ADVANCED DRY EYE TREATMENT AND MANAGEMENT

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1

[redacted]

- Ocular Therapeutix
- Glaukos
- Horizon
- Quidel
- Eyevance
- Alcon
- Tarsus
- Thea
- Kala
- Ivantis
- Orasis
- RVL
- Oyster Point
- Dompe

2

WHY IS THE CORNEA IMPORTANT?

3

[redacted]

- Shields the eye from germs, dust, other harmful matter
- Contributes between 65-75% refracting power to the eye
- Filters out some of the most harmful UV wavelengths

4

WHAT IS DRY EYE DISEASE?

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"Dry eye is a multifactorial disease of the ocular surface characterized by a loss of homeostasis of the tear film, and accompanied by ocular symptoms, in which tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play etiological roles."

[redacted]

7

[redacted]

Normal | Pre-Clinical DED | DED | Neurotrophic | Neuropathic

8

[redacted]

- Evaporative dry eye
  - Resulting from excessive tear evaporation
  - Evaporation leading to Tear hyperosmolarity
  - Normally functioning lacrimal gland
  - Eyelid related causes
    - Meibomian gland dysfunction
    - Inadequate lid closure/blink related
- Aqueous deficient dry eye (ADDE)
  - Resulting from from decreased tear secretion
  - Hyper-evaporative state leading to tear hyperosmolarity

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NOT MUTUALLY EXCLUSIVE, IT CAN BE BOTH!

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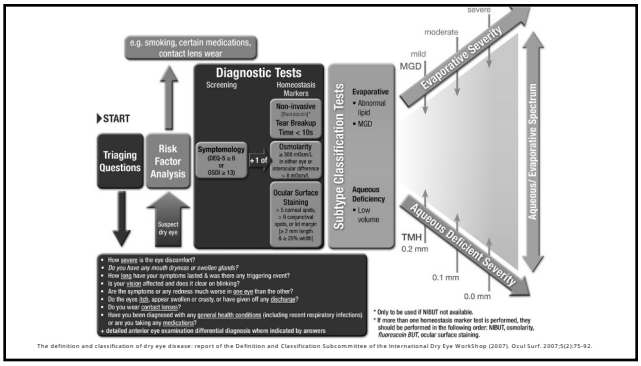

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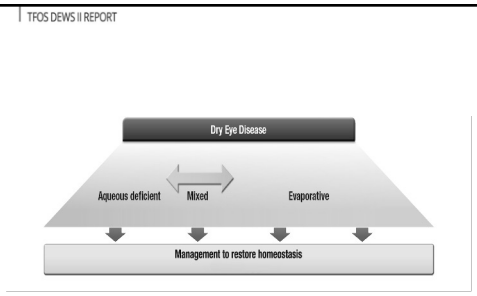

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- Environment
- Medications
- Contact lenses
- Ocular surgery

Irritants

Inflammation

- Rheumatoid Arthritis
- Lupus
- Sjogren's Syndrome
- Graft vs Host

Tear Deficiency/ Instability

- Post-menopause
- Meibomian Gland Dysfunction (MGD)

Signs and Symptoms of Ocular Surface Disease

REFERENCES: 1. Charnery L. Fluorometholone acetate: More benefit than meets the eye. *Ophthalmology Times*. 20196.
2. FLAREX [package insert]. Fort Worth, TX: Eyevance Pharmaceuticals, LLC; 2019.
3.*Leibowitz HM, Hyndiuk RA, Lindsey C, et al. Fluorometholone acetate: clinical evaluation in the treatment of external ocular inflammation. Ann Ophthalmol. 1984;16(12):1110-1115.

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- Graves Disease
- Thyroid eye disease
- Sleep apnea
- Diabetes
- Rheumatoid Arthrisis
- Sjogrens
- Lupus
- Chron's disease
- Rosacea
- Eczema
- Riley-Day syndrome
- Allergies
- Inflammatory disease

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- Ocular medications
  - Glaucoma drops
  - Preservatives
- Systemic medications
  - anti-depressents/anxiety
  - Sleeping pills
  - Pain relievers
- Parkinsons medications
- Chemotherapy
- Birth control and hormones
- Acne
- Allergy
- Diuretics
- Blood pressure medications

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IATROGENIC DRY EYE

Induced **unintentionally** by the medical treatment of a physician

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[redacted]

- Drug induced
  - Topical
  - Systemic
- Contact Lens induced
- Surgery/procedure induced
  - Ophthalmic
    - Refractive surgery
    - Cataract surgery
    - Keratoplasty (PK, LK, EK)
      - Lid surgery
      - Conjunctival surgery
  - Ophthalmic ctd
    - Glaucoma surgery
    - Vitreo-retinal surgery
    - Strabismus surgery
    - ICL
  - Procedures
    - Crosslinking
    - Botulinum toxin
    - Cosmetic procedures
- Non-ophthalmic
  - GVHD and others

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DRY EYE DIAGNOSIS

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[redacted]

- Questionnaires
  - SPEED
  - OSDI
- Multiple points of contact to start the discussion and engage the patient

20

SLIT LAMP EXAM

21

[redacted]

Look Lift Push Pull

22

[redacted]

- Any pitting?
- Any capping?
- Any lid structure abnormality?

23

[redacted]

- Cotton tip applicator
- Your clean finger
- Gland expressor
- Meibomian gland evaluator (J&J)

- Just do it!

24

[redacted]

- Grade expressibility
- Meibum quality can be described as clear, cloudy, granular or inspissated, grading as follows:
  - Grade 1: olive oil, clear
  - Grade 2: turbid, cloudy
  - Grade 3: cloudy with debris
  - Grade 4: toothpaste-like, or inspissated

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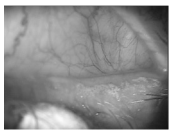
[redacted]

- Saponification
- Lid margin debris
- Lid margin biofilm
- Collarettes
- Telangiectasia
- Lid margin thickening



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Clinical Pearl: Have your patient look down to better identify demodex collarettes.

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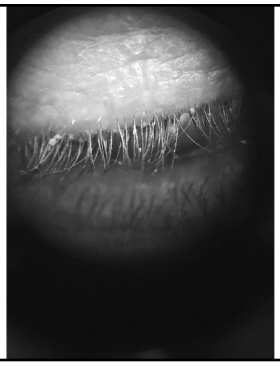

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VITAL DYE STAINING

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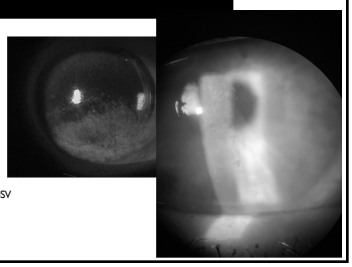
[redacted]

- Sodium Fluorescein
  - Corneal staining
    - Pattern
    - Location
    - Severity
  - Tear break up time
  - Wratten #12 filter helps
- Rose Bengal
  - Corneal irregularities to rule out HSV



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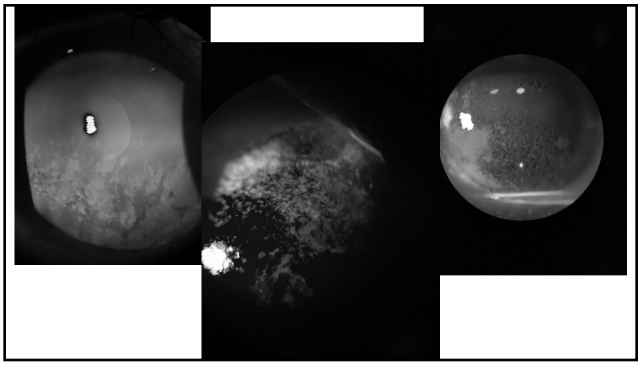

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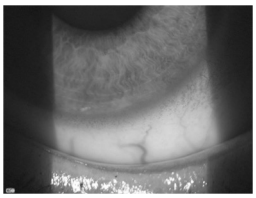
- Lissamine Green
  - Stains dead and degenerate cells
  - Lid margin for lid wiper epitheliopathy
  - Conjunctival staining



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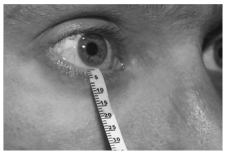
[redacted]

