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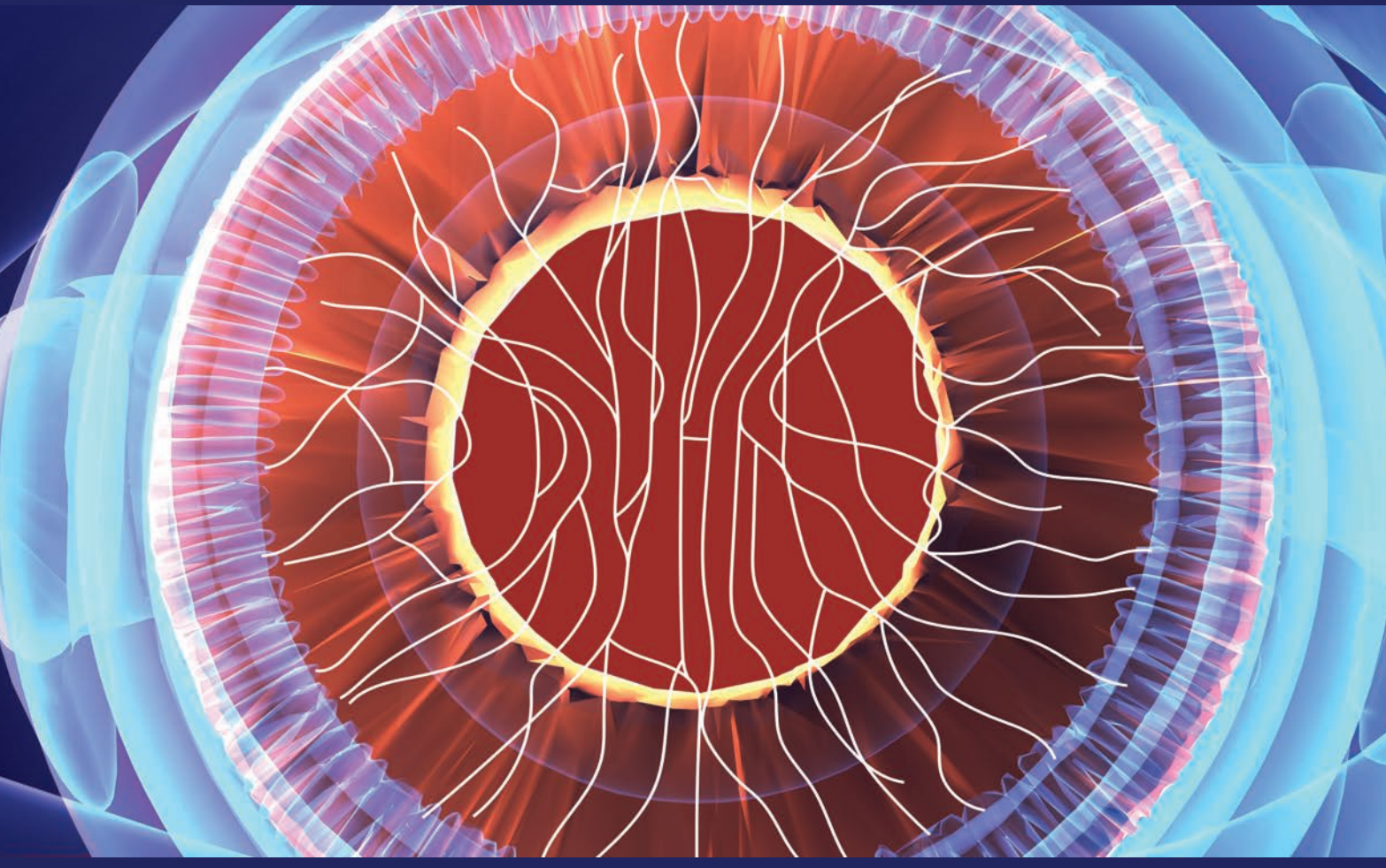
BELOW THE SURFACE

TARGETING CORNEAL NERVES IN THE TREATMENT OF OCULAR CONDITIONS



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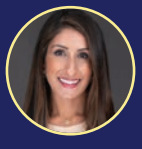

Preeya K. Gupta, MD (Chair) • Pedram Hamrah, MD • Melissa Toyos, MD

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Activity Description and Purpose

Corneal nerve dysfunction is the underlying cause of neurotrophic keratitis and has an etiologic role in the pathogenesis of dry eye disease and its symptoms. Knowledge of the mechanisms has implications for establishing a diagnosis in patients with ocular surface disease and using neuroregenerative therapy. This educational activity is based on the proceedings of a live CME symposium that took place on Saturday, October 1, 2022. The desired results of this activity are to increase understanding of the role of the corneal nerve in ocular surface health and disease as a foundation for enabling proper diagnosis and for selecting optimal treatment.

