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1

When the SPK Won't Go Away

Neurotrophic Keratitis Update

Damon Dierker, OD, FAAO

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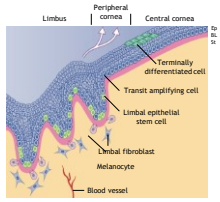
Corneal Epithelial Cells



- 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	

Adapted from 1. StemBook. Available at: http://www.stembook.org/node/588.html. Accessed July 2018.

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

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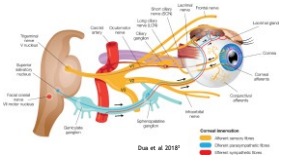
The Cornea has the Richest Innervation of All Body Tissues

- 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].

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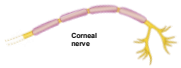
Role of Corneal Nerves



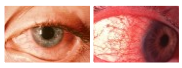
Corneal nerves react to injury at the ocular surface by registering pain and irritation and triggering **protective reflexes**, such as **tear production** and **blinking**[1]

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



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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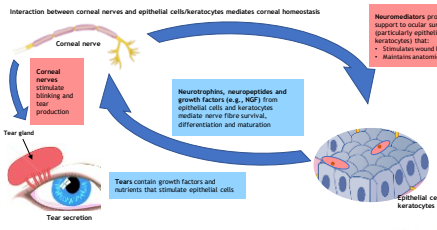
Corneal Homeostasis



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

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What is Neurotrophic Keratitis? (NK)

- Classified as rare disease, affecting ~65,000 individuals in U.S.
- Progressive, degenerative disease caused by impairment of trigeminal innervation
- Leads to corneal epithelial breakdown, compromised healing, and potentially to corneal ulceration, melting, perforation, and vision loss

Sacchetti M, Lambiase A. Diagnosis and management of neurotrophic keratitis. *Clin Ophthalmol*. 2014;8:571-579.

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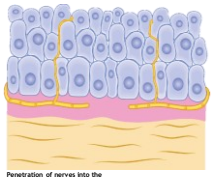
Pathophysiology of Neurotrophic Keratitis

- 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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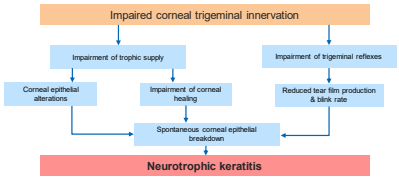
Trigeminal Nerve Damage Leads to NK



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

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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

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

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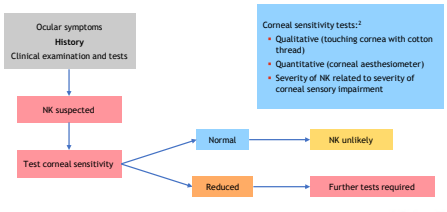
Assessment of Corneal Sensitivity is Needed to Diagnose NK



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.

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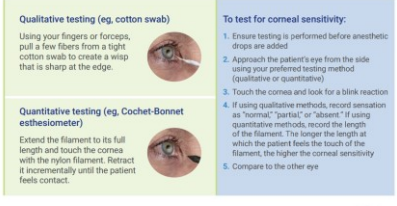
Corneal Sensitivity Testing for NK



https://cearvate.com/wp-content/uploads/2022/07/NK-Diagnosis-and-Staging-Tool-PDF.pdf

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Identifying Stage 1 NK - Exam

Predominantly Corneal Epithelial Changes

- **Corneal epithelial hyperplasia/irregularity**
- **Scattered small facets of dried epithelium**
- **Superficial punctate keratopathy (SPK)**
- **Rose Bengal staining of inferior conjunctiva**
- **Increased viscosity of tear mucus**
- **Decreased tear break-up time**
- **Superficial neovascularization/stromal scarring/dellen**

Sacchetti M and Lambiase A. Diagnosis and management of neurotrophic keratitis. Clinical Ophthalmology 2014; 8:571-579.

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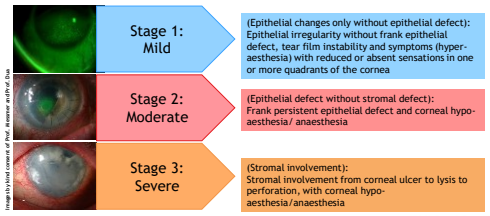
NK Classification



1. Dua HS, et al. Prog Retin Eye Res. 2018 doi: 10.1016/j.preteyeres.2018.04.003. [Epub ahead of print]. 2. 1. Semeraro F, et al. Ophthalmologica 2014;231:191-7; 2. Sacchetti M & Lambiase A. Clin Ophthal 2014:8 571-9.