- Test strip placed in later 1/3 of lower eye lid
  - Measure the amount of moistened paper after 5min
- Schirmer 1 =non anesthesia
  - Measures basic and reflex tearing
- Schirmer with anesthesia
  - Measures basal tear secretion
- <5mm severe dryness
- <10mm abnormally low level of tear production
- >10mm normal



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DIAGNOSTIC TOOLS

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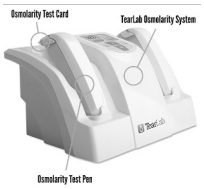
[redacted]

- Changes in osmolarity are cause by fluctuations in water content
  - Increased evaporation rate
  - Reduction in tear secretion
- Tear hyperosmolarity is a trigger for cascade of signaling events
  - Stimulates epithelial cell death
  - Leads to release of inflammatory cytokine production, cell death and loss of goblet cells



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[redacted]

- Most accepted < 308mOsm/L threshold to diagnose dry eye
  - Normal vs early stages
- > 316mOsm/L is an indicator for mild vs moderate-severe dry eye
- Variability between repeat measurements increases with severity
- Variability between eyes (Lemp et al)
  - 6.9 ±5.9mOsm/L mild
  - 11.7 ±10.9mOsm/L moderate
  - 26.5 ±22.7mOsm/L severe

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[redacted]

- Released in the hyperosmolarity cascade
  - Is an inflammatory marker
- Current option Inflammadry
  - Qualitative, but not quantitative
- Newer testing in development

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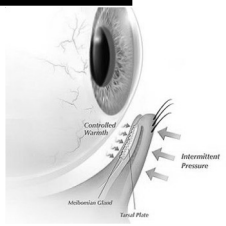
[redacted]

- Meibomian glands secrete the lipid layer of the tear film
- Meibomian gland dysfunction
  - Result of glands becoming clogged or atrophied
  - Leads to tear film disruption
    - Quicker evaporation of tears
    - Decreased tear break up time



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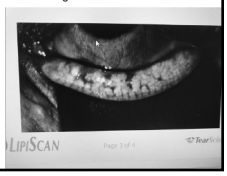
[redacted]

- Can look at meibomian gland structure with transilluminator or more accurately with meibography
- Infrared non contact viewing at the structure and health of the meibomian glands
  - Grading atrophy
    - Meiboscore
      - Grade 0 no atrophy
      - Grade 1 1-33%
      - Grade 2 34-66%
      - Grade 3 >66%



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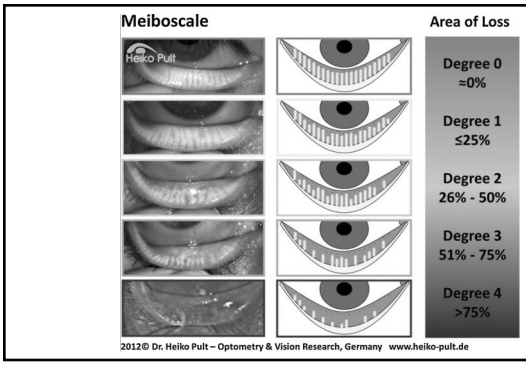

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DED/OSD TREATMENT

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TABLE 1 TFOS DEWS II Staged Management and Treatment Recommendations for DED[1]

STEP 1.

- Education regarding the condition, its management, treatment and prognosis
- Modification of local environment
- Education regarding potential dietary modifications (including oral essential fatty acid supplementation)
- Identification and potential modification/elimination of offending systemic and topical medications
- Ocular lubricants of various types (if MGD is present, then consider lipid-containing supplements)
- Lid hygiene and warm compresses of various types

STEP 2. IF ABOVE OPTIONS ARE INADEQUATE, CONSIDER:

- Non-preserved ocular lubricants to minimize preservative-induced toxicity
- Tea tree oil treatment for Demodex (if present)
- Tear conservation
  - Punctal occlusion
  - Moisture chamber spectacles/goggles
- Overnight treatments (such as ointment or moisture chamber devices)
- In-office, physical heating and expression of the meibomian glands (including device-assisted therapies, such as LipiFlow)
- In-office intense pulsed light therapy for MGD
- Prescription drugs to manage DEDd
  - Topical antibiotic or antibiotic/steroid combination applied to the lid margins for anterior blepharitis (if present)
  - Topical corticosteroid (limited-duration)
  - Topical secretagogues
  - Topical non-glucocorticoid immunomodulatory cyclosporine)
  - Topical LFA-1 antagonist drugs (such as lifitegrast)
  - Oral macrolide or tetracycline antibiotics

STEP 3. IF ABOVE OPTIONS ARE INADEQUATE, CONSIDER

- Oral secretagogues
- Autologous/allogeneic serum eye drops
- Therapeutic contact lens options
  - Soft bandage lenses
  - Rigid scleral lenses

STEP 4. IF ABOVE OPTIONS ARE INADEQUATE, CONSIDER

- Topical corticosteroid for longer duration
- Amniotic membrane grafts
- Surgical punctal occlusion
- Other surgical approaches (eg tarsorrhaphy, salivary gland transplantation)

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TABLE 3 CEDARS Treatment Options for Dysfunctional Tear Syndrome[3]

Treatment option	Aqueous tear deficiency	Blepharitis/meibomian gland dysfunction (evaporative or nonevaporative)	Goblet cell deficiency/mucin deficiency	Exposure-related DTS
First Line*	Tear supplements and lubricants (i.e. drops, gels, ointments, sprays, lubricating inserts) Nutritional Supplements Topical cyclosporine Topical lifitigrast Topical secretagogues Moisture chamber eyewear	Tear supplements and lubricants (i.e. drops, gels, ointments, sprays, lubricating inserts) Lid hygiene and lid scrubs (i.e. cleansers, warm compress, massage) Nutritional supplements Topical cyclosporine Topical lifitigrast Topical erythromycin/ bacitratcin Topical azithromycin Topical steroids or antibiotic/steroid	Tear supplements and lubricants (i.e. drops, gels, ointments, sprays, lubricating inserts) Topical cyclosporine Topical lifitigrast Vitamin A ointment -retinoic acid (compounded) Moisture chamber eyewear Topical secretagogues	Tear supplements and lubricants (i.e. drops, gels, ointments, sprays, lubricating inserts) Taping of the eyelids Moisture chamber eyewear
Second Line*	Oral secretagogues Topical hormones (compounded) Autologus serum (compounded) Albumin (compounded) Bandage contact lens/ scleral lens Topical dapsone (compounded) Topical tacrolimus (compounded) Topical N-acetylcysteine	Oral doxycycline/ tetracycline Tea tree oil Topical metronidazole ointment or drops (compounded) Topical doxycycline (compounded) Topical clindamycin (compounded) Topical dehydroepiandrosterone (compounded) Topical N-acetylcysteine	Scleral lens	Scleral lens
Procedures*	Punctal plugs Cautery occlusion Amniotic membrane	In-office thermal pulsation and or lid massage Debridement of the lid margin Intense pulsed light		Eyelid surgery (i.e. correction of lid malposition, tarsorrhaphy)

***The order of treatment in each category is left to the clinical judgement of the clinician and to the preferences of the patient**

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- Warm compresses
- Sleeping moisture goggles
- Humidifier
- Lid Hygiene
- Nutraceuticals

- Lifitegrast
- Cyclosporine
- Topical corticosteroid
- PF artificial tears
- Ophthalmic ointment

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[redacted]

- Varinicline solution nasal spray
- Activates the trigeminal parasympathetic pathway via the nose
  - Increased basal tear film production
  - Produced by 3 structures innervated
    - Lacrimal gland
    - Meibomian gland
    - Goblet cells

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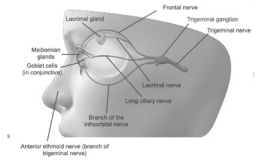
[redacted]



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[redacted]

- Punctal occlusion
  - Temporary or permanent
- Punctal cautery
- Duct probing
- IPL
- Thermal Expression
- Blepharo exfoliation

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ADVANCED DRY EYE TREATMENT

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- Rosacea and Blepharitis
  - Oral doxycycline or azithromycin
- Omega 3/6 FA
- Vitamin A ointment
- Sjogrens or more severe DES
  - Oral pilocarpine
- Autologous Serum
- Amniotic membranes
  - Cryopreserved or dry
- Amniotic membrane drops
  - Regener-Eyes