Target Audience

This educational activity is intended for ophthalmologists.

Learning Objectives

After completing this activity, participants will be better able to:

- Review the role of corneal nerves in maintaining ocular surface homeostasis
- Review the neurosensory etiologies of ocular surface diseases
- Review strategies for diagnosing diseases related to corneal nerve dysfunction
- Select optimal treatment strategies for patients with diseases related to corneal nerve dysfunction

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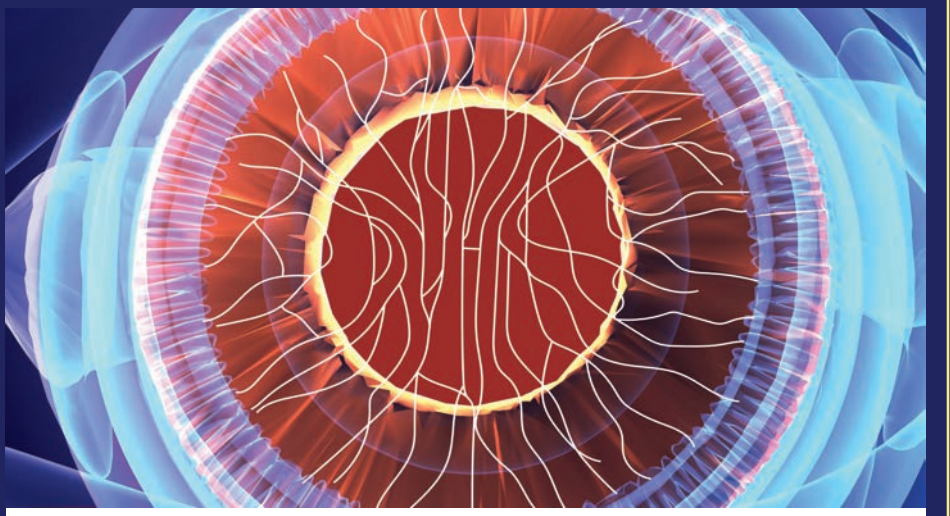
BELOW THE SURFACE

TARGETING CORNEAL NERVES IN THE TREATMENT OF OCULAR CONDITIONS



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Introduction

Understanding of the role of corneal innervation in both ocular surface health and disease has been increasing and has clinical relevance for patient care. Using narratives and case-based discussions, this educational activity reviews the relationships among corneal nerve dysfunction, neurotrophic keratitis (NK), and severe forms of dry eye disease (DED) and provides expert insights on the diagnostic workup for these potentially sight-threatening conditions and their management.

Case 1: Patient With Stage 1 Neurotrophic Keratitis

From the Files of Pedram Hamrah, MD

A 60-year-old White female presented because of decreased vision and pain OS over the past few months. Visual acuity (VA) was 20/20 OD and 20/300 OS. Slitlamp examination showed diffuse 4+ corneal staining **(Figure 1)**. She rated the pain severity OS as 9 on a scale of 0 to 10. The patient had diagnoses of keratoconjunctivitis sicca and Sjögren syndrome (SS), a history of herpes simplex keratitis, and neurotrophic ulcers OS. She had partial limbal stem cell deficiency, with vortex keratopathy superiorly. Corneal sensation, as measured by Cochet-Bonnet esthesiometry, was 6/6 OD and 0/6 OS. In vivo confocal microscopy (IVCM) OD showed a very mild decrease in corneal nerves. IVCM OS demonstrated complete loss of corneal nerves.

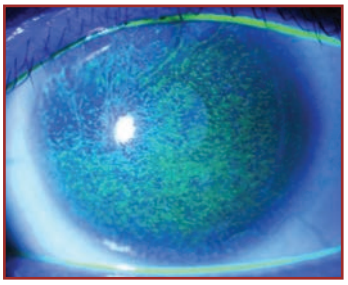

Figure 1. Slitlamp photograph of the patient in Case 1 shows diffuse 4+ corneal staining and superior vortex epitheliopathy

Previous treatments OS included artificial tears and ointment; bandage contact lens; topical steroids; topical cyclosporine, 0.05%, and compounded at a different concentration; cryopreserved amniotic membrane (2 times); autologous serum tears, 20%; and ocular patching. She had also used gabapentin, low-dose naltrexone, and loteprednol, 0.5%, once daily for pain. The patient was diagnosed with stage 1 NK.