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Therapies for Stage 1 NK

Traditional and Contemporary

- **Topical lubrication (preservative-free)**
- **Punctal occlusion**
- **Autologous serum/platelet-rich plasma**
- **Cytokine-derived drops**
- **Therapeutic contact lenses**
- **Self-retained amniotic membrane**
- **Recombinant human nerve growth factor (rhNGF)**

Di Zazzo, A et al. Neurotrophic keratopathy: Pros and cons of current treatments. The Ocular Surface 2019; 17(4):619-620.

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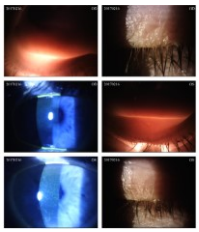
Case Example #1 - 67 yo female

- DED consult
- c/o blurry vision OU x years w/ minimal irritation
- s/p COU-IOL (monofocal)
- Type II DM for >20 years
- h/o cyclosporine/steroids/AT w/ limited success
- SPEED 12; TOT 354/320; IFD tr+/tr+
- BCVA 20/25 OU
- Decreased tear meniscus OU
- Anterior blepharitis
- Near absolute gland dropout
- Central SPK OS>OD
- Plan?



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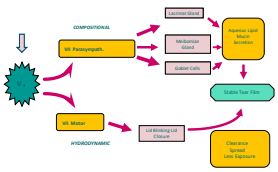
CRYOPRESERVED AM (CAM) ROLE IN DED W/ NK

- **Single placement** can help accelerate recovery of normal cornea & can **last for a long period** (> 3 months)[1,2,3]
- Promotes robust **symptom** and **sign** improvement in moderate to severe Dry Eye Disease[1,2]
- Emerging evidence that CAM promotes the **restoration of corneal nerves**[1,3]



1. **John T**, Tighe S, Sheha H. et al (2017). "Corneal Nerve Regeneration After Self-Retained Amniotic Membrane in Dry Eye Disease. Journal of Ophthalmology."
2. **McDonald et al**. (2018). "Treatment Outcomes in the Dry Eye Amniotic Membrane (DREAM) Study." Clinical Ophthalmology.
3. **Morkin, M. I. and P. Hamrah** (2018). "Efficacy of self-retained cryopreserved amniotic membrane for treatment of neuropathic corneal pain." Ocul Surf 16(1): 132-138.

28

WHAT IS THE DIFFERENCE BETWEEN CRYOPRESERVED AND DEHYDRATED AM?

Cryopreservation maintains the quantity, quality, and activity of the bio-signaling factors found in fresh amnion

Dehydration shown to compromise structural integrity of tissues and results in a lack of active bio-signaling factors

Cooke et al. *Journal of Wound Care*. **2014** 23:465-76

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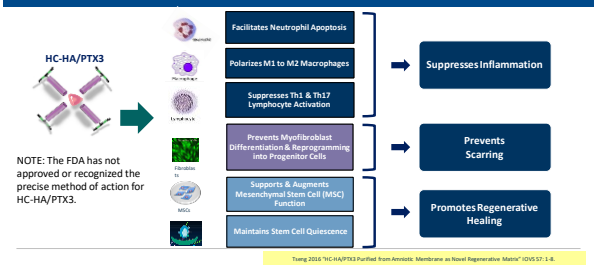
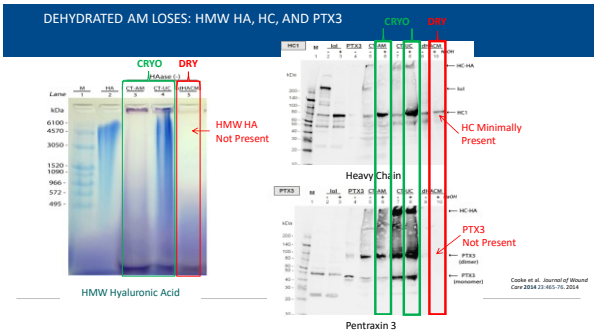
HC-HA/PTX3 ORCHESTRATES REGENERATIVE HEALING



Tseng 2016 "HC-HA/PTX3 Purified from Amniotic Membrane as Novel Regenerative Matrix" IOVS 57: 1-8.