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- Steroids are ok!
  - Steroid response (less than 15%)
  - Cataracts
- Dry eye flares
  - 2-4 week use vs every day
- Topical steroids
  - Eysuvis on label FDA approved for signs and symptoms of dry eye
  - Fluoromethalone, loteprednol, prednisolone, dexamethasone
  - PF compounded dexamethasone
  - PF loteprednol ointment

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- Moderate and severe DRY EYE
- Chemical burns
- Corneal abrasions
- Corneal ulcers
- **CPT Code 65778** (placement of amniotic membrane on the ocular surface; without sutures) (0 day global period)

ICD-10	Indication	ICD-10	Indication
H16.23	Neurotrophic Keratoconjunctivitis	H18.52	Epithelial Corneal Dystrophy
H16.21	Exposure Keratoconjunctivitis	H18.83	Recurrent Erosion of the Cornea
H16.12	Filamentary Keratitis	H16.0	Corneal Ulcer
H16.14	Punctate Keratitis	B00.52	Dendritic Corneal ulcer

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Pro Tip: put the dried amniotic membrane in the contact lens well with a drop of artificial tear BEFORE applying to the eye

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[redacted]

- Vitamin A regulates the proliferation and differentiation of corneal epithelial cells,
  - Preserves conjunctival goblet cells
- Vitamin A is an essential nutrient present naturally in tear film of healthy eyes
- Vitamin A plays an important role in production of the mucin layer

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A comparison of vitamin a and cyclosporine a 0.05% eye drops for treatment of dry eye syndrome

Eun Chul Kim [1], Jun-Sub Choi, Choun-Ki Joo

Affiliations + expand

PMID: 18848318 DOI: 10.1016/j.ajo.2008.08.015

Abstract

Purpose: To compare the efficacy of vitamin A (retinyl palmitate) and cyclosporine A 0.05% eye drops in treating patients with dry eye disease.

Results: Both vitamin A eye drops and topical cyclosporine A 0.05% treatments led to significant improvement in blurred vision, tear film BUT, Schirmer I score results, and impression cytologic findings in patients with dry eye syndrome ($P < .05$) compared to the control group treated with preservative-free artificial tears alone.

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CONTACT LENSES: MORE HARM OR HELP?

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[redacted]

- Toxicity from storage solution
- Toxicity/allergies to particulates and build up
  - Poor cleaning
- Poor compliance
- Allergies to CL material
- Risk of infection

58

[redacted]

- Temporary use vs long term use
- Provides protection of cornea
  - Mechanical rubbing
  - Helps facilitate healing
- Provides pain relief
- Preference over pressure patching
  - Can instill medications
  - Can maintain use of vision
- Change out 1 x month at doctor vs self change (dailies)
- Must maintain constant use of ocular antibiotics while in place if sleeping in

59

[redacted]

- Provides constant lubrication
  - Autologous serum or Amniotic membrane drop within?
- Provides coverage and protection of cornea
  - Mechanical rubbing
  - Helps facilitate healing
- Superior optics

- Cant sleep in
- Poor fit may cause limbal rubbing
- Often not covered by insurance
- Time consuming to fit

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EPITHELIAL BASEMENT MEMBRANE DYSTROPHY

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[redacted]

- Abnormal production of epithelial basement membrane
  - Extends to epithelium
  - Causes multiple basement membrane layers
  - Trapped epithelial cells form Cogan microcysts
- Degenerative
  - Occasionally autosomal dominant
    - Transforming growth factor beta-induced gene (TGFBI) on chromosome 5q31

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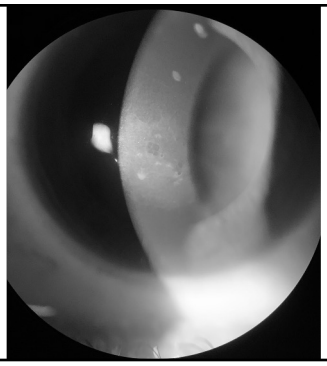

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[redacted]

- Commonly asymptomatic
- Recurrent corneal erosions
- Distortion to vision
  - Monocular shadows or diplopia
- Increased halos or glare

64

[redacted]

- Corneal staining, NaFl
  - Map like lines
  - Microcycts
  - Finger print like epithelial lesions
- Retroillumination can help to highlight these findings

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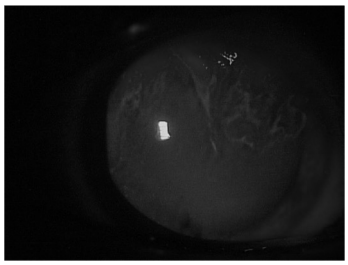

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[redacted]

- Controlling ongoing ocular surface disease
  - Decrease the inflammation and MMP9
- Sodium Chloride solution or ointment
- Freshkote?
- Surgical
  - Lamellar Keratoplasty
    - Debridement of epithelium with a diamond burr polishing or excimer laser phototherapeutic keratectomy (PTK)

67

[redacted]

- Typically triggered by an injury to the cornea
  - Most common fingernail
- Poor healing causes weak links between the hemidesmosomes in the basement membrane
  - Corneal swelling occurs during sleep 2/2 decreased oxygen exchange with the cornea
  - Swelling causes the poorly bound tissue to break and results in an epithelial defect or area of localized loose epithelium

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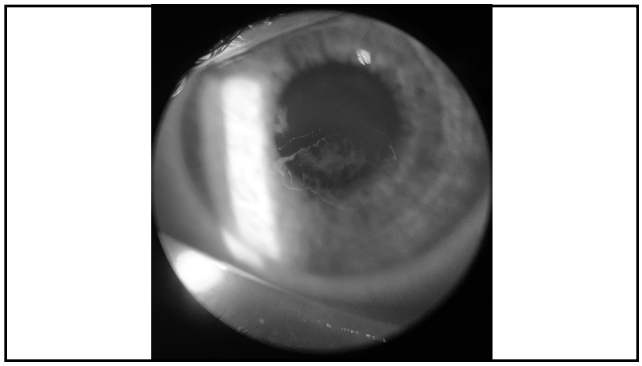

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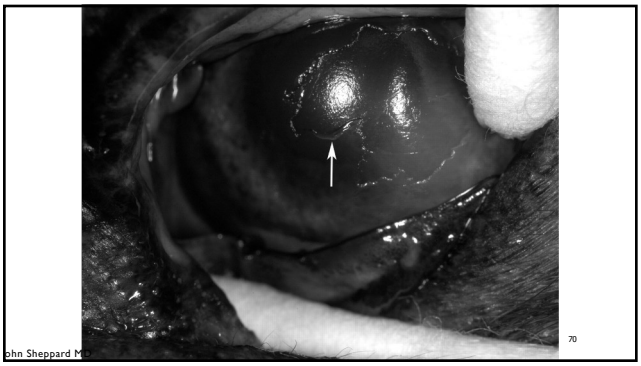

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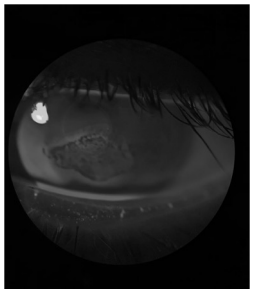
- Painful Epithelial Loss
- Dystrophy or Injury
- Early Morning Pain
- Rapid Eye Opening
- Fingernails
- Showering
- Swimming
- Low Humidity



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[redacted]

- Lubrication
- Hypertonic drops and ointment
- Pressure patching
- Topical corticosteroids
- Oral doxycycline
- Bandage soft contact lens
- Anterior stomal micropuncture
- Epithelial debridement or Lam-K
  - With diamond burr or PTK

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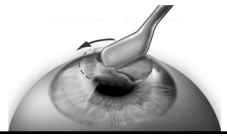
LAMELLAR KERATOPLASTY

- Corneal epithelium is removed down to Bowman's layer
- Can be performed in slit lamp or operating room using Weck-cel sponge or scarifier blade, and cleaned up with diamond burr
  - After removal surface is polished with cellulose sponge, antibiotics, and THBL placed



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[redacted]

- Indications:
  - ABMD
  - Salzmanns nodular degeneration
  - Band Keratopathy
  - RCE
  - Corneal scars

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[redacted]

- After lam K
  - Maintain THBL for 3 months
  - Oral Doxycycline
  - Topical Antibiotics
  - Topical Steroids
  - Vitamin C
- Control of ocular surface disease

