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UNDERSTANDING, DIAGNOSING, AND TREATING NEUROTROPHIC KERATITIS IN 2020

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Understanding, Diagnosing, and Treating Neurotrophic Keratitis in 2020

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CONTENT SOURCE

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ACTIVITY DESCRIPTION

Eye care providers may not understand what neurotrophic keratitis is or how it differs from other corneal diseases. In addition; eye care practitioners may be unaware of treatments in development, or the already approved treatments for neurotrophic keratitis. They also may not understand the mechanism of action of these newer treatments. This supplement features four experts in neurotrophic keratitis who review important issues related to managing patients, including the scope and causes of the disease, comorbid systemic conditions, ocular exam, and corneal sensation.

TARGET AUDIENCE

This certified CME activity is designed for anterior segment specialists, general ophthalmologists, and other eye care providers involved in the management of corneal disorders.

LEARNING OBJECTIVES

Upon completion of this activity, the participant should be able to:

- **Describe** the stages of neurotrophic keratitis and how to differentiate it from similar diseases.
- **Recognize** the various potential causes of neurotrophic keratitis and when referrals may be necessary.
- **Summarize** mechanisms of action of newer treatments and when they should be introduced into treatment regimens for neurotrophic keratitis.
- **Identify** the relationships between disease characteristics, drug, treatment frequency, visual, and anatomic outcomes.

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1. Please rate your confidence in your ability to identify and treat patients with neurotrophic keratitis (based on a scale of 1 to 5, with 1 = "Not at all confident" and 5= "Very confident").

a. 1
b. 2
c. 3
d. 4
e. 5

2. A 53-year-old woman with a diagnosis of neurotrophic keratitis presents to your office. Which of the following are reasonable options for treatment (more than one may apply)?

a. Artificial tears
b. Topical Ointment
c. Latanoprost topical drops
d. Cenegermin

3. What is the most common etiology of neurotrophic keratitis?

a. Postsurgical damage to ciliary nerves
b. Postherpetic infections
c. Diabetes mellitus
d. Corneal dystrophies

4. What is the hallmark finding of neurotrophic keratitis?

a. Punctate epithelial erosions
b. Abnormal Schirmer test
c. Abnormal corneal sensitivity testing
d. Lid laxity

5. A 72-year-old man with primary open-angle glaucoma presents with blurry vision. On exam, he has an epithelial defect with rolled edges. He has decreased corneal sensitivity. Which of the following made him at risk for this diagnosis (more than one may apply)?

a. Use of multiple topical glaucoma medications
b. Blepharitis
c. His age
d. History of glaucoma

6. Which of the following is an example of a quantitative corneal sensitivity test?

a. Cochet-Bonnet esthesiometer
b. Cotton swab
c. Dental floss

7. To which stage of neurotrophic keratitis does the following description apply: "Persistent epithelial defect with smooth rolled edges; stromal opacity"?

a. Stage 1
b. Stage 2
c. Stage 3

8. Which of the following is an appropriate therapy for stage 3 neurotrophic keratitis?

a. Recombinant human nerve growth factor
b. Preservative free artificial tears
c. Punctal occlusion
d. Hydrogel contact lens

9. A 67-year-old female with a nonhealing corneal epithelial defect presents to your office. She has a history of bilateral LASIK and herpes zoster ophthalmicus. She has previously attempted amniotic membrane allograft, bandage contact lens, and autologous serum tears for treatment, yet her persistent epithelial defect remains. Which of the following is an appropriate treatment for this patient?

a. Start cenegermin 20 mcg/mL
b. Punctal occlusion
c. Preservative free artificial tears

10. In the cenegermin clinical trials, what was the most common adverse reaction?

a. Eye irritation
b. Red eye
c. Eye pain following instillation

11. A 40-year-old male with a history of diabetes and bilateral LASIK OU presents with diffuse punctate epitheliopathy, decreased tear break-up time, and stromal haze. Which of the following is an appropriate treatment for this patient?

a. Scleral lens
b. Preservative free artificial tears
c. Amniotic membrane
d. Tarsorrhaphy

Understanding, Diagnosing, and Treating Neurotrophic Keratitis in 2020

BREAKING THE CYCLE OF RECURRENCE

Novel recombinant human nerve growth factor heals persistent epithelial defects.

BY FRANCIS S. MAH, MD

Neurotrophic keratitis is a rare, degenerative disease of the cornea caused by damage to the trigeminal nerve, which leads to loss of corneal sensitivity, corneal epithelial breakdown, impaired healing, and, ultimately, corneal ulceration, stromal melting and perforation.[1] The hallmark of this disease is decreased corneal sensation and decreased or no pain.

Our expert faculty of cornea specialists explores the various aspects of this disease that are problematic for us on a day-to-day basis. They share cases, diagnostic pearls, and insights on the most effective therapies, including the first and only medication approved specifically for the treatment of neurotrophic keratitis.

"The essential component of neurotrophic keratitis is loss of corneal sensation."

—FRANCIS S. MAH, MD

ABOUT NEUROTROPHIC KERATITIS

Prevalence. Neurotrophic keratitis is considered a rare or orphan disease in that it affects fewer than five individuals in 10,000.[2] While the prevalence of the disease is difficult to determine, it is estimated that there are about 1.6 or fewer cases per 10,000.[3] Our best data are extrapolated from the most common conditions associated with neurotrophic keratitis, ie:

- 12.8% of patients with herpes zoster keratitis develop neurotrophic keratitis.
- 6% of patients with herpes simplex keratitis develop neurotrophic keratitis.
- 2.8% of patients with postsurgical nerve damage develop neurotrophic keratitis.

Based on these data, there are probably fewer than 65,000 cases in the United States.[4]

Pathophysiology. The cornea is among the most sensitive and densely innervated tissues in the human body.[5,6] Corneal innervation is essential as the corneal epithelial cells act in a mutually supportive relationship with corneal nerves.[2,3,5,6] The corneal nerves maintain corneal integrity to perform protective functions, such as blinking and tearing. They also provide trophic support with various different neuropeptides that promote epithelial cell proliferation, migration, and adhesion. Epithelial cells also improve homeostasis by providing some neurotrophic factors, such as neuronal extension and survival for the corneal nerves. Corneal nerve damage leads to loss of corneal sensation, epithelial breakdown, and poor healing, because the protective functions and the trophic supports have been lost.[2,3,5,6] That affects the epithelial cells, which then lose that feedback to the corneal nerves.

Etiologies. There are several categories of etiologies associated with neurotrophic keratitis. Overall, herpes simplex virus and herpes zoster virus are the leading causes of neurotrophic keratitis.[2,7] Additional causes include trauma to the ciliary nerves by laser treatment, abuse of topical anesthetic drops, and long-term contact lens wear.[7] Diabetes tops the list of systemic diseases associated with neurotrophic keratitis. Fifth-nerve palsy, which may be iatrogenically induced by ocular surgeries, may also lead to neurotrophic keratitis.

Comorbidities. Chronic comorbidities may confound the diagnosis and possibly worsen the prognosis for neurotrophic keratitis, thus underscoring the need for a thorough diagnostic workup and confirmatory testing. Comorbidities include dry eyes, blepharitis, exposure keratitis, topical drug toxicity, mild chemical injuries, contact lens-related disorders, and limbal stem cell deficiency.[4]

The essential component of neurotrophic keratitis is loss of corneal sensation. A differential diagnosis should rule out neuropathic pain, which is characterized by pain without staining and pain in response to minimal or no stimulus.