Pathophysiology of Neurotrophic Keratitis

Neurotrophic keratitis is a degenerative disease caused by impaired corneal sensory innervation that can develop as a result of damage or dysfunction to the trigeminal nerve or its branches.[1,2] Sensory branches of the ophthalmic division of the trigeminal nerve innervate the cornea, lacrimal glands, conjunctiva, and eyelids and play a critical role in maintaining ocular surface homeostasis and corneal epithelial integrity by interacting with corneal epithelial cells in a mutually supportive relationship **(Figure 2)**.[1,2] Stimulation of corneal sensory nerves triggers reflex tearing and blinking to lubricate and protect the ocular surface. In addition, the nerves release neuromediators that provide trophic

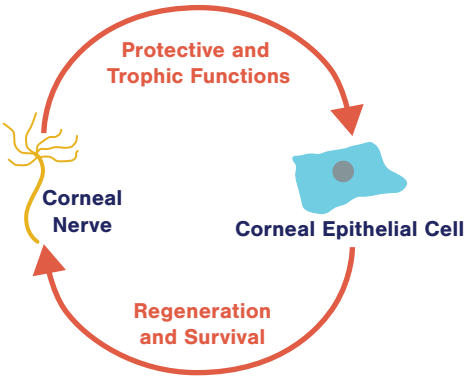

Figure 2. Corneal nerves and corneal epithelial cells interact in a mutually supportive relationship.[1,2] Impairment of corneal nerves initiates a vicious cycle causing and perpetuating progression of neurotrophic keratitis.

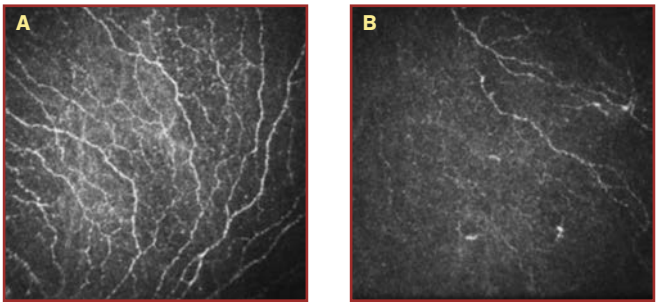

Figure 3. Images from in vivo confocal microscopy show an intact corneal nerve plexus in a healthy eye (A) and reduced nerve density and branching in an eye with stage 2 (moderate) neurotrophic keratitis (B)[1]

support to corneal epithelial cells and promote healing. When corneal nerve function is impaired, the resulting loss of protective reflexes and trophic factors allows for corneal epithelial breakdown, with a risk of progression to persistent epithelial defects, corneal ulceration, stromal melting, and perforation. Damage to the corneal epithelial cells perpetuates corneal nerve damage because the epithelial cells release neurotrophic factors that promote corneal nerve regeneration and survival.

Diagnosing Neurotrophic Keratitis

Diagnosis of NK is based on findings of a condition associated with trigeminal nerve impairment, corneal epitheliopathy or more severe damage, and decreased corneal sensitivity.[3] Patients with NK can also present with decreased blink rate, red eye, photophobia, fluctuating vision, foreign body sensation, and decreased visual quality from reduced contrast sensitivity.[4] Symptom severity typically decreases paradoxically with advancing disease owing to increasing loss of corneal nerves.[3] Therefore, NK should be suspected in any patient whose ocular symptoms are disproportionally less than the clinical signs.

IVCM, which allows visualization of corneal nerves, can identify neuronal loss in eyes with NK **(Figure 3)**.[1] In clinical practice, however, decreased or absent corneal sensitivity is the hallmark of NK. Corneal sensitivity can be tested qualitatively by simply evaluating the patient's response when the cornea is touched using a wisped end of a cotton-tipped applicator or a piece of dental floss.[5] Esthesiometry instruments provide a semiquantitative measurement of corneal sensitivity and include the Cochet-Bonnet esthesiometer, which applies mechanical stimulation with a nylon filament, and the Belmonte esthesiometer, a noncontact device that stimulates the cornea with a gas jet.

There is a long list of etiologies for NK **(Table 1)**.[5] Some of the more common causes are ocular herpetic infection, chronic DED, long-term contact lens wear, topical drug toxicity, chemical injury, and cranial neurosurgery.