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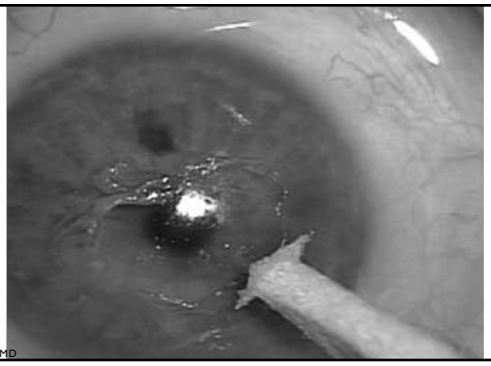

ohn Sheppard MD

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SALZMANNS NODULAR DEGENERATION

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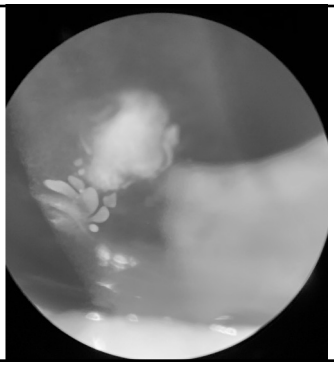

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[redacted]

- Women>Men
- History of chronic keratopathy
  - Interstitial keratitis
  - Vernal keratoconjunctivitis
  - Keratoconjunctivitis sicca
  - Phlyctenulosis
  - Trachoma

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[redacted]

- Often asymptomatic
- May affect vision if paracentral or central cornea
- Foreign body sensation

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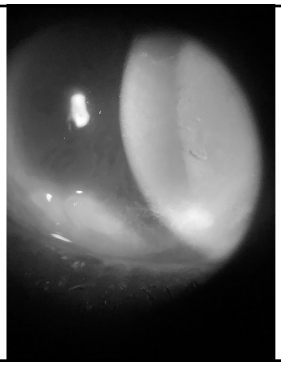

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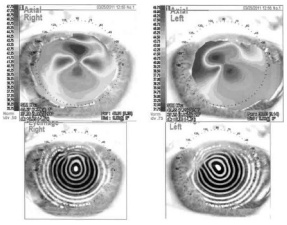
[redacted]

- Single or multiple white, grayish or bluish elevated nodules anywhere on the surface
- Longstanding nodules may have iron pigment deposits at base



82

[redacted]

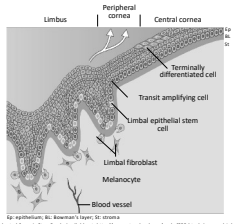
- Liberal lubrication
- Control dryness and inflammation
- Superficial keratectomy with blade or PTK
  - Topical mitomycin C
- Lamellar keratoplasty

83

NEUROTROPHIC KERATITIS

84

[redacted]



Ep: epithelium; Bc: Bowman's layer; St: stroma
Adapted from 1. Stembook. Available at: http://www.stembook.org/node/688.html. Accessed July 2018.

- Corneal integrity and function depends on a constant replenishment of epithelial cells
- Stem cells located in the limbus divide asymmetrically to produce:
  - More stem cells
  - Cells that differentiate into epithelial cells as they migrate out of the limbus
- In the healthy cornea, production of new epithelial cells is sufficient to replace cells lost at the epithelial surface
- Corneal epithelial cells and keratocytes regulate the survival, differentiation and maturation of nerve fibres by releasing neurotrophins and growth factors, such as:

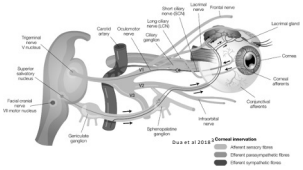
NGF	BDNF
NT-3	CNTF
NT-4	GDNF
EGF	

Mastropasqua L, et al. J Cell Pathol. 2017;232:717–24; 2. Adapted from Shaheen B, et al. Surv Ophthalmol. 2014;59:263–85.

85

[redacted]

- Healthy cornea contains no blood vessels and is extremely sensitive to pain[1]
- Corneal sensory nerves originate from the ophthalmic branch of the fifth cranial nerve[1]
- Trigeminal nerve bundles lose their perineurium and myelin sheaths where they enter the corneal stroma at the corneoscleral limbus, thus maintaining transparency of the cornea[1,2]
- The cornea also receives some sympathetic innervation from the superior cervical ganglion[2]



1. Mastropasqua L, et al. J Cell Pathol. 2017;232:717–24; 2. Müller LJ, et al. Exp Eye Res. 2003;76:521–42; 3. Dua HS, et al. Prog Retin Eye Res. 2018 doi: 10.1016/j.preteyeres.2018.04.003. [Epub ahead of print].

86

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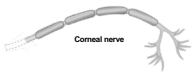


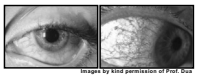
Corneal nerves react to injury at the ocular surface by registering pain and irritation and triggering **protective reflexes**, such as **tear production** and **blinking**[1]

They also release neuromediators that provide **trophic support** to corneal epithelial cells and keratocytes[1,2]

When corneal sensory nerves are damaged, these mechanisms are altered leading **to impaired corneal renewal and healing**, and reduced tear formation[1]

Neuromediators[1]

- Substance P
- Neurokinin A
- Calcitonon gene-related peptide
- Acetylcholine
- Cholecystokinin
- Galanin
- Noradrenaline
- Serotonin
- Neuropeptide Y
- Vasointestinal peptide
- Met-enkephalin
- Brain natriuretic peptide
- Vasopressin
- Neurotensin
- Beta endorphin



Images by kind permission of Prof. Dua

1. Mastropasqua L, et al. J Cell Pathol. 2017;232:717–24; 2. Müller LJ, et al. Exp Eye Res. 2003;76:521–42.

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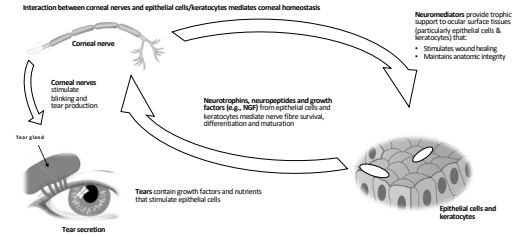
Corneal homeostasis

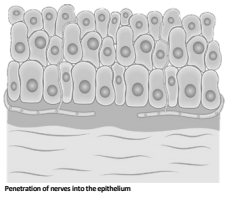


Adapted from Mastropasqua L, et al. J Cell Pathol. 2017;232:717–24.

88

[redacted]

- The loss of corneal sensory innervation via damage to the trigeminal nerve reduces release of neuromediators that provide trophic (nutritional) support to the ocular surface tissues, stimulate wound healing and maintain anatomic integrity
- Impairment of corneal sensitivity also affects tear film production and blink rate due to the reduction of trigeminal reflexes
- Impairment of trigeminal innervation leads to decreased corneal epithelium renewal and healing rate, and ultimately the development of NK



Penetration of nerves into the epithelium

1. Mastropasqua L, et al. J Cell Pathol. 2017;232:717–24; 2. Müller LJ, et al. Exp Eye Res. 2003;76:521–42.

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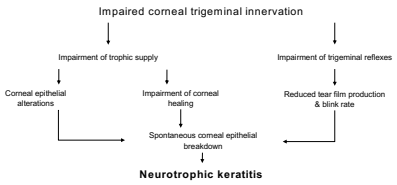
Trigeminal nerve damage leading to NK[1]



Adapted from 1. Mastropasqua L, et al. J Cell Pathol. 2017;232:717–24.