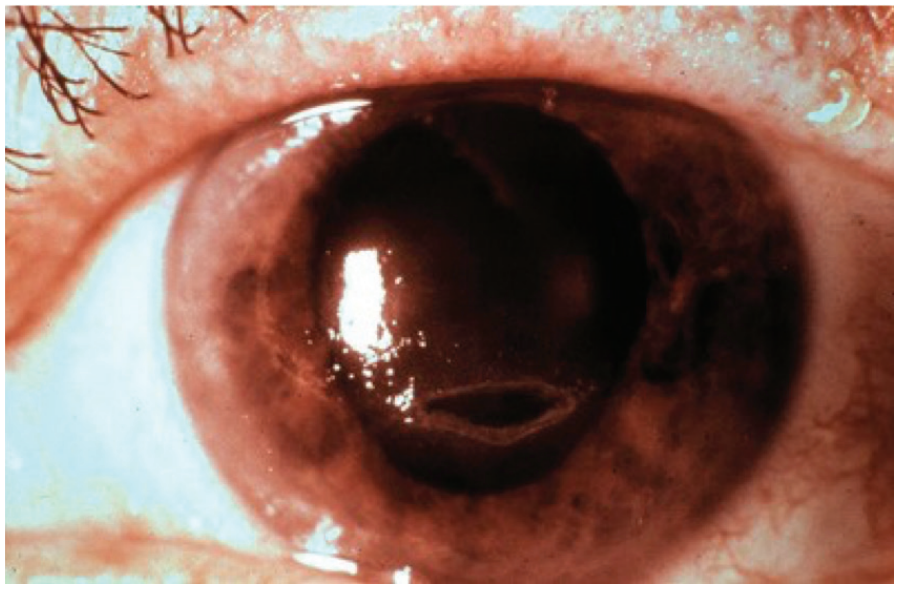

Figure 1. Note the classic, boat-shaped epithelial defect.

Treatment Progress

Healed within 2 weeks using ointment qid OD

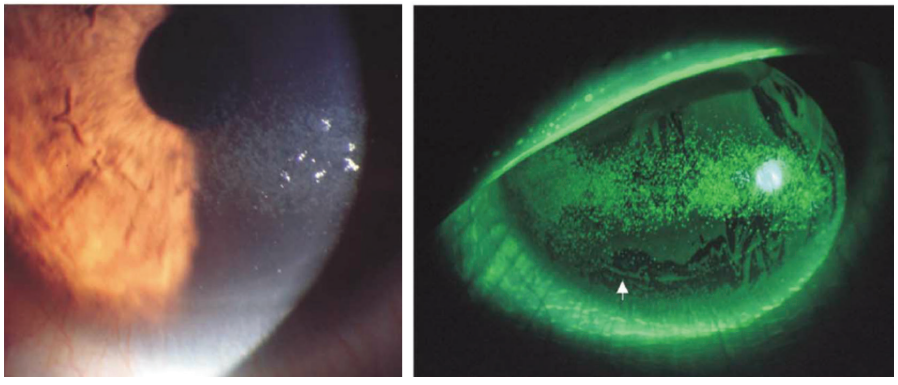

Figure 2. While the epithelial defect healed, the corneal surface is not completely healthy.

CASE: TRIGEMINAL NEURALGIA AND LASIK-INDUCED NEUROTROPHIC KERATITIS

A 53-year-old woman presents with a long-standing history of painful trigeminal neuralgia for which she has seen numerous specialists. In 2017, she underwent uncomplicated bilateral LASIK surgery, and 2 months later, she was diagnosed with right-sided trigeminal neuralgia. A rhizotomy of the ganglion did not relieve the trigeminal neuralgia pain, and, adding insult to injury, it caused right-sided facial and eye anesthesia.

This case is very close to me, because the patient works in our billing office, and I was hearing about her issues daily. The patient was seeing the neuro-ophthalmologist in our group, primarily because of the trigeminal neuralgia and the facial and eye numbness, but she also reported decreased central vision, which became hazy as the day progressed. She had no ocular pain.

The patient was using artificial tears throughout the day, which helped her vision for brief periods. She reported that her vision became so blurry later in the day that she would cover her right eye because it was bothering her that she couldn't see with both eyes. The neuro-ophthalmologist tested the patient's corneal sensitivity and found complete corneal anesthesia. The patient was referred to me for treatment of a large central corneal abrasion on the right eye.

INITIAL FINDINGS, EARLY TREATMENT

When I first saw my patient, she was using ciprofloxacin 3 or 4 times a day, as prescribed by the neuro-ophthalmologist. Her visual acuity was 20/40 in the right eye (no improvement with pinhole) and 20/40 in her unaffected left eye (20/20 with pinhole). Her right eye had a classic boat-shaped epithelial defect with graying edges (Figure 1).

I prescribed erythromycin ointment four times a day, and the abrasion healed within 2 weeks. Figure 2 shows staining across the central cornea, and the LASIK flap is visible. The epithelial defect healed, but the corneal surface is not completely healthy.

The patient did not like using the ointment, because it blurred her vision. As soon the epithelial defect healed, she wanted to reduce or stop the ointment and use only artificial tears. During the next 12 months, every time the patient stopped using the ointment, another epithelial defect would form. She would come in, not because of pain, but because her vision was decreased. This happened four times during the year following the first time I saw her.

We also tried various other therapies, including self-retained amniotic membrane and a scleral contact lens, which the patient couldn't tolerate, and we discussed a tarsorrhaphy. I warned the patient about the risk of ulceration, scarring, and infection from a persistent epithelial defect.

Impaired corneal trigeminal innervation triggers a cascade of responses that lead to neurotrophic keratitis.[1] Impairment of the trophic supply causes corneal epithelial alterations and impairment of corneal healing, while impairment of the trigeminal reflexes causes reduced tear production and blink rates. These responses can lead to spontaneous corneal epithelial breakdowns like my patient was experiencing as soon as she stopped any of the therapies that healed the epithelial defect.

The patient underwent tarsorrhaphy, which she absolutely hated because of the way it looked. Every day, she would ask if she could have it reversed.

NOVEL THERAPY TARGETS NEUROTROPHIC KERATITIS

In early 2019, cenegermin-bkbj ophthalmic solution 0.002%, a novel recombinant human nerve growth factor, became available in the United States for the treatment of neurotrophic keratitis. I discussed this therapy with my patient, and she agreed to try it.

In late January, I prescribed cenegermin-bkbj, and the patient received the medication in mid February. The day after she picked up the medication, she made an appointment with our oculoplastic surgeon to have the tarsorrhaphy reversed.

