen deposition
  - stimulation of angiogenesis
Thymosin β4

- Animal studies:
  - Rat full-thickness wound model:
    - Treatment with Tβ4 increased collagen deposition and angiogenesis and stimulated keratocyte migration and re-epithelialization
- Human studies:
  - Phase I: safe and well-tolerated in skin
  - Compassionate use study in the eye:
    - 4 patients with chronic neurotrophic PED


A Randomized, Double-Mask, Placebo-Controlled, Dose-Response, Phase 2 Study of the Safety and Efficacy of Thymosin Beta 4 in the Treatment of Diabetic Patients’ Corneal Wounds Resulting From Epithelial Debridement During Vitrectomy

Design

- Patients who underwent corneal epithelial debridement during diabetic vitrectomy surgery were enrolled.
- Three groups of patients (Tβ4 0.01%, 0.1%, and 0.3%) were to be enrolled sequentially in a dose-escalation fashion dependent on reaching acceptable safety results at each dose level.

Results

- Due to slow patient accrual, the study was terminated after 12 patients completed enrollment in the low dose (0.01%) group
- No SAE’s occurred in this study
No difference in time to healing ($p=0.09$)

Discussion

- Efficacy and the assessment of safety of Tβ4 may have been compromised by treatment with a subpotent drug product
- Elevated baseline HbA1c levels among the majority of patients receiving Tβ4 may have confounded efficacy results by possibly lengthening healing time compared with patients receiving placebo (post hoc investigation)

Nexagon® (NEXAGON)

- Being developed for the treatment of ocular and skin wounds
- Active ingredient is CODA001
  - Unmodified 30-mer DNA oligonucleotide molecule

Nexagon® (NEXAGON)

- Mechanism of action:
  - Modulation of gap junction communication in injured tissue to block mechanisms that impair wound healing
  - Selective inhibitor of connexin43 expression
    - Binds to mRNA that codes for connexin43
    - Down-regulates its production in cells
**Connexin43**

- One of 20 different human connexins
  - Constituent proteins of gap junctions
- Communication through connexin43 gap junction channels plays a major role in wound healing
  - Dying cells induce apoptosis in neighboring cells in direct proportion to the number and density of gap junctions within the dying cells (“bystander death”)
  - Leads to an increase in wound size (“lesion spread”)

**NEXAGON**

- Has been shown to bring about a transient down-regulation of connexin43 protein levels
  - Reduced lesion spread
  - Dramatic increase in the rate of wound closure
  - Reduce inflammation
  - Reduce the extent of granulation tissue deposition
  - Smaller, less distorted scar

**NEXAGON in Skin**

- Pre-clinical models:
  - Acceleration of initial phase of healing process by down-regulating the pathologically high levels of connexin43 seen at the edges of chronic wound models

- Used in randomized clinical trial of dermal lesions and venous stasis ulcers demonstrating:
  - Safety
  - More rapid healing of lesions
  - Complete healing of previously chronic lesions
NEXAGON in the Eye

- NEX-OCU-001:
  - Phase 1 dose-rising safety study
  - 0.1, 1.0, 3.0, and 10 µg NEXAGON
  - After PRK
  - 26 participants
  - No side effects or dose-limiting toxicities at any dose

Summary of Compassionate Use

- No safety concerns at dose administered
- 3 eyes had rapid re-epithelialization after 1 application
- 3 eyes had 2 applications: multiple applications safe and may be effective and necessary

Case 1: Cement Injury

Case 2: Firework Injury
Prospective, Phase 2, double-masked, vehicle-controlled, dose-escalation study to evaluate the efficacy and safety of Nexagon (1µg, 3µg, and 10µg) in the healing of persistent corneal epithelial defects (PED) after corneal epithelial debridement during diabetic vitrectomy surgery.

Subjects
- 72 subjects (3 years) with a PED as a result of epithelial debridement during diabetic vitrectomy surgery.

General Study Design
- 72 patients randomized in 1:3 (vehicle:drug) ratio:
  - Drug dose 1 µg: 18 patients
  - Drug dose 3 µg: 18 patients
  - Drug dose 10 µg: 18 patients
  - Vehicle only: 18 patients
- Adverse events reviewed before proceeding to next level.

Endpoints
- Primary:
  - Complete healing of the epithelial defect at Day 14 in the study eye.
Inclusion Criteria

- Have a PED:
  - “a corneal epithelial defect persisting for at least 14 days and not longer than 28 days.”
  - Not shown improvement despite conventional treatment such as tear supplements and BCL
  - Original defect resulting after epithelial debridement during diabetic vitrectomy surgery

Overall Study Timetable

<table>
<thead>
<tr>
<th>Date</th>
<th>Planned Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>January 2011</td>
<td>Earliest project start date:</td>
</tr>
<tr>
<td></td>
<td>Finalize personnel</td>
</tr>
<tr>
<td></td>
<td>Finalize MOP, IRB, IND, and 1st meeting of DSMC</td>
</tr>
<tr>
<td>December 2013</td>
<td>Meet enrollment goal of 72 patients</td>
</tr>
<tr>
<td>February 2014</td>
<td>Finish 28 day follow-ups, close out database</td>
</tr>
<tr>
<td>July 2014</td>
<td>Analyze, publish, and disseminate results</td>
</tr>
</tbody>
</table>

Conclusions

- PED are a clinical challenge
- Many treatment modalities
  - None universally successful
- Autologous serum appears to be very effective
  - Hurdles to widespread use
- Investigational products in the pipeline

Study Information / Contacts

**PI:** Bennie H. Jeng, MD
Beckman Vision Center, UCSF
(415) 206-8304
jengb@vision.ucsf.edu

**Study Coordinator:** Marcela Estrada
(415) 206-3123
estradam@sfgh.ucsf.edu

**Funding:** R01 FD003708-01

Registered on Clinicaltrials.gov