90

Etiologies Associated with NK

Ocular
- Herpes (simplex or zoster) infection
- Other infections e.g acanthamoeba
- Chemical or physical burn
- Abuse of topical anaesthetics
- Drug toxicity
- Chronic ocular surface injury or inflammation
- Ocular surgery
- Cataract surgery
- LASIK, PRK
- PK and DALK
- Collagen crosslinking for keratoconus
- Vitrectomy for retinal detachment
- Photocoagulation for diabetic retinopathy
- Postsurgical or laser treatment
- Routine laser for proliferative diabetic retinopathy
- Contact lenses
- Orbital neoplasia
- Corneal dystrophies

Central nervous system
- Neoplasm
- Aneurysms
- Stroke
- Degenerative CNS disorders
- Post-neurosurgical procedures
  - For acoustic neuroma
  - For trigeminal neuralgia
- Other surgical injury to trigeminal nerve

Systemic
- Diabetes mellitus
- Leprosy
- Vitamin A deficiency
- Amyloidosis
- Multiple sclerosis

Genetic
- Riley-Day syndrome (familial dysautonomia)
- Goldenhar-Gorlin syndrome
- Mobius syndrome
- Familial corneal hypoaesthesia

DALK=deep anterior lamellar keratoplasty; LASIK=laser in situ keratomileusis; PK=penetrating keratoplasty; PRK=photorefractive keratectomy

1. Dua HS, et al. Prog Retin Eye Res. 2018 doi: 10.1016/j.preteyeres.2018.04.003.

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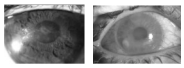
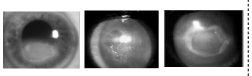
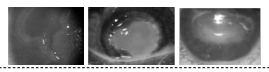
Mackie's Neurotrophic Keratitis Classification illustrates disease progression and the devastating effect on the cornea

NK is characterized by a decrease in corneal sensitivity

- Stage I
  - Corneal epithelial hyperplasia and irregularity
  - Superficial punctate keratopathy
  - Increased viscosity of tear mucus and decreased break-up time
- Stage II
  - Persistent epithelial defect – smooth and rolled edges
  - Descemet's membrane folds and stromal swelling
  - Anterior chamber inflammatory reaction with hypopyon (rare)
- Stage III
  - Corneal ulcer
  - Corneal perforation
  - Corneal stromal melting







Trial Population

92

92

Assessment of corneal sensitivity is essential to confirm NK diagnosis[1]

Ocular symptoms

History

Clinical examination and tests

↓

NK suspected

↓

Test corneal sensitivity

→ Normal → NK unlikely

→ Reduced → Further tests required

Corneal sensitivity tests:[2]

- Qualitative (touching cornea with cotton thread)
- Quantitative (corneal aesthesiometer)
- Severity of NK related to severity of corneal sensory impairment

Adapted from 1. Dua HS, et al. Prog Retin Eye Res. 2018 doi: 10.1016/j.preteyeres.2018.04.003. [Epub ahead of print]; 2. Sacchetti M & Lambiase A. Clin Ophthal 2014:8 571–6.

93

[redacted]

- Quantitative Aesthesiometer
  - Non-contact air test
  - Corneal touch
    - Cochet-Bonnet
- Non Quantitative
  - Cotton tip applicator
  - Dental floss

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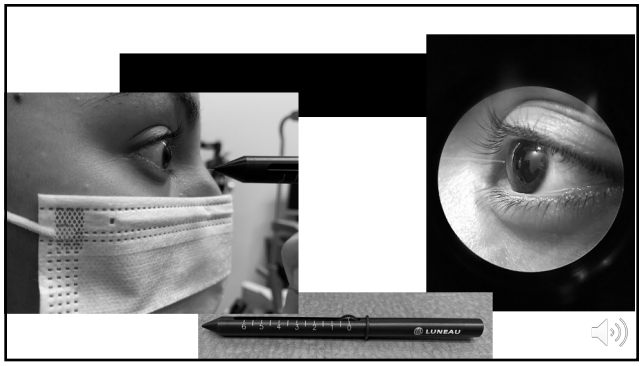

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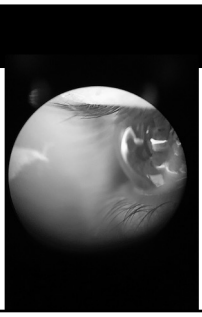

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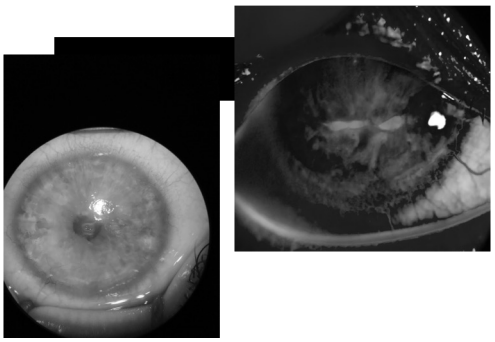
[redacted]

- 17YOA White Female
- Painful, persistent epithelial Defects OU x 2 months
- 100% Desensitized corneas OU

- Autoimmune polyendocrinopathy

97



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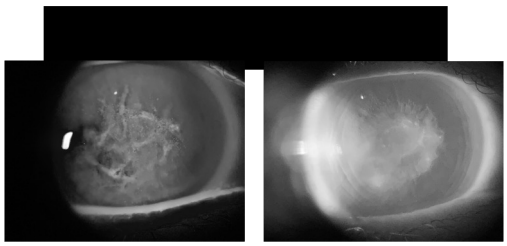
TREATMENT

99

[redacted]

- Remove any ocular medication that may be associated with toxicity
  - Preservative free options, tears and ointments
- Treat other associated ocular problems
  - LSCD
  - OSD/DED
  - Exposure keratitis

100



101

- Promote healing of epithelial defect and prevent corneal ulcer
- Monitor patient frequently
- Topical antibiotics
- Steroids sparingly
- Bandage contact lens
- Vitamin A ointment
- Amniotic membranes
- Autologous serum eye drops
  - Growth factors, neuromediators, cytokines, vitamins

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- Khokhar et al 2005
- 30 patients given either amniotic membrane or tarsorraphy and bandage CL
- 3 months
  - 10/15 patients receiving tarsorraphy or bandage CL had full epithelialization and healing
  - 11/15 patients receiving amniotic membrane tx had full epithelization and healing

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- Matsumoto et al 2004
- Complete healing of all the 14 eyes with NK treated with autologous serum drops and an increase in corneal sensitivity in 64.2% of cases
- The study demonstrated that serum harbors neurotrophins and growth factors to the ocular surface.
- More recent studies confirmed that autologous serum eye drops allowed high rates of corneal healing, and also the improvement of corneal nerve morphology with increased number, length, width, and density

104

[redacted]

- Tarsorraphy
- LSC transplant
- Cyanoacrylate glue for small perforations
- Penetrating keratoplasty
- Lamellar keratoplasty

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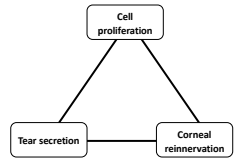
NEW TREATMENT WITH NGF

106

Endogenous nerve growth factor (NGF) and its role in NK:

Neurotrophic keratitis (NK) is a result from impaired trigeminal corneal innervation	Endogenous NGF maintains corneal integrity by three mechanisms

- ↓ Lacrimation and blink reflex
- ↓ Epithelial cell vitality, metabolism, mitosis
- ↓ Epithelial trophism and repair
- ↑ Stromal and intracellular edema
- ↓ Microvilli
- ↓ Development of the basal lamina



Nerve damage ⇨ loss of corneal sensitivity ⇨ NK

Mastropasqua et al. (2017) J Cell Physiol 232:717-24

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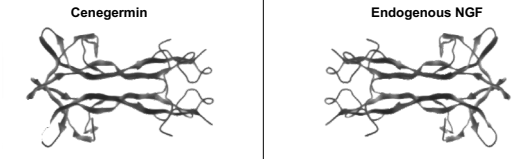
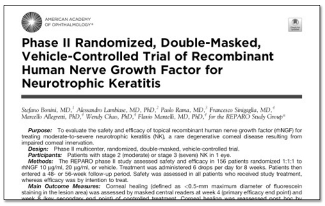
Cenegermin-bkbj Structurally Identical to Endogenous NGF in the Ocular Tissues



Voelker R. New Drug Treats Rare, Debilitating Neurotrophic Keratitis. *JAMA*. 2018;320(13):1309.