After an 8-week course of six drops a day, the epithelial defect was completely healed. One year later, the cornea remains healed, and the patient is using only artificial tears. The patient's visual acuity—which was the only indicator that the epithelium was breaking down—has remained stable at 20/25. ■

1. Mastropasqua L, Massaro-Giordano G, Nubile M, et al. Understanding the pathogenesis of neurotrophic keratitis: the role of corneal nerves. *J Cell Physiol.* 2017;232(4):717-724.
2. Dua HS, Said DG, Messmer EM, et al. Neurotrophic keratopathy. *Prog Retin Eye Res.* 2018;66:107-131.
3. Saad S, Abdelmassih Y, Saad R, et al. Neurotrophic keratitis: frequency, etiologies, clinical management and outcomes. *Ocular Surf.* 2020;18(2):231-236.
4. Sacchetti M, Lambiase A. Diagnosis and management of neurotrophic keratitis. *Clin Ophthalmol.* 2014;8:571-579.
5. Sheha H, Tighe S, Hashem O, et al. Update on cenegermin eye drops in the treatment of neurotrophic keratitis. *Clin Ophthalmol.* 2019;13:1973-1980.
6. Versura P, Giannaccare G, Pellegrini M, et al. Neurotrophic keratitis: current challenges and future prospects. *Eye Brain.* 2018;10:37-45.
7. Medscape. Neurotrophic keratitis. https://emedicine.medscape.com/article/1194889-overview. Accessed July 13, 2020.

DIAGNOSTIC CLUES

Thorough history-taking and confirmatory testing reveal neurotrophic keratitis.

BY KAROLINNE MAIA ROCHA, MD, PHD

A 75-year-old man was referred to me with a history of lattice dystrophy and recurrent epithelial defects with reduced corneal sensitivity in the right eye. He underwent two penetrating keratoplasties in that eye 15 years ago. One year after the first corneal transplantation, he developed cold sores along with dendritic epithelial keratitis in the right eye. He has been taking valacyclovir for many years. The patient has had cataract extraction and IOL implantation in both eyes, and he has glaucoma. When I saw him for the first time, he was using loteprednol in his right eye and brimonidine and dorzolamide/timolol in both eyes.

The patient's distance-corrected visual acuity was 20/150 in the right eye and 20/40 in the left eye. Intraocular pressures were within normal limits. On slit lamp examination, stromal haze was visible centrally. I also noted recurrence of the lattice dystrophy at the graft-host junction in the periphery, extending centrally. The corneal surface was irregular with a 4.2 mm x 4.6 mm central ulcer with smooth, rolled edges (Figure 1). I diagnosed stage 3 neurotrophic keratitis.

DIAGNOSTIC CONSIDERATIONS

Patients with neurotrophic keratitis have decreased corneal sensation with mild or no pain, and corneal epithelium irregularities with or without epithelial defects. Stromal involvement is usually oval shaped with smooth, rolled edges. Corneal ulcers, melting, and perforation may occur.

This patient had several risk factors for neurotrophic keratitis: a history of herpetic keratitis, ocular surgery, long-term contact lens wear, and chronic use of topical medications. He had been using dorzolamide, timolol, brimonidine, and steroids for a long time in the setting of the recurrent lattice dystrophy.

A thorough clinical history is crucial to confirm a diagnosis of neurotrophic keratitis. Patients should be asked about infectious diseases, trauma, prior surgeries, systemic or chronic diseases, chemical burns, medications, and congenital acquired corneal disorders. Corneal sensitivity testing is a must and should be followed by a comprehensive dilated eye examination (*See Panel Discussion on Corneal Sensitivity*). Corneal staining is important, as is a Schirmer tear test. Corneal cultures should be taken to rule out secondary infection. In vivo confocal microscopy may reveal affected corneal sub-basal nerves, and the patient should be evaluated for systemic disorders.

Confocal microscopy is a dynamic test, and in this case, it was somewhat difficult to locate the sub-basal nerves, but they were definitely reduced in this patient (Figure 2).

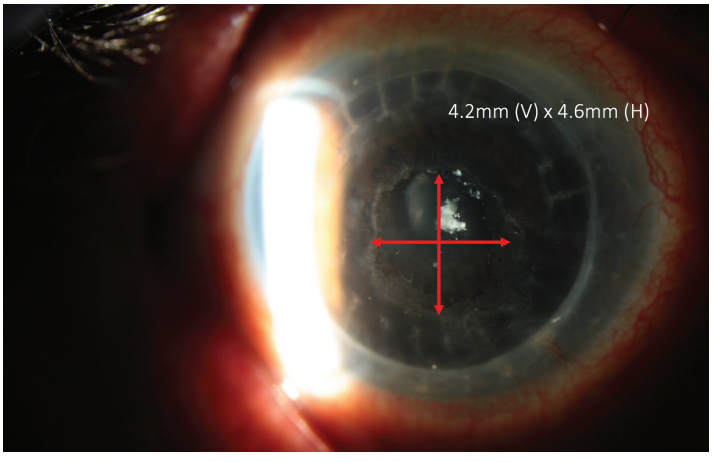

Figure 1. The patient presented with lattice dystrophy at the graft-host junction and an irregular corneal surface with a central ulcer.

SUCCESSFUL THERAPY WITH CENEGERMIN-BKBJ

This patient had been suffering for years with persistent epithelial defects and had undergone numerous treatments, including a bandage contact lens plus amniotic membrane, serum tears, topical steroids, and tarsorrhaphy.

I prescribed the novel recombinant human nerve growth factor cenegermin-bkbj six times a day for 8 weeks. By week 4, the ulcer was much improved, and at the end of the 8 weeks, complete corneal healing was achieved (Figure 3).

The patient's visual acuity was 20/50 in the right eye, and the corneal haze was definitely improved. Figure 4 shows the confocal microscopy after treatment with cenegermin-bkbj. Six months after completing the 8-week course of cenegermin-bkbj therapy, the patient's cornea remained healed.

PANEL DISCUSSION: PRACTICAL GUIDE TO CORNEAL SENSITIVITY TESTING

Karolinne Maia Rocha, MD, PhD: Reduced or absent corneal sensation is a key indicator of neurotrophic keratitis, which is the reason why we stress when including corneal sensitivity testing in your workup.

Marjan Farid, MD: Corneal sensitivity testing seems to have fallen off of our algorithm, but it's definitely making a comeback. As a cornea specialist, I believe it is essential.

Stephen C. Pflugfelder, MD: This is a key test for any patient who has severe epitheliopathy or a corneal epithelial defect, when there's a possibility of a neurotrophic component.

Dr. Rocha: A corneal sensitivity test can be qualitative, using a cotton swab, dental floss, or a corner of a tissue, or quantitative, using an esthesiometer.

Dr. Farid, how have you incorporated this test into your practice and what method do you use?

Dr. Farid: Importantly, we train our technicians to not instill proparacaine in the eyes of patients in whom we suspect neurotrophic keratitis. For the test, I use a wisp of cotton from a cotton-tipped swab. I test the unaffected cornea first and look for the normal response. Then I tested the diseased cornea to determine qualitatively the difference or decline in sensation. I record the result as normal, reduced, or no sensitivity.

Dr. Pflugfelder: I also use that technique. It's a practical way to test corneal sensitivity, and it's a test we can perform just about anywhere.

Some clinicians are fortunate to have a handheld esthesiometer to quantitatively or semi-quantitatively check corneal sensitivity. There is a learning curve, however, and sometimes, I find the responses are somewhat equivocal, because the patient can see my hand approaching with the device.

Dr. Rocha: The Cochet-Bonnet esthesiometer, which is often used in basic research and some clinical trials, has a retractable nylon monofilament. To use this device, you extend the monofilament to its full length of 6.0 cm and then retract it incrementally in 0.5-cm steps until the patient can feel it. You repeat these steps in each quadrant and record the length. The shorter the length, the less the sensation. Then you test the fellow eye for comparison.