30

DEHYDRATED AM LOSES: HMW HA, HC, AND PTX3



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Improvements in Clinical Signs and Symptoms of DED (John, et al)

Outcome Measure	Baseline	1 Month	3 Months	P-Value
Pain Score	7.1 ± 1.5	2.2 ± 1.1	1.0 ± 0.0	P ≤ 0.001
SPEED Questionnaire	21.8 ± 3.2	5.9 ± 3.1	2.8 ± 1.9	P ≤ 0.001
Corneal Staining	2.8 ± 0.4	0.8 ± 0.4	0.6 ± 0.5	P ≤ 0.001
TFBUT	8.3 ± 2.5	13.9 ± 2.2	15.0 ± 0.0	P ≤ 0.001
DEWS Score	2.9 ± 0.3	1.1 ± 0.3	1.0 ± 0.0	P ≤ 0.001

1. John T, Tighe S, Sheha H. et al (2017). "Corneal Nerve Regeneration After Self-Retained Amniotic Membrane in Dry Eye Disease. Journal of Ophthalmology."

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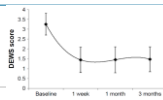
IMPROVEMENTS IN CLINICAL SIGNS AND SYMPTOMS OF DED (MCDONALD, ET AL)

Outcome Measure	Baseline	3 Months	P-Value
DEWS Score	3.3 ± 0.6	1.4 ± 0.6	P ≤ 0.001
Corneal Signs Score	3.5 ± 0.7	2.0 ± 1.0	P ≤ 0.001
Corneal Staining Score	2.6 ± 0.7	1.0 ± 1.0	P ≤ 0.001
Ocular Discomfort Score	3.0 ± 0.8	1.3 ± 0.7	P ≤ 0.001
Visual Symptoms Score	2.6 ± 0.9	1.0 ± 1.0	P ≤ 0.001



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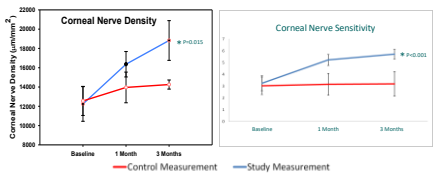
Improvements in Corneal Nerve Density & Sensitivity (John, et al)



1. John T, Tighe S, Sheha H. et al (2017). "Corneal Nerve Regeneration After Self-Retained Amniotic Membrane in Dry Eye Disease. Journal of Ophthalmology."

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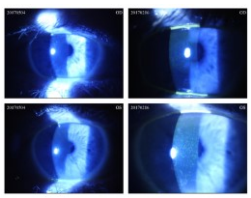
Case Example #1

- **67 yo WF**
- 3/9/17 CAM OS
- 3/13/17 CAM removal
- 4/27/17 CAM OD
- 5/1/17 CAM
- 5/4/17 Refraction and photos
  - 20/20 BCVA OU
- Plan?



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Case Example #2 – 71 yo male

- Referred by OMD for OSD eval prior to cataract surgery
- CC: blurry Va and light sensitivity OU
- Chronic DED, currently on cyclosporine and AT
- Failed lifitegrast
- h/o Sjogrens and Lupus
- SPEED 15/28
- Osmolarity 308 OD, 282 OS
- BCVA 20/40 OD, 20/70 OS
- MGE normal OU
- No lissamine green staining OU
- 3+ central SPK OD, 1+ OS
- 2+ NS/C OU
- ERM OS>OD

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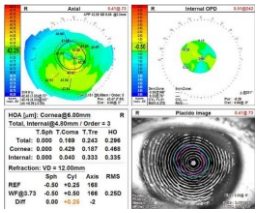
Case Example #2

- 1/13/22 – see topo OD
  - Start topical steroids
- 1/28/22
  - No improvement
  - Test corneal sensivity – reduced
  - Placed CAM OD
- 1/31/22
  - Removed CAM OD, minimal improvement
  - Opt to hold off on CAM OS
- 2/18/22
  - No change in corneal appearance



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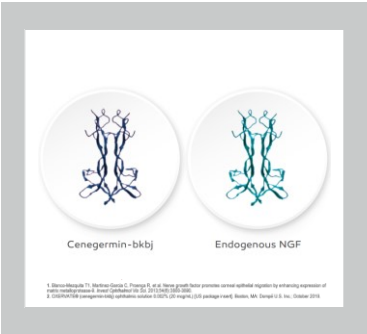
Recombinant human nerve growth factor (rhNGF)

- Cenegermin (Oxervate – Dompe)
- 1st topical biologic approved for ophthalmic use
- Structurally identical to endogenous NGF
- NGF supports corneal integrity through 3 mechanisms:
  - **Corneal innervation**
  - **Tear secretion**
  - **Epithelial cell growth**



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Oxervate – What's In The Bottle?