108

cenegermin-bkbj 20 mcg/ml was approved by FDA in August 2018


AMERICAN ACADEMY OF OPHTHALMOLOGY®

Phase II Randomized, Double-Masked, Vehicle-Controlled Trial of Recombinant Human Nerve Growth Factor for Neurotrophic Keratitis

*Stefano Bonini, MD,[1] Alessandro Lambiase, MD, PhD,[2] Paolo Rama, MD,[3] Francesco Sinigaglia, MD,[4] Marcello Allegretti, PhD,[4] Wendy Chao, PhD,[4] Flavio Mantelli, MD, PhD,[4] for the REPARO Study Group**

Purpose: To evaluate the safety and efficacy of topical recombinant human nerve growth factor (rhNGF) for treating moderate-to-severe neurotrophic keratitis (NK), a rare degenerative corneal disease resulting from impaired corneal innervation.
Design: Phase II multicenter, randomized, double-masked, vehicle-controlled trial.
Participants: Patients with stage 2 (moderate) or stage 3 (severe) NK in 1 eye.
Methods: The REPARO phase II study assessed safety and efficacy in 156 patients randomized 1:1:1 to rhNGF 10 µg/ml, 20 µg/ml, or vehicle. Treatment was administered 6 drops per day for 8 weeks. Patients then entered a 48- or 56-week follow-up period. Safety was assessed in all patients who received study treatment, whereas efficacy was by intention to treat.
Main Outcome Measures: Corneal healing (defined as <0.5-mm maximum diameter of fluorescein staining in the lesion area) was assessed by masked central readers at week 4 (primary efficacy end point) and

- Approved for the treatment of neurotrophic keratitis in adults and children age 2 and older
- Available for ordering since January 2019
- Developed by Dompé pharmaceuticals, available through specialty pharmacy

Bonini S, Lambiase A, Rama P *et al.* Phase II Randomized, Double-Masked, Vehicle-Controlled Trial of Recombinant Human Nerve Growth Factor for Neurotrophic Keratitis. *Ophthalmology* 2018;125:1332-1343.

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Pivotal Studies Overview

	REPARO[1] (n=156)	NGF0214[2] (n=48)
Geography	Europe	USA
Design	3 treatment arms*: vehicle, cenegermin 10 mcg/mL, cenegermin 20 mcg/mL	2 treatment arms: vehicle, cenegermin 20 mcg/mL
Course of Therapy	8 weeks	8 weeks
Duration of follow-up	48 weeks	24 weeks
Uni/bilateral disease	Unilateral	Unilateral and bilateral
Endpoints	**Complete corneal healing**† at Week 8 (based on a post-hoc analysis‡) Primary analysis was <0.5 mm maximum diameter of fluorescein staining in the lesion area at Week 4	**Complete corneal healing**† at Week 8

*The formulation that was tested in study NGF0214 included the antioxidant methionine and is the final formulation that is marketed. More than one study was conducted with the final commercial formulation. No difference in safety was seen in any of the trials.
†Defined as 0.0 mm maximum diameter of fluorescein staining in the lesion area) and no persistent staining in the rest of the cornea.
‡FDA approval was based on complete corneal healing defined as absence of staining of the corneal lesion and no persistent staining in the rest of the cornea after 8 weeks of treatment.

Please see Important Safety Information in this presentation and a Dompé representative for Full Prescribing Information

1. Bonini S, Lambiase A, Rama P et al. Phase II Randomized, Double-Masked, Vehicle-Controlled Trial of Recombinant Human Nerve Growth Factor for Neurotrophic Keratitis. *Ophthalmology*. 2018;125:1332-1343. **2.** Pflugfelder SC, Massaro-Giordano M, Perez VL et al. Topical Recombinant Human Nerve Growth Factor (Cenegermin) for Neurotrophic Keratopathy: A Multicenter Randomized Vehicle-Controlled Pivotal Trial. *Ophthalmology*. 2020;127(1):14-26.

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Trials Included a Diverse Pool of Patients

REPARO Study[1,3]	OXERVATE (n=52)	Vehicle (n=52)
Primary NK diagnosis*, no. (%)		
Stage 2 (moderate)	27 (51.9)	28 (53.8)
Stage 3 (severe)	25 (48.1)	24 (46.2)

NGF0214 Study[2,3]	OXERVATE (n=24)	Vehicle (n=24)
Primary NK diagnosis*, no. (%)		
Stage 2 (moderate)	15 (62.5)	18 (75.0)
Stage 3 (severe)	9 (37.5)	6 (25.0)

*Based on Mackie classification.

The formulation that was tested in REPARO (Study NGF0212) did not include the antioxidant methionine and is not the final formulation that is marketed as OXERVATE. Methionine is an excipient added to the commercial formulation to improve its stability. More than one study was conducted with the final commercial formulation. No difference in safety was seen in either of the trials.

Please see Important Safety Information in this presentation and a Dompé representative for Full Prescribing Information

1. Bonini S, Lambiase A, Rama P et al. Phase II Randomized, Double-Masked, Vehicle-Controlled Trial of Recombinant Human Nerve Growth Factor for Neurotrophic Keratitis. *Ophthalmology* 2018;125:1332-1343. **2.** Pflugfelder SC, Massaro-Giordano M, Perez VL et al. Topical Recombinant Human Nerve Growth Factor (Cenegermin) for Neurotrophic Keratopathy: A Multicenter Randomized Vehicle-Controlled Pivotal Trial. *Ophthalmology*. 2020;127(1):14-26. 3. Drug Approval package; OXERVATE (Cenegermin-bkbj). Accessdata.fda.gov. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/761094Orig1s000SumR.pdf. Published 2018. Accessed November 13, 2018.

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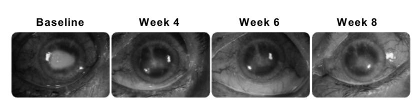
Primary Efficacy Measure: Complete Corneal Healing

Original Endpoint (EMA)[1]:
<0.5 mm lesion staining



Revised Endpoint (FDA)[2]:
0 mm staining in lesion area; no other residual staining

Last post-baseline observation carried forward; chi-squared test.

1. Data on file. NGF0212 (REPARO) CSR.
2. Data on file. NGF0214 CSR.

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CenegerminDosing and Administration

2 — Every 2 hours instill 1 drop of (cenegermin-bkbj) ophthalmic solution 0.002% in the affected eye(s)

6 — Apply 6 times daily

8 — Continue for 8 weeks

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Investigational Drug HGF

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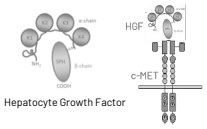
CSB-001 is 5 amino acid deleted - hepatocyte growth factor (HGF)

- A paracrine growth factor, secreted by mesenchymal cells
- Heterodimeric molecule
  - 69 kD α-chain [K1-K4 Kringle domains]
  - 34 kD β-chain
- dHGF is an isoform of full length HGF
- A single receptor – c-MET, present in cornea

Therapeutic benefits of dHGF are well suited to NK
- Epitheliotrophic – Accelerates healing
- Anti-fibrotic – Reduced scarring Improves vision outcomes
- Neurotrophic – Promotes corneal nerve regeneration
- Anti-inflammatory – Reduces nerve damage

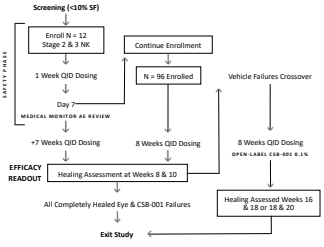


Hepatocyte Growth Factor

Nat Rev Mol Cell Biol. 2003 Dec;4(12):915-25.

115

CSB-C20-003 study enrolling stage 2 and 3 neurotrophic keratitis subjects



Design Summary
- Randomized vehicle-controlled, double-masked phase
  - CSB-001 0.1% vs CSB-001 Vehicle
  - 1:1 randomization
- Open-label phase
  - Vehicle-arm eyes not healed at Weeks 8 or 10 crossover to CSB-001 for 8 weeks
- Powered to show 30% difference between vehicle and active in achieving complete corneal healing
  - Primary EP – Complete corneal healing (yes/no) assessed by reading center
- Design supports pivotal status
- Subjects that heal in either the randomized or open-label phase rollover to 48-week durability of healing study

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116

[redacted]

- 40 YOA White Female
- Got rock salt in her OS 2 years previously in NYC when walking around outside her hotel.
- Pain and light sensitivity still present and persistent.
  - No improvement with aggressive dry eye treatment
  - Only improvement is with sun glasses and photochromatic CL

117

[redacted]

- Corneal sensitivity
  - 100% sensitivity OD; 50% sensitivity OS
- Started on topical cenegermin Q2hr x 8 weeks
  - Improvement to approximately 70% sensitivity OS

118

NEUROPATHIC CORNEAL PAIN

119

[redacted]

- Persistent ocular pain
  - Burning
  - Increased light sensitivity
  - Increased sensitivity to wind
  - Shooting pains from one or both eyes
- May be present WITH or WITHOUT ocular surface abnormalities

120

[redacted]