In the Figure, I am testing a patient whom I saw just a few weeks ago. (Note her mask and my gloved hand, as we are observing COVID-19 precautions.) The patient has diabetes and has had LASIK surgery. She presented with diffuse staining, irregular epithelium, and reduced corneal sensitivity. She had severe epitheliopathy, but she did not have an ulcer or an epithelial defect. This is stage 1 neurotrophic keratitis.

When assessing corneal sensitivity, keep the following in mind:

- Sensitivity is greatest in the central cornea.
- The cornea is more sensitive in the temporal limbus than the inferior limbus.
- Sensitivity decreases rapidly as distance from the limbus increases.
- Sensitivity diminishes with increasing age.

Figure. An esthesiometer enables us to test corneal sensitivity quantitatively.

- In elderly patients, the cornea is more sensitive in the periphery.
- Iris color does not affect corneal sensitivity.
- Reduced corneal sensitivity has been reported in patients with type 1 and type 2 diabetes.[1,2]

1. Faulkner WJ, Varley GA. Corneal diagnostic techniques. In: Krachmer JH, Mannis MJ, Holland EJ, eds. *Cornea: Fundamentals of Corneal and External Disease.* 2nd ed. Vol. 1 Philadelphia: Elsevier/Mosby; 2005:229–235.
2. External Disease and Cornea, Section 8. Basic and Clinical Science Course, American Academy of Ophthalmology, 2010.

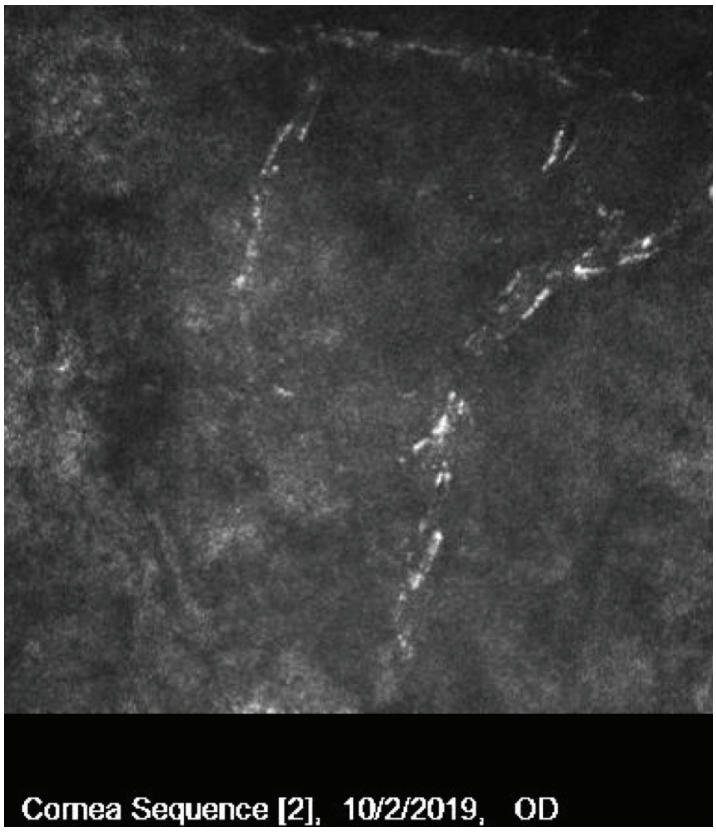

Figure 2. Note reduced corneal sub-basal nerves.

CONCLUSION

Thorough history-taking is a key component of the patient assessment, particularly when neurotrophic keratitis is suspected. When performing your examination, remember that an epithelial defect may not be present in stage 1 neurotrophic keratitis. Corneal sensitivity testing is essential. Ancillary testing may include a Schirmer tear test, cornea cultures, confocal microscopy, if available, and systemic diseases should be ruled out. ■

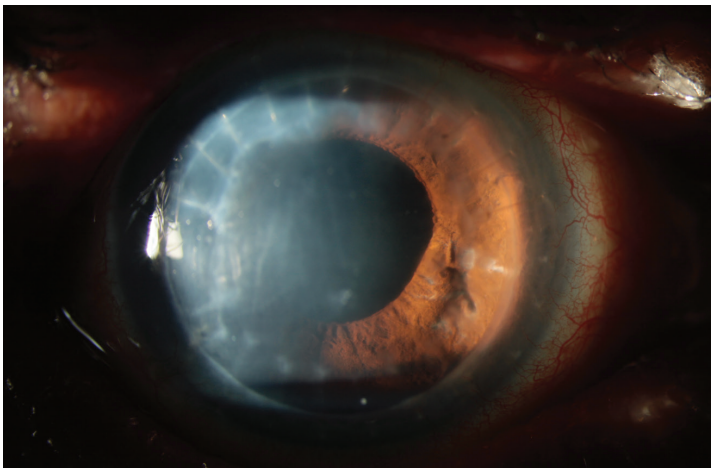

Figure 3. The cornea was completely healed after an 8-week course of treatment with cenegermin-bkbj.

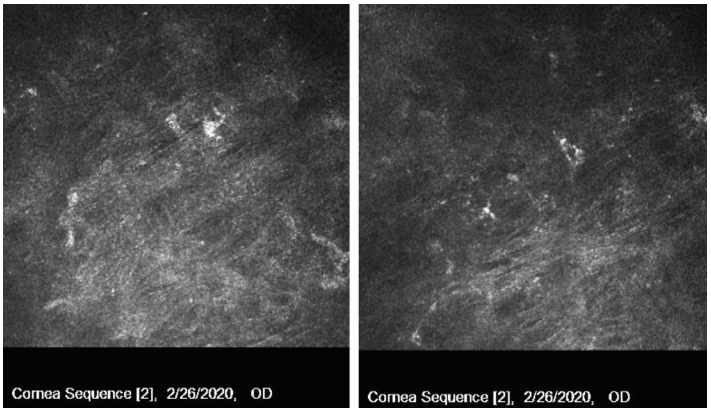

Figure 4. Confocal microscopy after treatment with cenegermin-bkbj.

GUIDANCE FOR TREATING NEUROTROPHIC KERATITIS

Disease stage and comorbidities are key factors.

BY STEPHEN C. PFLUGFELDER, MD

A 56-year-old man with type 1 diabetes since childhood had a history of proliferative diabetic retinopathy and a nonclearing vitreous hemorrhage in the right eye. He was referred to me by a retina colleague for treatment of a nonhealing corneal epithelial defect that developed about 6 weeks after combined phacoemulsification/IOL implantation and pars plana vitrectomy. At the time he was referred, he was using topical prednisolone acetate and moxifloxacin, both twice a day.

The patient had the characteristic oval epithelial defect with rolled edges and some mild anterior stromal haze with no thinning (Figure 1). In my experience, that characteristic appearance and a central or inferior oval-shaped epithelial defect always suggest neurotrophic keratitis.

Corneal sensitivity with the Cochet-Bonnet esthesiometer was 1/6, with 6 being normal in most middle-aged patients. Tear production was reduced, with Schirmer scores of 7 mm of wetting in each eye. The blink rate was reduced at about 10 times per minute.