Neurotrophic Keratitis Staging

Once NK is diagnosed, the Mackie classification system is the most widely used method for grading its severity.[6] Others have since adapted this classification to describe the 3 stages of NK as defined by different levels of corneal damage and changes in corneal sensation **(Table 2)**.[5-7]

Discussion

Dr Hamrah: We use the Cochet-Bonnet esthesiometer to assess corneal sensation in clinical practice. I like that it provides a numerical result that both allows me to follow patients for their response to treatment and offers a more sensitive measure for making an intereye comparison. Approximately 15% of patients with NK have bilateral disease and will have reduced corneal sensation in both eyes.[8] When testing corneal sensation with a cotton wisp or dental floss, clinicians may fail to recognize reduced sensitivity if the response to stimulation seems similar in the 2 eyes.

We also have access to IVCM. I like to use it to assess the sub-basal corneal nerve plexus if I suspect NK and cannot test corneal

Table 1. Etiologies of Neurotrophic Keratitis[5]

Central Nervous System	Genetic	Ocular
• Neoplasm • Aneurysms • Stroke • Degenerative central nervous system disorders • Postneurosurgical procedures – For acoustic neuroma – For trigeminal neuralgia • Other surgical injury to trigeminal nerve	• Riley-Day syndrome (familial dysautonomia) • Goldenhar-Gorlin syndrome • Mobius syndrome • Familial corneal hypoesthesia	• Herpes (simplex or zoster) or other infection • Chemical or physical burn • Abuse of topical anesthetics • Drug toxicity • Chronic ocular surface injury or inflammation • Ocular surgery • Cataract surgery • LASIK, PRK • Penetrating keratoplasty and deep anterior lamellar keratoplasty • Collagen crosslinking for keratoconus • Vitrectomy for retinal detachment • Postsurgical or laser treatment • Routine laser for proliferative diabetic retinopathy • Contact lenses • Orbital neoplasia

Abbreviations: LASIK, laser-assisted in situ keratomileusis; PRK, photorefractive keratectomy.

Table 2. Stages of Neurotrophic Keratitis[5-7]

Stage	Examination Findings	Corneal Sensation
1: Mild	• Punctate keratopathy • Epithelial hyperplasia and irregularity • Superficial neovascularization • Stromal scarring	Reduced or aberrant corneal sensation
2: Moderate	• Persistent epithelial defect • Loose and opaque epithelium around the defect • Rolled edges of the defect • Stromal swelling • Anterior chamber reaction • Sterile hypopyon (rare)	Corneal anesthesia
3: Severe	• Stromal involvement (thinning, perforation)	Corneal anesthesia

sensation because the patient already received anesthetic drops. We observe significant reduction in corneal nerve density in all stages of NK. Seeing their baseline IVCM images and then nerve growth after starting effective treatment also motivates patients to be compliant with treatments recommended for preventing recurrence.

How do you diagnose early NK?

Dr Gupta: I think that early NK is often missed and misdiagnosed as severe DED. I urge clinicians to check corneal sensation in any patient who has chronic punctate epithelial keratitis that is resistant to traditional therapies. I also routinely check corneal sensation in patients with moderate to severe corneal staining, and I am careful to review their medical and medication history for an NK etiology. Having a high level of suspicion for NK is my number one pearl for diagnosing early disease.

Dr Toyos: We use either dental floss or a cotton wisp to check corneal sensitivity and do the testing in all 5 zones. We also use a Cochet-Bonnet esthesiometer, but primarily for research. I think that early NK is greatly underdiagnosed and that increasing access to IVCM will do for its detection what macular optical coherence tomography did for finding cystoid macular edema after cataract surgery. We do not know what we are missing until we start looking for it.

Dr Gupta: Is IVCM imaging difficult?

Dr Hamrah: All our photographers receive training in the technique; there is a learning curve of approximately 1 month to attain proper skill. The imaging itself takes approximately 5 to 10 minutes. Commercial software for automated image analysis is lacking, but artificial intelligence–based systems should be available in the next few years.

Dr Toyos: The IVCM technology is evolving. Today's equipment is very different from what was available 5 to 10 years ago. Further improvements are on the horizon.