- Active Ingredient – cenegermin (recombinant human nerve growth factor)
- Indication – treatment of neurotrophic keratitis (all stages)
- Dosing – one drop in affected eye 6 times per day (every 2 hours) for 8 weeks
- Contraindications – none
- Warnings – remove contact lenses before using and wait 15 minutes before reinsertion
- Adverse reactions
  - Eye pain (16%)
  - Ocular hyperemia/eye inflammation/increased lacrimation (>5%)

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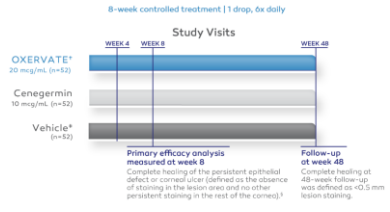
REPARO – European trial for NK (n=156)



https://oxervate.com/hcp/efficacy-safety/#study-design

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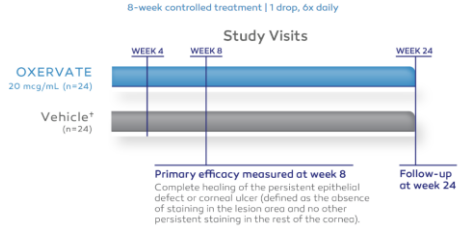
NGF0214 – US Trial for NK (n=48)



https://oxervate.com/hcp/efficacy-safety/#study-design

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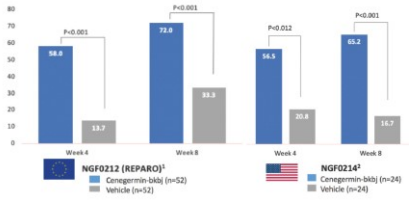
Cenegermin for NK -Results



https://oxervate.com/hcp/efficacy-safety/#study-design

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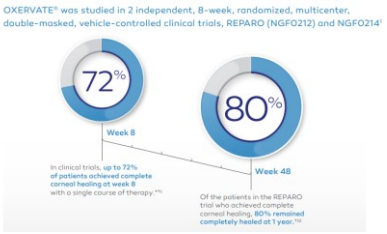
Cenegermin for NK - Results



https://oxervate.com/hcp/efficacy-safety/#study-design

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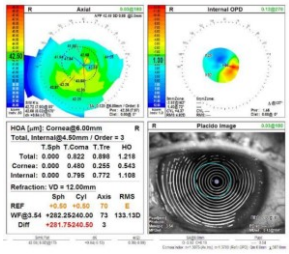
Case Example #2

- 2/18/22
  - Rx and submit paperwork for cenegermin
- 4/15/22
  - Started cenegermin 2 weeks prior, stable acuity and exam
- 5/27/22 – see topo OD
  - Finished cenegermin course
  - Mild pain during treatment
  - Still bothered by glare
  - BCVA OD 20/25, 20/50 OS
  - SPK resolved OU
  - Cataract/ERM stable OU
  - Continue cyclosporine and AT, refer back to OMD



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Stage 1 NK - Recent Publications

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Efficacy of rhNGF in Stage 1 NK – Aug 2022

- Retrospective case series included 17 patients with stage 1 NK
- 3 sites (Tufts Medical Center, University of Pennsylvania, Scripps)
- Patient inclusion criteria:
  - Diffuse punctate epitheliopathy (central staining at least grade 2 – Oxford)
  - Decreased corneal sensitivity (CB esthesiometry or cotton swab)
  - Unresponsive to previous therapy
  - Mean age 67 w/ 94% female
  - Etiology included long-standing DED (64.7%), hx of ocular surgery (35.2%), HSK (11.7%), and 82.4% were multifactorial in nature

Saricay LY, Bayraktutar BN, Lilley J, Mah FS, Massaro-Giordano M, Hamrah P. Efficacy of Recombinant Human Nerve Growth Factor in Stage 1 Neurotrophic Keratopathy. Ophthalmology. 2022 Aug 13:S0161-6420(22)00633-9

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Efficacy of rhNGF in Stage 1 NK – Results

- At baseline, prior to rhNGF treatment, mean CFS score was 4.0 +/-1.0, which significantly improved to 1.06 +/- 0.77 after 8 weeks of rhNGF therapy (p<0.001)
- At baseline, mean BCVA was 20/40 (range 20/20-20/400), which improved to 20/30 (range 20/20-20/200) (p=0.0013)
- No patients experienced vision reduction w/ rhNGF therapy
- After treatment, the mean total nerve density, main trunk nerve density, and branch nerve density increased respectively (p=0.006, p=0.013, p=0.004) compared to baseline
- 10/17 had eye pain, no one discontinued therapy