These test results signal the effect of reduced corneal sensitivity on the lacrimal functional unit, which controls production, distribution, and clearance of tears.[1] Most patients with neurotrophic problems

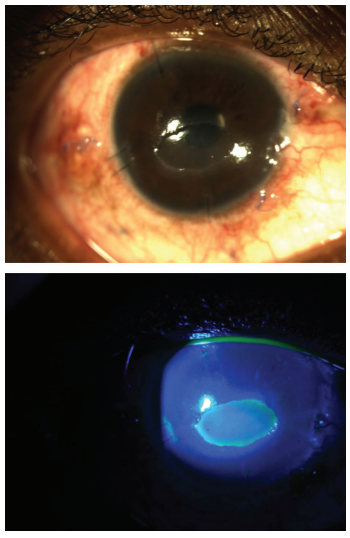

Figure 1. Note the characteristic oval epithelial defect with rolled edges and mild anterior stromal haze.

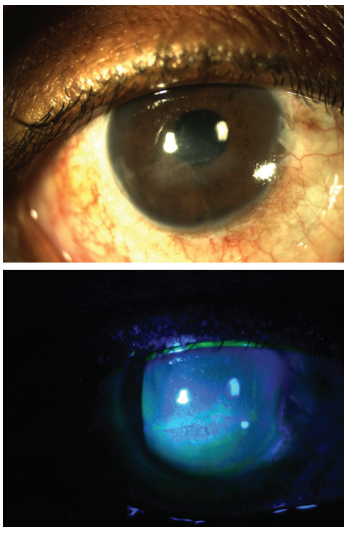

Figure 2. After 1 month of traditional therapies, the epithelial defect had healed to a ridge with surrounding punctate epitheliopathy.

have reduced tear production, and they don't blink, thus worsening the disease and making it more prone to corneal epithelial defects. I diagnosed stage 2 neurotrophic keratitis in this patient.

INITIAL TREATMENT PLAN

My treatment plan for this patient included removal of the loose sutures, as they sometimes trap mucus or interfere with tear spread, and preservative-free artificial tears. I highly recommend preservative-free formulations of all topical medications for these patients whenever possible.

I placed a latest-generation silicone hydrogel therapeutic contact lens and inserted absorbable punctal plugs. I often use punctal plugs, because these patients have evidence of dry eye, and there are some reports of healing of neurotrophic epithelial defects with punctal occlusion alone.[2] I prescribed moxifloxacin twice a day. I like that antibiotic because it's self-preserved, thus avoiding a toxic preservative. I offered the patient the option to be fitted with a scleral contact lens, as there's evidence behind use of that, and he agreed.[3]

About that time, the FDA approved cenegermin-bkbj ophthalmic solution 0.002%, a recombinant human nerve growth factor, for the treatment of neurotrophic keratitis, so we discussed that medication.

ONE-MONTH FOLLOW-UP

After about 1 month of the previously described therapies, I removed the contact lens. The epithelial defect had healed to a ridge with surrounding punctate epitheliopathy (Figure 2). (*See Panel Discussion on Sraping*).

Patients with neurotrophic keratitis frequently have punctate epitheliopathy in the central exposure zone, as well as increased permeability to fluorescein, indicating that the epithelium is not healthy in that area. Interestingly, they rarely heal to a smooth, regular epithelium. That often reduces the quality of their vision, and they may develop anterior stromal or subepithelial haze in the region. That's one of the reasons why we want to heal the epithelium as quickly as possible to minimize permanent stromal changes.

I explained to the patient that he likely will have a recurring problem because of his reduced corneal sensitivity and diabetes. He opted to start the cenegermin-bkbj and completed the 8-week course of therapy.

SEVERITY-BASED THERAPY OPTIONS

Increasing consensus and evidence-based recommendations support the use of therapies based on the clinical severity of neurotrophic keratitis.[2,4] In the mid-1990s, Mackie proposed a 3-stage severity classification scheme.[5]

Stage I is characterized by punctate epitheliopathy with fluorescein and lissamine green staining of the cornea and the conjunctiva, along with decreased tear breakup time and stromal haze in the area of the epitheliopathy. At this stage, neurotrophic keratitis is often misdiagnosed as dry eye. If a patient who is being treated for dry eye doesn't improve, there may be a neurotrophic component. Corneal sensitivity testing is indicated.

PANEL DISCUSSION: TO SCRAPE OR NOT TO SCRAPE?

Karolinne Maia Rocha, MD, PhD: Dr. Pflugfelder, when a patient has stage 2 or stage 3 neurotrophic keratitis, do you usually do a scraping to remove dead cells before starting therapy?

Stephen C. Pflugfelder, MD: That's a really good point, and that's come up several times. Some noted cornea specialists in my area routinely scrape the edges of the heaped up epithelium. They feel that doing so may promote epithelial healing. Personally, I haven't done it so much. Do you do that?

Dr. Rocha: I do it only if I see necrotic cells with rolled and elevated edges; then I just clean up a bit.

Dr. Pflugfelder: If a patient has been using a medication that deposits in that area, I may try to rub off the deposits.

Dr. Rocha: Yes. Drug precipitation and corneal deposits can be observed with ciprofloxacin drops.

Francis S. Mah, MD: Rolled edges is an interesting discussion point for cornea specialists. I was taught to remove that grayish, rolled edge—to "freshen up" the edge, so to speak—to allow the advancing epithelium to vault over those edges. I was somewhat surprised when I first heard that some people don't do that. Whether or not you do it seems to depend on where and with whom you trained.

Severity Based Therapy

Stage	Therapy
1	Preservative-free artificial tears formulations Punctal occlusion Hydrogel contact lens *(consider large diameter)* Recombinant human NGF (rhNGF, cenegermin) Serum/plasma/platelet rich plasma
2	*Supportive therapies plus:* rhNGF Scleral lens (± serum/plasma) Amniotic membrane Botulinum induced ptosis, Tarsorrhaphy
3	rhNGF Keratoplasty + scleral lens, tarsorrhaphy, neurotization

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

Figure 3. A recommended treatment scheme based on Mackie's three stages of neurotrophic keratitis.

Stage 2 is characterized by a persistent corneal epithelial defect with smooth, rolled edges. The stromal opacity may worsen in the area of the defect.

In stage 3, the stroma starts to thin and ulcerate, and in some cases, corneal perforation occurs rapidly. For that reason, treatment in stage 2 should be aggressive to prevent progression to stage 3. Within a week or two, the disease can progress from just an epithelial defect to a deep stromal ulceration, descemetocele, or even perforation, and these patients are not good candidates for penetrating keratoplasty.

Figure 3 shows one recommended treatment scheme based on these three stages.[2]

In stage I, supportive therapy is recommended to treat the underlying tear deficiency. This would include preservative-free artificial tears, punctal occlusion, and a hydrogel contact lens. If the lens tends to fall off because of dryness, a large-diameter lens (16 mm or 18 mm) often stays on better.

I would certainly consider prescribing cenegermin-bkbj for stage 1 disease, particularly for a patient who has an underlying chronic disease such as the patient I described earlier. Cenegermin-bkbj is also indicated for neurologic disorders such as Riley-Day syndrome, a life-long disease for which you may want to consider a more biologic therapy. Autologous blood products such as serum, plasma, or platelet-rich plasma may also be beneficial. Serum/plasma therapy has been used for decades to treat neurotrophic keratitis (*See Panel Discussion on Blood Products*).