- Suggested that there is an initial insult to the eye causing chronic nerve abnormality
- The initial trigger may be any of the following:
  - trauma (e.g., corneal abrasion, radiation therapy)
  - chemical exposures (e.g., preservatives in topical medications, chemical burns, systemic chemotherapy)
  - infection (e.g., herpes simplex virus, herpes zoster virus)
  - eye surgery (e.g., refractive, cataract, glaucoma, and retinal surgery)
    systemic disease (e.g., autoimmune or inflammatory conditions, diabetes, fibromyalgia)
  - other neurological disease (e.g., trigeminal neuralgia, migraine)

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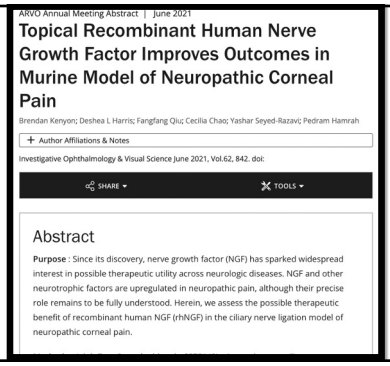

ARVO Annual Meeting Abstract | June 2021

Topical Recombinant Human Nerve Growth Factor Improves Outcomes in Murine Model of Neuropathic Corneal Pain

Brendan Kenyon; Deshea L Harris; Fangfang Qiu; Cecilia Chao; Yashar Seyed-Razavi; Pedram Hamrah

+ Author Affiliations & Notes

Investigative Ophthalmology & Visual Science June 2021, Vol.62, 842. doi:

SHARE TOOLS

Abstract

Purpose : Since its discovery, nerve growth factor (NGF) has sparked widespread interest in possible therapeutic utility across neurologic diseases. NGF and other neurotrophic factors are upregulated in neuropathic pain, although their precise role remains to be fully understood. Herein, we assess the possible therapeutic benefit of recombinant human NGF (rhNGF) in the ciliary nerve ligation model of neuropathic corneal pain.

122

[redacted]

- Adult Male mice underwent ciliary nerve ligationc to induce NCP
- Treated with 6 10uL drops/day of 0.02mg/mL rhNGF or vehicle
- Outcomes @ day 7,10,14:
  - corneal fluorescein stain
  - Cochet-Bonnet esthesiometry
  - L-metnthol for assessment of pain by paw wipe response
- Day 14 trigeminal ganglia were removed and analyzed for neurotrophic factors and cytokines

123

[redacted]

- Did not alter the corneal fluorescein staining or the corneal sensitivity in either group
- Reduction in several neurotrophic factors in the treatment group vs the vehicle only
- No increase in pro-imflammatory cytokines

- **Findings suggest that topical rhNGF treatment improves pain outcomes in our neuropathic corneal pain and warrant future studies in the clinic**
- **Topical rhNGF treatment alters expression of neurotrophic factors, but not pro-inflammatory cytokines within the TG**

124

[redacted]

- 47 YOA African American Female
- Reffered by Optometrist for corneal evlautation. Oting and constant foreign body sensation, discharge worsening. Recently began to have light sensitivity and sensation that her eye was on fire
  - THBL given with antibiotic and steroid
  - Removed yesterday and continues to have no improvement
  - OS>OD

125

[redacted]

- BCVA OD 20/20; OS 20/30
- Lids: clear OU
- Conj: white and queit with no follicles or papillae OU
- Cornea: OD 4 second TBUT, tr SPK, ABMD/ OS ABMD, 1+SPK
- AC: deep, dark and quiet OU
- Lens: Tr NS OU
- Corneal sensitivities: OD inf 2 quadrants 100% desensitized, 50% Sup/temp/ OS all 4 quadrants 100% desensitization

126

[redacted]

- PF Dexamethasone QID OU
- PF Tears PRN
- Prokera placed in office OS

127

[redacted]

- Improved Sensitivity OU by approximately 50-75%, improvement in symptoms OS
- Corneal findings: OU ABMD tr-1+SPK
- Continue Topical treatment, hold on Prokera OD

128

[redacted]

- Patient came in early 2/2 worsening of symptoms OS
- OU: ABMD, 9 second TBUT, tr-1+ SPK OU
- Time to elevate treatment. . ..
  - Cenegermin Q2hr x 8 weeks

129

[redacted]

- Cornea: No staining, 10second TBUT OU
- Improvement in symptoms of light sensitivity and pain
- Corneal Sensitivity: OD>OS 25% desensitization

130

[redacted]

- Patient was able to drive to appointment without sun glasses
- Corneal Sensitivity: 10% or less desensitization OU
- Re-treat?

131

[redacted]

- 47 YOA African American Female
- Referred by Optometrist for corneal evlautation. Oting and constant foreign body sensation, discharge worsening. Recently began to have light sensitivity and sensation that her eye was on fire
  - THBL given with antibiotic and steroid
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132

[redacted]

- BCVA OD 20/20; OS 20/30
- Lids: clear OU
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- Improved Sensitivity OU by approximately 50-75%, improvement in symptoms OS

- Corneal findings: OU ABMD tr-1+SPK

- Continue Topical treatment, hold on Prokera OD

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[redacted]

- Patient came in early 2/2 worsening of symptoms OS
- OU: ABMD, 9 second TBUT, tr-1+ SPK OU
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  - Cenegermin Q2hr x 8 weeks

136

[redacted]

- Cornea: No staining, 10second TBUT OU
- Improvement in symptoms of light sensitivity and pain
- Corneal Sensitivity: OD>OS 25% desensitization

137

[redacted]

- Patient was able to drive to appointment without sun glasses
- Corneal Sensitivity: 10% or less desensitization OU
- Re-treat?

138

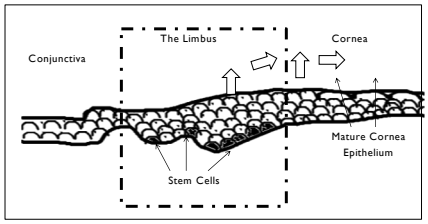
LIMBAL STEM CELL DEFICIENCY

139

[redacted]

- Regenerate the entire corneal epithelium
  - **Produces the basal cell layer of the epithelium.**
  - Then basal cells migrate toward the center of the cornea
  - As move toward center also move up to become wing cells and eventually upwards to become surface cells
  - Then shed into the tear film
- Turnover of the epithelium cells is approximately 7 days
- Prevent the conjunctival epithelial cells from migrating onto the corneal surface

140



141

[redacted]

- When limbal stem cells begin to struggle and poorly function, the epithelial cell layer and its reproduction becomes compromised
- Loss or deficiency of stem cells in the limbus which are vital for re-population of the corneal epithelium and to the barrier function of the limbus
- Once limbal stem cells are damaged the epithelium will be replaced by conjunctival goblet cells

142

[redacted]

- Acquired
  - Trauma
    - Ocular surgeries
    - Chemical injury
    - Radiation
  - Contact lens
  - Mitomycin C, glaucoma drops, preservative sensitivity
  - Thermal injury
  - Inflammatory
  - Autoimmune

143

[redacted]

- DED
  - Sjogrens Syndrome
  - Rosacea/MGD
- Allergic Eye Disease
  - Vernal keratoconjunctivitis
  - Atopic Disease
- Chronic limbitis
- Bullous Keratopathy
- Neurotrophic keratopathy from trigeminal neuralgia
- Diabetes mellitus
- Herpes simplex/Herpes Zoster

144

[redacted]

AUTOIMMUNE CAUSES

- Sjogrens Syndrome
- Stevens Johnson syndrome
- Mucous membrane pemphigoid

CONGENITAL

- Aniridia
- Autoimmune Polyglandular Syndrome
- Keratitis, Icthyosis, and Deafness Syndrome

145

[redacted]

- Decreased vision
- Photophobia
- Tearing
- Blepharospasm
- Recurrent pain

146

[redacted]

- 57YOA causcasian male
- CC: Progressive decrease in vision over the last 1 month with sharp change in the last week.
- OHx: CL overwearer (when prompted says he has had to peel them off his eyes the last few months)
- No systemic Hx or medications

147

[redacted]

- BCVA OD: 20/400; OS: HM 5Ft
- IOP App 16mmHg OD and OS
- SLE:
  - OS>OD: 3+ stippling in whorl like pattern, moderate haze with central line (conjunctivalization)

148

IS IT LSCD OR NK……..OR BOTH!