Saricay LY, Bayraktutar BN, Lilley J, Mah FS, Massaro-Giordano M, Hamrah P. Efficacy of Recombinant Human Nerve Growth Factor in Stage 1 Neurotrophic Keratopathy. Ophthalmology. 2022 Aug 13:S0161-6420(22)00633-9

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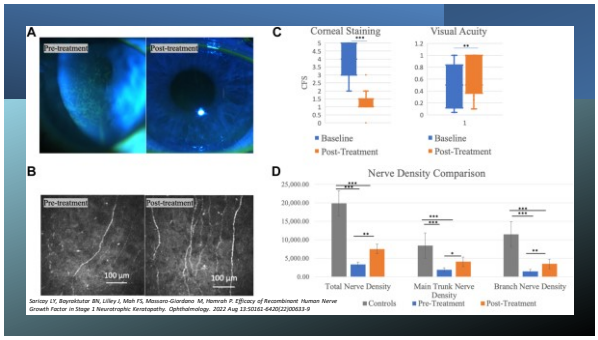

Soriano LY, Bayraktutar BN, Lilley J, Mah FS, Massaro-Giordano M, Hamrah P. Efficacy of Recombinant Human Nerve Growth Factor in Stage 1 Neurotrophic Keratopathy. Ophthalmology. 2021 Aug 13:S0161-6420(21)00633-9

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Topical human recombinant nerve growth factor for stage 1 Neurotrophic Keratitis: Retrospective case series of cenegermin treatment

Alice T. Epitropoulos [a,*], Jamie L. Weiss [b]

- Retrospective case series in patients treated w/ rhNGF vs previous standard of care treatment
- Corneal sensation was measured in the central and peripheral cornea pre/post treatment and recorded as present, reduced, or absent
- Corneal staining was assessed with a fluorescein strip and photos were obtained before and after treatment

Epitropoulos AT, Weiss JL. Topical human recombinant nerve growth factor for stage 1 Neurotrophic Keratitis: Retrospective case series of cenegermin treatment. Am J Ophthalmol Case Rep. 2022 Jul 2;27:101649.

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Topical human recombinant nerve growth factor for stage 1 Neurotrophic Keratitis: Retrospective case series of cenegermin treatment

Alice T. Epitropoulos [a,*], Jamie L. Weiss [b]

- All patients had clinically significant improvements in corneal staining
- Improvements were reported in qualitative corneal sensation
- 75% of patients had significant improvement in BCVA
- All patients reported decreased photophobia and improvement in quality of life
- Adverse events reported during treatment included eye pain, achiness, tenderness, soreness, and headache sensation, which were believed to occur due to corneal nerve regeneration

Epitropoulos AT, Weiss JL. Topical human recombinant nerve growth factor for stage 1 Neurotrophic Keratitis: Retrospective case series of cenegermin treatment. Am J Ophthalmol Case Rep. 2022 Jul 2;27:101649.

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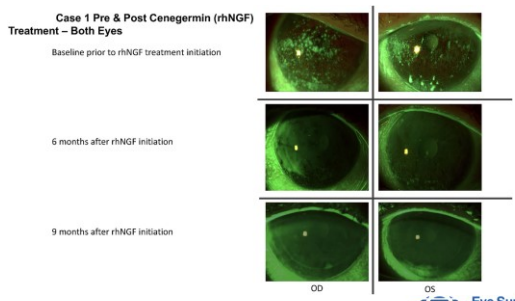

Epitropoulos AT, Weiss JL. Topical human recombinant nerve growth factor for stage 1 Neurotrophic Keratitis: Retrospective case series of cenegermin treatment. Am J Ophthalmol Case Rep. 2022 Jul 2;27:101649.

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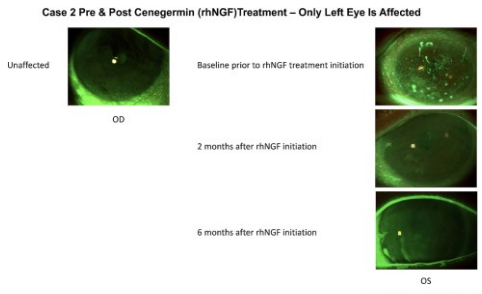

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Summary

- Stage 1 NK is commonly encountered in optometry practices but rarely diagnosed
- Corneal sensitivity testing is essential to diagnose NK
- Suspect NK in patients with SPK recalcitrant to conventional therapy
- New biologic treatment options exist for NK

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Thank You!

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