In stage 2, with an epithelial defect, you can continue the stage 1 therapies, including cenegermin-bkbj. A scleral contact lens may improve vision, and serum or plasma can be placed in the reservoir of the lens.

Perry Rosenthal, MD, rekindled interest in scleral contact lenses in the 1990s because of changes in lens design and development of more oxygen-permeable materials. Romero-Rangel and colleagues reported on a series of cases using fluid-filled scleral lenses for treatment of neurotrophic keratitis with good success.[3] Scleral lenses have proven to heal corneal epithelial defects that were refractory to conventional bandage contact lenses. In another series, nine cases that did not respond to a bandage contact lens did respond to a scleral lens.[6] Recently, there's been a trend in some patients to consider continuous overnight wear for one or several days with close monitoring to accelerate healing.[7] So scleral lenses, like hydrogel lenses, often can be used in conjunction with other treatments, such as autologous blood products or cenegermin-bkbj.

Other options include amniotic membrane, either self-retaining or sutured, and eyelid closure with botulinum-induced ptosis or tarsorrhaphy.

Amniotic membrane has been used frequently to treat neurotrophic keratitis, and there have been some randomized trials. One in particular reported healing of refractory neurotrophic ulcers with conventional therapy (lubrication plus a bandage contact lens or tarsorrhaphy) or amniotic membrane transplantation.[8] Healing rates were similar in the two groups: 67% with conventional therapy and 73% with amniotic membrane transplantation. Another study found amniotic membrane grafts were equivalent to autologous serum in healing neurotrophic ulcers: about 70% for autologous serum

PANEL DISCUSSION: TREATING NEUROTROPHIC KERATITIS WITH BLOOD PRODUCTS

Stephen C. Pflugfelder, MD: Dr. Rocha, have you used or are you currently using blood products to treat neurotrophic keratitis?

Karolinne Maia Rocha, MD, PhD: I think it's a great option, particularly for patients with comorbidities, such as severe dry eye or limbal stem cell deficiency. It's definitely better than artificial tears alone, and serum tears have minimal side effects.

Dr. Pflugfelder: Dr. Farid, do you use serum or plasma? If so, have you encountered any hurdles in doing that?

Marjan Farid, MD: I've been using autologous serum drops successfully for 12 years in patients with severe dry eye and various types of ocular surface diseases, including neurotrophic keratitis. I think it's a great adjunct. The challenge has been locating a compounding pharmacy and a phlebotomist or phlebotomy laboratory to collaborate on making the product. There are now a couple of national organizations that will send a phlebotomist to the patient's home for the blood draw. The turnaround to get the product into the patient's hands is usually within a week. I believe it's becoming more systematized and potentially more available for widespread use.

Dr. Pflugfelder: I agree, I've used it widely in the past. Another hurdle is the cost, because, unfortunately, insurance doesn't cover it, so it's usually out of pocket. Cenegermin-bkbj is often covered by a patient's prescription drug plan.

and 73% for amniotic membrane transplantation.[9] If the disease advances to stage 3 where there's a deep ulcer or descemetocele, then multilayer amniotic membrane transplantation has been reported to help heal and thicken the cornea in that area.[10]

In stage 3 neurotrophic keratitis, cenegermin-bkbj is indicated, if it hasn't been started already. To spare patients from undergoing keratoplasty, a scleral lens, tarsorrhaphy, or corneal neurotization should be considered.

During the last decade, there have been an increasing number of reports of clinicians performing corneal neurotization. The initial report was from Elbaz and colleagues in Toronto, where corneal sensitivity was restored after a sural nerve graft.[11] A free sural nerve graft was coapted end-to-side with a supratrochlear nerve, and the distal portion of the nerve was separated into fascicles that were distributed around the corneal limbus. Initially, the patient had no corneal sensitivity in five zones on the cornea, but after 161 days, normal corneal sensation had been restored. This procedure is being offered at some academic centers.

SUMMARY

Neurotrophic keratitis is caused by various conditions, most often herpes viruses, and disease severity ranges from diffuse epitheliopathy to corneal ulceration and perforation. While I recommend treating the disease based on severity, I do advise aggressive treatment in stage 2 to avoid rapid progression.

While the efficacy of many therapies is based on low levels of evidence, cenegermin-bkbj is a validated, highly effective, FDA-approved medication that should be considered a first-line option. I encourage a proactive approach to minimize recurrent corneal epithelial breakdown, stromal scarring and thinning, and vision loss. ■

1. Stern ME, Gao J, Siemasko KF, et al. The role of the lacrimal functional unit in the pathophysiology of dry eye. *Exp Eye Res.* 2004;78(3):409-416.
2. Sacchetti M, Lambiase A. Diagnosis and management of neurotrophic keratitis. *Clin Ophthalmol.* 2014;8:571-579.
3. Romero-Rangel T, Stavrou P, Cotter J, et al. Gas-permeable scleral contact lens therapy in ocular surface disease. *Am J Ophthalmol.* 2000;130(1):25-32.
4. Versura P, Giannaccare G, Pellegrini M, et al. Neurotrophic keratitis: current challenges and future prospects. *Eye Brain.* 2018;10:37-45.
5. Mackie IA. Neuroparalytic keratitis. In: Fraunfelder F, Roy FH, Meyer SM, eds. *Current Ocular Therapy*. Philadelphia, PA: W.B. Saunders; 1995.
6. Ling JD, Gire A, Pflugfelder SC. PROSE therapy used to minimize corneal trauma in patients with corneal epithelial defects. *Am J Ophthalmol.* 2013;155(4):615-619.
7. Lim P, Ridges R, Jacobs DS, et al. Treatment of persistent corneal epithelial defect with overnight wear of a prosthetic device for the ocular surface. *Am J Ophthalmol.* 2013;156(6):1095-1101.
8. Khokhar S, Natung T, Sony P, et al. Amniotic membrane transplantation in refractory neurotrophic corneal ulcers: a randomized, controlled clinical trial. *Cornea*. 2005;24(6):654-660.
9. Turkoglu E, Celik E, Alagoz G. A comparison of the efficacy of autologous serum eye drops with amniotic membrane transplantation in neurotrophic keratitis. *Semin Ophthalmol.* 2014;29(3):119-126.
10. Kruse FE, Rohrschneider K, Völcker HE. Multilayer amniotic membrane transplantation for reconstruction of deep corneal ulcers. *Ophthalmology*. 1999;106(8):1504-1511.
11. Elbaz U, Bains R, Zuker RM, et al. Restoration of corneal sensation with regional nerve transfers and nerve grafts: a new approach to a difficult problem. *JAMA Ophthalmol.* 2014;132(11):1289-1295.

HEALING AND MAINTAINING CORNEAL INTEGRITY

New medication moves to the forefront of neurotrophic keratitis therapy.

BY MARJAN FARID, MD

This 75-year-old man was referred to me about 18 months ago with a nonhealing corneal epithelial defect. He had bilateral LASIK about a decade ago. He had a history of herpes zoster ophthalmicus on the side of the affected cornea a year before the nonhealing corneal epithelial defect developed. The patient reported he'd had a corneal abrasion about a year before seeing me and that it healed after 2 weeks of aggressive lubrication and antibiotic treatment.