Neurotrophic Keratitis Management

The goals of treatment of NK are to prevent progression of corneal damage and to promote epithelial healing. Therapy should be prompt and based on NK stage/severity.[5] The interventions include various topical, systemic, surgical, and nonsurgical procedural modalities.[3,5,9,10]

Discontinuing unnecessary topical medications and preservative-containing artificial tear products is fundamental for managing NK regardless of severity, as is identifying and addressing any modifiable systemic therapies that may be exacerbating the disease.[3,5,9] In addition to using artificial tear products for ocular surface lubrication, punctal occlusion can be done to increase tear retention. Topical anti-inflammatory therapy has a role for treating existing inflammation that can cause ocular surface damage and suppress nerve regrowth.

Blood-derived products such as autologous serum or plasma rich protein (PRP) contain growth factors and other mediators that promote healing and are more easily accessible than in the past, but still require that the patient undergo phlebotomy every few months. The products also require refrigeration and frequent instillation. Historically, they have not been covered by insurance, but that situation is changing as well. Some evidence suggests that umbilical cord serum drops may be more effective than the products derived from peripheral blood, perhaps because umbilical cord serum contains higher concentrations of substance P and nerve growth factor (NGF).[11]

Bandage contact lenses and scleral lenses provide comfort and help to promote epithelial healing by decreasing ocular surface exposure and protecting against lid irritation.[3,5,9] Scleral lenses can also temporarily improve vision. These devices, however, are only palliative, and their prolonged use can be associated with secondary infections, especially if the patient is being treated with a topical steroid.

Amniotic membrane can also be used in stage 1 NK.[12] The self-retaining cryopreserved amniotic membrane is a convenient option for acute in-office use and provides growth factors that promote healing, whereas freeze-dried products serve only as a protective barrier because the dehydration process causes structural degradation and loss of growth factors.[13] Placement of any amniotic membrane blurs vision, which can be particularly objectionable for patients with stage 1 NK. Corneal calcification can also occur with amniotic membranes.[14]

Topical cenegermin, 0.002%, (recombinant human NGF) is intended to target the underlying cause of NK. It is approved for treating all stages of the disease and is administered 6 times daily (every 2 hours) for 8 weeks.[10] The safety and efficacy of cenegermin for treating NK was demonstrated in US and European randomized, double-masked, vehicle-controlled studies, in which complete healing rates after 8 weeks of treatment were 65.2% and 72%, respectively, with cenegermin vs 16.7% and 33.3%, respectively, with vehicle ($P < .001$ for both comparisons) **(Figure 4)**.[10,15,16] There was no statistically significant differences among the groups in improvement in corneal sensitivity measured by Cochet-Bonnet esthesiometry or in VA measures.[15] Eye pain was the most frequent adverse event in the cenegermin (16%) and vehicle (8%) groups, followed by ocular hyperemia (7% and 3%, respectively) and increased lacrimation (5% and 3%, respectively).[17]

All patients enrolled in the randomized, vehicle-controlled, cenegermin clinical trials had stage 2 or stage 3 NK.[15,16] A recently published multicenter, retrospective study including 17 patients with stage 1 NK refractory to conventional medical therapy demonstrates the efficacy and safety of cenegermin for treating earlier disease. In this study, mean corneal staining score improved from 4.0 prior to starting cenegermin to 1.1 after 8 weeks of treatment ($P < .001$). Mean (range) best-corrected VA (BCVA) improved from 20/40 (20/20 to 20/400) pretreatment to 20/30 (20/20 to 20/200) posttreatment ($P = .0013$). IVCM in a subset of patients showed significant increases in corneal nerve density

measurements, although they remained significantly lower than those measured in healthy control eyes. Ten patients (58.8%) reported mild to moderate discomfort during treatment, but no patient stopped using cenegermin.

Interventions that may be added for stage 2 NK include nighttime occlusion and correction of lid malposition.[5] Temporary surgical tarsorrhaphy or tarsorrhaphy induced with onabotulinumtoxinA injection can also be used.[3,5]

Time is of the essence when treating stage 3 disease because the lesion can quickly progress to perforation.[5,9] Core treatments for stage 3 NK include cenegermin, amniotic membrane transplantation, conjunctival flaps, or tectonic lamellar grafts.[3,5,9,10]