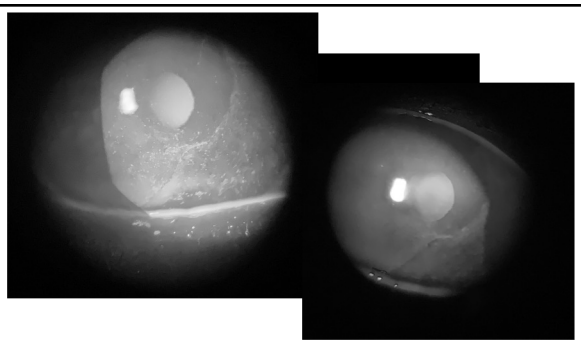
149

[redacted]

- Topical corticosteroid BID OU
- Cyclosporine BID OU
- Hylo Vit A ointment at night
- PF AT every 2 hours or more

- Next appointment No Touch

150



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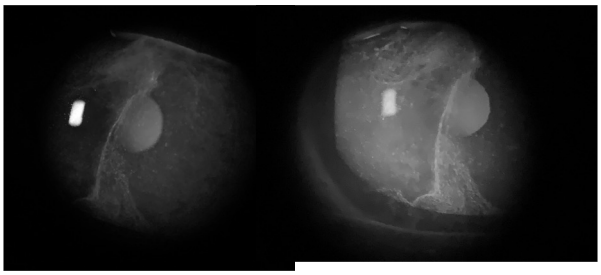


152

[redacted]

- Vision improved
  - BCVA OD 20/70; OS 20/400
- Corneal desensitization checked
  - 100% desensitized OU
- Dry AMG OS
  - Continue all other therapies except Hylo Vit A OS discontinue, start Moxifloxacin BID OS

- Returned last week; significant improvement in signs and symptoms
- BCVA OD 20/50; OS 20/100
- Dry AMG placed OS again
  - FOLLOW UP 20/40 OD and OS!!!!!!!

153

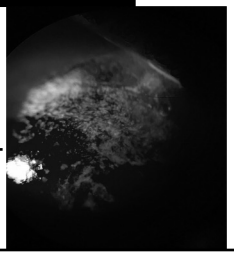
[redacted]

- Chronic DED can lead to or exacerbate LSCD
- Not mutually exclusive

154

[redacted]

- Stippled superficial punctate late flourescein staining
  - Stained cells are more elongated and pill shaped than in SPK from DED
  - Early LSCD staining more concentrated peripheral near limbal area
  - More progressed LSCD staining spread central and becomes more diffuse
    - Natural migration of epithelial cells
    - Whorl like pattern staining (**WHORL LIKE EPITHELIOPATHY**).
- Ingrowth of opaque epithelium
- Superficial neovascularization



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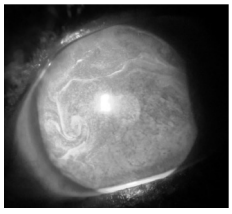


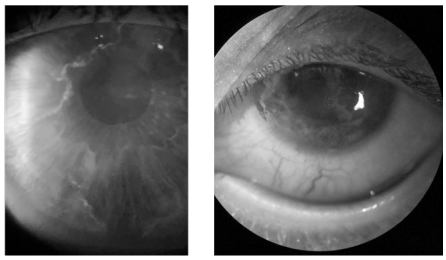
156

[redacted]

- **Conjunctivalization**
  - Corneal surface stains abnormally because the conjunctival epithelium is more permeable to the stain than true corneal epithelium
- More prone to recurrent or non-healing epithelial defects
- Stromal scarring or melting
  - Expect more pain and vision loss

157

[redacted]



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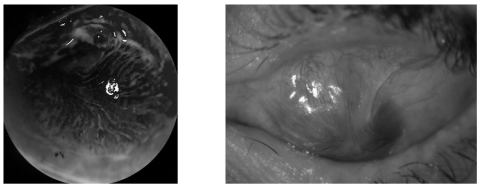
[redacted]



159

[redacted]

- Remove traumatic or toxic insults that may be the cause
  - Discontinue contact lens wear
    - Possible refit in scleral
    - Bandage CL?
  - Discontinue or switch topical medications
    - Glaucoma medications
    - Preservative sensitivity
      - BAK

160

- Treating underlying systemic causes
  - Autoimmune control
- Improve tear film and control inflammation
  - Vitamin A ointment QHS
  - Topical steroids
    - Compounded Preservative Free option
  - Topical cyclosporine
  - Preservative free AT
  - Punctal Plugs
- Amniotic membrane
  - Dehydrated vs cryopreserved
- Amniotic membrane drops
  - Can be costly and not covered by insurance currently
- Serum Tears
  - Can be costly and inconvenient
- Oxervate
  - Neurotrophic keratitis

161

- Limbal Stem Cell Transplant
  - Keratolimbal allograft (KLAL)
  - Conjunctival limbal autograft (CLAU)
  - Living related conjunctival limbal allograft (LR-CLAL)
  - Combined conjunctival limbal and KLAL (C-KLAL)
  - Cultured limbal epithelial transplantation (CLET)
  - Simple limbal epithelial transplantation (SLET)
- **TISSUES COME FROM THE PATIENT, A CADAVER OR FAMILY MEMBER**

162

Long-Term Ocular Surface Stability in Conjunctival Limbal Autograft Donor Eyes

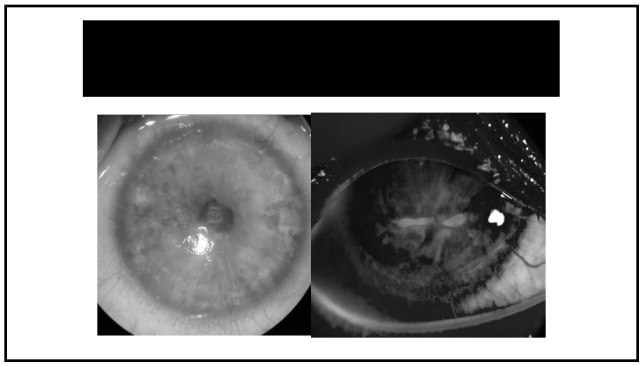
Albert Y. Cheung, MD,† Enrica Sarnicola, MD,*†‡ and Edward J. Holland, MD*†*

49 CLAU procedures performed from 2006 -2016

- 28 CLAU, 19 CLAU/KLAL, 2 CLAU/LR-CLAL
- All donor eyes had a stable ocular surface at last f/u
- Followed for mean 36.8 months
- Mean preoperative BCVA (20/24)
- Mean postoperative BCVA (20/22)

163

164



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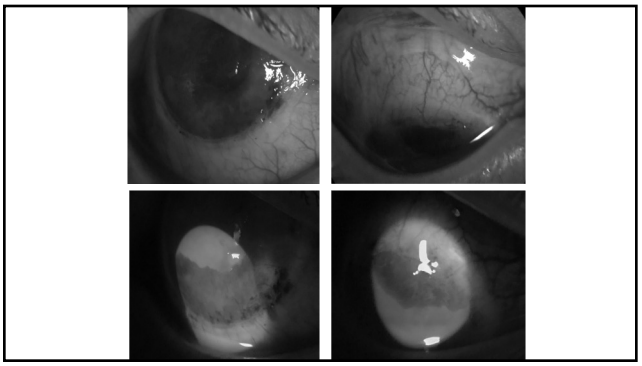

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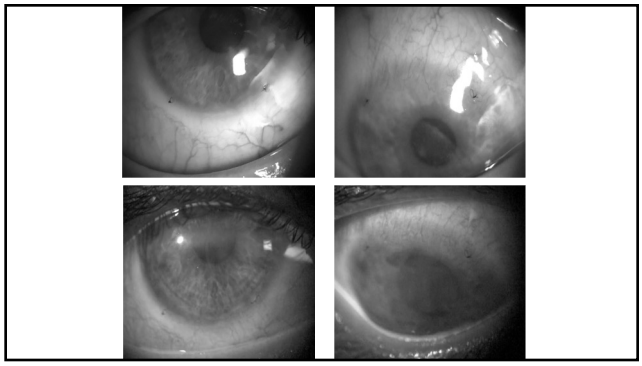

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QUESTIONS?

168

THANK YOU!

Dr.CeceliaKoetting@gmail.com

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