Several red flags in this patient's history point toward a diagnosis of neurotrophic keratitis. Certainly, LASIK is a risk factor, but the major one is the history of shingles or herpetic eye disease. I suspect the corneal abrasion a year ago was the patient's first episode of epithelial breakdown from the neurotrophic keratitis. A simple corneal abrasion should not have taken 2 weeks to heal.

When I first saw the patient, he was previously treated with bandage contact lenses, a processed, sutureless amniotic membrane allograft, and biologic corneal bandage devices. His referring doctor had also prescribed autologous serum drops. Despite these treatments, the persistent epithelial defect was not resolving. The patient was using antibiotic drops (we ruled out concomitant bacterial infection), preservative-free artificial tears, and oral antivirals. Corneal sensitivity testing revealed almost a complete absence of sensation on the affected cornea. That cinched the diagnosis of a neurotrophic corneal epithelial defect, neurotrophic keratitis stage 2. I prescribed cenegermin-bkbj.

After 4 weeks of treatment, the epithelial defect was significantly improved, and by 8 weeks, it was completely resolved (Figure 1).

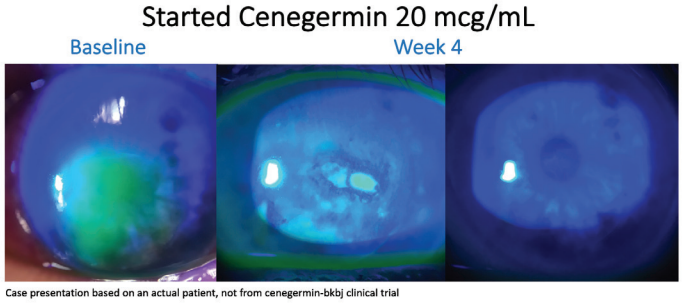

Figure 1. After 8 weeks of cenegermin-bkbj, the epithelial defect had healed, and the tear film was smooth.

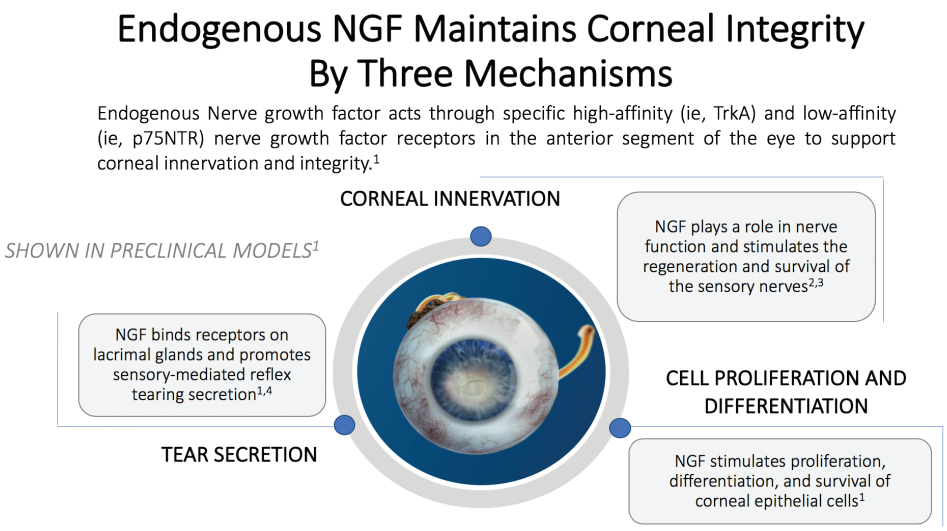

Figure 2. Cenegermin-bkbj mimics endogenous nerve growth factor.

More importantly, there was no punctate staining of the cornea and a smooth tear film.

The cenegermin-bkbj healed the epithelium, and also the tear film and the tear milieu; and the subepithelial haze was gone. This was one of the first patients I treated with cenegermin-bkbj, and I was impressed with this outcome.

ABOUT CENEGERMIN-BKBJ

Cenegermin-bkbj is a recombinant human nerve growth factor (NGF) that is structurally identical to human NGF produced in ocular tissues. The medication was approved by the FDA in early 2019 to treat neurotrophic keratitis. It is a biologic agent prepared by a specialty pharmacy and shipped to the patient weekly. The patient assembles, prepares, and instills the medication 6 times a day for a total of 8 weeks.

Recombinant human NGF mimics endogenous NGF, which not only regenerates the nerves but also maintains corneal integrity by three mechanisms (Figure 2).

First, it plays a role in nerve function and stimulates the regeneration and survival of the sensory nerves of the cornea.[1,2] Second, it stimulates proliferation, differentiation, and survival of the corneal epithelial cells.[3] There's a nice interplay between the nerves and the epithelium. The epithelial cells release endogenous NGF to the nerves, and then the nerves release trophic factors to the epithelium. Third, it helps improve the tear film. It binds onto the receptors of the lacrimal gland and promotes sensory-mediated reflex tearing.[1,4]

TOPLINE TRIAL DATA

Two large pivotal trials examined the efficacy of cenegermin-bkbj. In the US trial, NGF0214, 48 patients with unilateral or bilateral disease were randomly assigned to vehicle or cenegermin-bkbj 20 mcg/mL for 8 weeks.[5] These patients had stage 2 or stage 3 neurotrophic keratitis with a large epithelial defect or a defect with some stromal involvement. After 8 weeks, 65.2% of treated patients achieved their end point, which was complete corneal healing with zero millimeters of staining in the lesion area and no other persistent staining in the rest of the cornea.

The European trial, NGF0212, also known as the REPARO trial, enrolled a total of 156 patients with unilateral disease and randomly assigned them to vehicle, cenegermin-bkbj 10 µg/mL, or cenegermin-bkbj 20 µg/mL.[6] Seventy-two percent of the treated eyes showed complete healing after 8 weeks of the treatment, which is exciting, particularly compared with many other treatments that we're using today. Even more exciting, 80% of patients who achieved complete corneal healing at 8 weeks maintained full healing at 48 weeks after just one 8-week treatment cycle. That's something I haven't seen in my practice with any other therapies. Our traditional treatments may be able to heal the epithelial defects, but these corneas tend to break down again.

RENEWED EMPHASIS ON EARLY DIAGNOSIS

The patient whom I discussed earlier is now about 18 months out from his 8-week course of therapy with cenegermin-bkbj, and his cornea looks healthy, still without staining, he has an excellent tear film, and no breakdown.

Since treating that patient, I'm really trying to identify neurotrophic keratitis early and start patients on treatment before they develop long-term subepithelial haze and scarring. ■

1. Müller LJ, Marfurt CF, Kruse F, et al. Corneal nerves: structure, contents and function. *Exp Eye Res.* 2003;76(5):521-542.
2. Sacchetti M, Lambiase A. Diagnosis and management of neurotrophic keratitis. *Clin Ophthalmol.* 2014;8:571-579.
3. Mastropasqua L, Massaro-Giordano G, Nubile M, et al. Understanding the pathogenesis of neurotrophic keratitis: the role of corneal nerves. *J Cell Physiol.* 2017;232(4):717-724.
4. Muzi S, Colafrancesco V, Sornelli F, et al. Nerve growth factor in the developing and adult lacrimal glands of rat with and without inherited retinitis pigmentosa. *Cornea*. 2010;29(10):1163-1168.
5. 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.
6. 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(9):1332-1343.