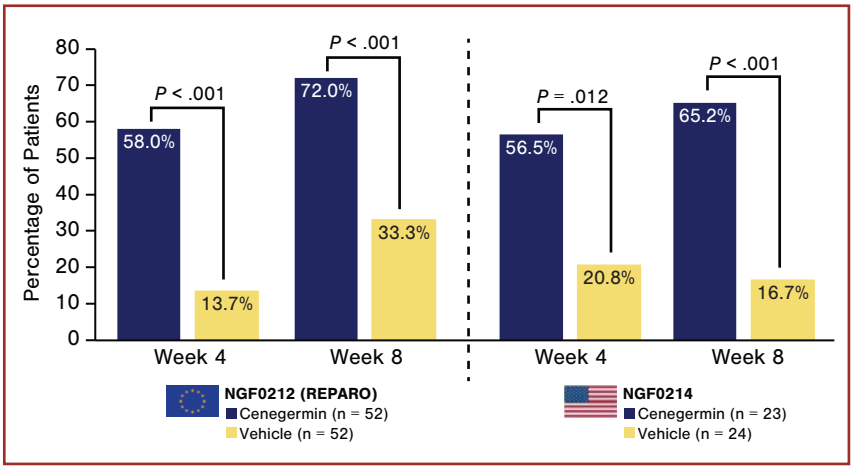

Figure 4. Complete corneal healing rates in the US and European clinical trials of cenegermin for treating stage 2 and stage 3 neurotrophic keratitis[10,15,16]

Note: Complete corneal healing defined as 0-mm staining in the lesion area and no other persistent staining in the rest of the cornea after 8 weeks of treatment (last post baseline observation carried forward; chi-squared test)

Discussion

Dr Hamrah: How do you decide which treatment to use for NK in a particular patient?

Dr Gupta: The milder the disease, the less urgent the situation, so I can be less aggressive with my initial treatment for patients with stage 1 NK. I like to use amniotic membrane even for early NK because I find it can be very effective. I also use a topical steroid if there is no contraindication, and adjust topical treatments to eliminate exposure to preservatives.

Dr Hamrah: I like to use a soft bandage contact lens for NK because it can be easily placed in the office. I prefer a larger-diameter contour contact lens that is vaulted and does not touch the eye. Scleral lenses can also be beneficial for stage 1 or stage 2 NK, but I do not use them for stage 3 disease because their need for fitting delays treatment initiation.[3,5]

Long-term (12-month) prospective studies of small groups of patients reported healing rates of 89% to 100% with amniotic membrane grafts.[12] Visual acuity, however, was not preserved or improved in all cases; in my experience, the healing rate ranges from 60% to 80% and depends on disease severity.

If I am using an amniotic membrane, I replace it within 7 days or sooner, even if the membrane has not yet dissolved. In patients experiencing pain, I usually take the self-retaining membrane off its ring and sandwich it between 2 soft lenses. I use umbilical serum drops for initial treatment or after healing is achieved with cenegermin or amniotic membrane to prevent regression.

Case 1 Conclusion

The patient in Case 1, who had stage 1 NK, was treated with cenegermin. This patient was also included in a recent multicenter retrospective analysis of patients with stage 1 NK who were treated with cenegermin.[18] In this study, cenegermin was well tolerated and patients experienced significant improvement in BCVA and corneal fluorescein staining scores.

Case 2: More Than Just Dry Eyes

From the Files of Melissa Toyos, MD

A 52-year-old White female with severe DED and essential blepharospasm was seen on referral from her neuro-ophthalmologist. The blepharospasm was so intense that the patient could open her lids only by prying them open mechanically. She had seen 2 other neuro-ophthalmologists, 2 oculoplastic surgeons, 1 neurologist, and 3 optometrists. Previous treatment included artificial tears, lifitegrast, cyclosporine, and onabotulinumtoxinA injections (6 bottles). The patient had glaucoma, allergies, type 2 diabetes, depression, and a family history of autoimmune disease. Her medications included oral cetirizine, antidepressants, metformin, insulin, and a topical glaucoma medication. She was scheduled with another physician for myectomy to remove muscles in the periocular region.

On examination, tear breakup time was 3.4 seconds OD and 4.4 seconds OS. Meibography showed areas of gland dropout, shortening, and disorganization, especially in the lower lids **(Figure 5)**. Serologic tests for SS biomarkers were ordered and came back positive for antinuclear antibody.