UNDERSTANDING, DIAGNOSING, AND TREATING NEUROTROPHIC KERATITIS IN 2020

Release Date: August 2020
Expiration Date: September 2021

INSTRUCTIONS FOR CME CREDIT

To receive credit, you must complete the attached Pretest/Posttest/Activity Evaluation/Satisfaction Measures Form and mail or fax to Evolve Medical Education LLC; 353 West Lancaster Avenue, Second Floor, Wayne, PA 19087; Fax: (215) 933-3950. To answer these questions online and receive real-time results, please visit evolvemeded.com and click http://evolvemeded.com/online-courses/2010-supplement. If you are experiencing problems with the online test, please email us at info@evolvemeded.com. Certificates are issued electronically; please be certain to provide your email address below.

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License Number _____ OE Tracker Number _____

DEMOGRAPHIC INFORMATION

Profession
___ MD/DO
___ OD
___ NP
___ Nurse/APN
___ PA
___ Other

Years in Practice
___ >20
___ 11-20
___ 6-10
___ 1-5
___ <1

Patients Seen Per Week (with the disease targeted in this activity)
___ 0
___ 1-15
___ 16-30
___ 31-50
___ >50

Region
___ Northeast
___ Northwest
___ Midwest
___ Southeast
___ Southwest

Setting
___ Solo Practice
___ Community Hospital
___ Government or VA
___ Group Practice
___ Other
___ I do not actively practice

Models of Care
___ Fee for Service
___ ACO
___ Patient-Centered Medical Home
___ Capitation
___ Bundled Payments
___ Other

LEARNING OBJECTIVES

DID THE PROGRAM MEET THE FOLLOWING EDUCATIONAL OBJECTIVES?	AGREE	NEUTRAL	DISAGREE
Describe the stages of neurotrophic keratitis and how to differentiate it from similar diseases.	_____	_____	_____
Recognize the various potential causes of neurotrophic keratitis and when referrals may be necessary.	_____	_____	_____
Summarize mechanisms of action of newer treatments and when they should be introduced into treatment regimens for neurotrophic keratitis.	_____	_____	_____
Identify the relationships between disease characteristics, drug, treatment frequency, visual and anatomic outcomes.	_____	_____	_____

POSTTEST QUESTIONS

1. Based on this activity, please rate your confidence in your ability to identify and treat patients with neurotrophic keratitis (based on a scale of 1 to 5, with 1 = "Not at all confident" and 5= "Very confident").

a. 1
b. 2
c. 3
d. 4
e. 5

2. A 53-year-old woman with a diagnosis of neurotrophic keratitis presents to your office. Which of the following are reasonable options for treatment (more than one may apply)?

a. Artificial tears
b. Topical Ointment
c. Latanoprost topical drops
d. Cenegermin

3. What is the most common etiology of neurotrophic keratitis?

a. Postsurgical damage to ciliary nerves
b. Postherpetic infections
c. Diabetes mellitus
d. Corneal dystrophies

4. What is the hallmark finding of neurotrophic keratitis?

a. Punctate epithelial erosions
b. Abnormal Schirmer test
c. Abnormal corneal sensitivity testing
d. Lid laxity

5. A 72-year-old man with primary open-angle glaucoma presents with blurry vision. On exam, he has an epithelial defect with rolled edges. He has decreased corneal sensitivity. Which of the following made him at risk for this diagnosis (more than one may apply)?

a. Use of multiple topical glaucoma medications
b. Blepharitis
c. His age
d. History of glaucoma

6. Which of the following is an example of a quantitative corneal sensitivity test?

a. Cochet-Bonnet esthesiometer
b. Cotton swab
c. Dental floss

7. To which stage of neurotrophic keratitis does the following description apply: "Persistent epithelial defect with smooth rolled edges; stromal opacity"?

a. Stage 1
b. Stage 2
c. Stage 3

8. Which of the following is an appropriate therapy for stage 3 neurotrophic keratitis?

a. Recombinant human nerve growth factor
b. Preservative free artificial tears
c. Punctal occlusion
d. Hydrogel contact lens

9. A 67-year-old female with a nonhealing corneal epithelial defect presents to your office. She has a history of bilateral LASIK and herpes zoster ophthalmicus. She has previously attempted amniotic membrane allograft, bandage contact lens, and autologous serum tears for treatment, yet her persistent epithelial defect remains. Which of the following is an appropriate treatment for this patient?

a. Start cenegermin 20 mcg/mL
b. Punctal occlusion
c. Preservative free artificial tears

10. In the cenegermin clinical trials, what was the most common adverse reaction?

a. Eye irritation
b. Red eye
c. Eye pain following instillation

11. A 40-year-old male with a history of diabetes and bilateral LASIK OU presents with diffuse punctate epitheliopathy, decreased tear break-up time, and stromal haze. Which of the following is an appropriate treatment for this patient?

a. Scleral lens
b. Preservative free artificial tears
c. Amniotic membrane
d. Tarsorrhaphy

ACTIVITY EVALUATION

YOUR RESPONSES TO THE QUESTIONS BELOW WILL HELP US EVALUATE THIS CME/CE ACTIVITY. THEY WILL PROVIDE US WITH EVIDENCE THAT IMPROVEMENTS WERE MADE IN PATIENT CARE AS A RESULT OF THIS ACTIVITY.

Your responses to the questions below will help us evaluate this CME activity. They will provide us with evidence that improvements were made in patient care as a result of this activity.

Rate your knowledge/skill level prior to participating in this course: 5 = High, 1 = Low _____

Rate your knowledge/skill level after participating in this course: 5 = High, 1 = Low _____

This activity improved my competence in managing patients with this disease/condition/symptom. ____ Yes ____ No

Probability of changing practice behavior based on this activity: _____ High _____ Low ____No change needed

If you plan to change your practice behavior, what type of changes do you plan to implement? (check all that apply)

Change in pharmaceutical therapy ____ Change in nonpharmaceutical therapy ____

Change in diagnostic testing _____ Choice of treatment/management approach ____

Change in current practice for referral _____ Change in differential diagnosis _____

My practice has been reinforced _____ I do not plan to implement any new changes in practice ___

Please identify any barriers to change (check all that apply):

____ Cost ____ Lack of consensus or professional guidelines ____ Lack of administrative support ____ Lack of experience

____ Lack of time to assess/counsel patients ____ Lack of opportunity (patients) ____ Reimbursement/insurance issues ____ Lack of resources (equipment)

____ Patient compliance issues ____ No barriers ____ Other. Please specify: _____

The design of the program was effective for the content conveyed ___ Yes ___ No

The content supported the identified learning objectives ___ Yes ___ No

The content was free of commercial bias ___ Yes ___ No

The content was relative to your practice ___ Yes ___ No

The faculty was effective ___ Yes ___ No

You were satisfied overall with the activity ___ Yes ___ No

Would you recommend this program to your colleagues ___ Yes ___ No

Please check the Core Competencies (as defined by the Accreditation Council for Graduate Medical Education) that were enhanced through your participation in this activity:

____ Patient Care ____ Practice-Based Learning and Improvement ____ Professionalism ____ Medical Knowledge

____ Interpersonal and Communication Skills ____ System-Based Practice

Additional comments:

_____

_____

_____ I certify that I have participated in this entire activity.

This information will help evaluate this CME activity; may we contact you by email in 3 months to see if you have made this change? If so, please provide your email address below.

_____