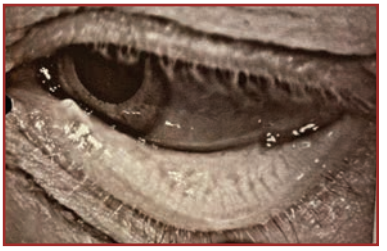

Figure 5. Meibography of the patient in Case 2 shows meibomian gland dropout, shortening, and disorganization

Discussion

Dr Toyos: This patient had a family history of an autoimmune disease. Many patients I see with severe DED have a positive personal or family history that raises my suspicion for SS-related DED. If the patient reports not having a personal history of an autoimmune disease, I often ask about family members. It is not unusual that I find a first-degree relative who has SS, eczema, Hashimoto syndrome, ulcerative colitis, or some other autoimmune disease, which suggests to me that the patient has a genetic predisposition that could be underlying the ocular surface disease.

When I suspect SS, I order the newer serology test that assesses classic SS biomarkers plus autoantibodies to carbonic anhydrase VI, parotid secretory protein, and salivary gland protein-1, all of which have been suggested to be early biomarkers for SS.[19]

What would be your approach for evaluating this patient?

Dr Hamrah: If the antibody test results for SS were negative, I might order a lip biopsy. I would then send the patient to a rheumatologist for a workup. The reason is that with decreased tear production, dry eyes, and dry mouth, seronegative SS cannot be ruled out because a negative serology does not rule out SS.

Diagnosis of Sjögren Syndrome

The workup for DED when SS is suspected includes standard assessments for DED. Ocular surface staining and Schirmer scores are included in the diagnostic criteria specific for primary SS that were issued in 2016 by the American College of Rheumatology and European League Against Rheumatism.[20] According to the criteria, the diagnosis is established according to a scoring system that considers these tests along with findings from lip biopsy, serology testing for anti-SSA/Ro antibodies, and/or unstimulated whole saliva flow rate.

Discussion

Dr Toyos: How would you treat this patient?

Dr Gupta: This is a complex case because the patient has SS along with blepharospasm, corneal disease, and depression. I would approach 1 issue at a time, and first focus on her SS and the associated inflammation. I also strongly believe in identifying and treating meibomian gland dysfunction (MGD) in patients with SS. Although SS is classically associated with lacrimal gland damage, it is an autoimmune disorder with chronic inflammation that affects the meibomian glands. There is evidence of severe meibomian gland destruction in patients with SS-DED and that MGD is underdiagnosed in this population.[21,22]

Dr Toyos: Treatment for DED should also address contributing factors. This patient is on topical glaucoma medications that may play a role in her disease. She is also on antidepressants that are known to cause dry eye.[23] Antidepressants should never be stopped abruptly, but once DED is improved, we can work with the prescribing physician to see about decreasing the antidepressant dose. Depression is more common among individuals with DED, although it is unclear if DED symptoms are contributing to the depression.[23]

Dr Gupta: In my experience, switching patients to another antidepressant has not been very helpful for improving DED, but trying to lower the antidepressant dose may be beneficial. I tell patients there are some factors contributing to their DED that we cannot change, and treatment with an antidepressant might be one of them.[23]

Treating Severe Dry Eye Disease

An array of options can be considered for treating SS-related and other forms of severe DED. The list includes ocular lubricants (thicker preservative-free formulations are preferable), cyclosporine, lifitegrast, steroids, punctal occlusion, cellulose cul-de-sac inserts, autologous serum, PRP, and vitamin B_{12} injections.[24-27] Newer treatments include varenicline nasal spray to stimulate natural tear production and intense pulsed light (IPL) that is approved for treating DED due to MGD and has been shown to significantly reduce inflammatory markers and improve the character and function of meibomian glands.[28-30]

Topical cenegermin, 0.002%, 3 times daily for 4 weeks is currently being investigated as a treatment for severe SS-related DED in 2 phase 3 vehicle-controlled studies (PROTEGO-1 and PROTEGO-2).[31,32] A dose-ranging phase 2 vehicle-controlled study (NGF0118) investigated cenegermin, 0.002%, twice daily or 3 times daily for treating moderate to severe DED.[33] Eligible patients had a history of DED for at least 6 months, ocular surface staining score > 3 (National Eye Institute), Symptom Assessment Questionnaire in Dry Eye (SANDE) score > 25 mm, Schirmer I value > 2 to < 10 mm/5 min, and tear breakup time < 10 seconds in the worse eye. The primary end point analysis of change from baseline to week 4 in Schirmer I showed statistical superiority for both cenegermin dosing regimens compared with vehicle **(Figure 6A)**.[33] In secondary end point analyses, cenegermin twice daily and 3 times daily were also associated with significantly higher responder rates than that of vehicle. Only the 3-times-daily regimen was associated with significantly greater improvements in the global and dryness or irritation SANDE scores compared with vehicle **(Figure 6B)**, which supports investigation of the 3-times-daily regimen in the phase 3 studies. The most common ocular adverse event in the cenegermin groups was lid or ocular pain, which was generally mild and self-limited. There were no serious adverse events.

Oral treatments used for SS-related dry mouth (pilocarpine and off-label cevimeline) might also improve DED.[34,35] Hydroxychloroquine and cyclophosphamide have been used off-label as immunomodulatory treatment for SS, but appear to have either no benefit on or the potential to worsen DED.[36,37] Repository corticotropin has multiple indications, including treatment of inflammatory ocular conditions.[38]

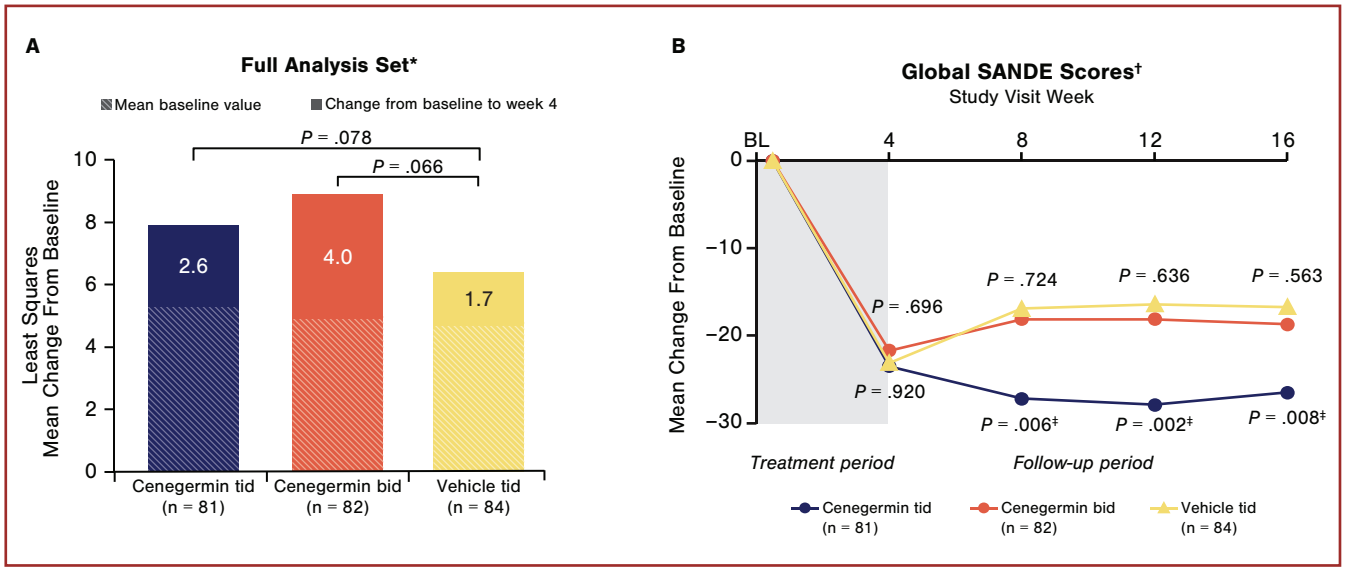

Figure 6. Cenegermin twice daily and 3 times daily was statistically superior to vehicle for improving Schirmer I (A).[33] Only the 3-times-daily dose significantly improved the global Symptom Assessment Questionnaire in Dry Eye score compared with vehicle (B).

Abbreviation: BL, baseline.

* All patients randomly assigned who took ≥ 1 dose of cenegermin and had ≥ 1 postbaseline efficacy measurement for the primary end point

† Data reported from the full analysis set

‡ Statistically significant comparisons of cenegermin vs vehicle ($P < .025$)

Case 2 Continued

The patient was switched from her preservative-containing glaucoma medication to tafluprost and scheduled for selective laser trabeculoplasty. In addition, she was told to use an artificial tear that contained less boric acid than the product she was using. She was started on biweekly IPL sessions at 12 J/cm^2. After 16 sessions, she was able to open her eyes without using her fingers to lift the lids and had returned to work, but still sought greater eye comfort. She started PRP, which helped her pain. Repository corticotropin was also tried but caused hyperglycemia and dehydration, which temporarily worsened her DED.

Discussion

Dr Toyos: I think ophthalmologists are knowledgeable about the potential for ocular surface toxicity using medications containing benzalkonium chloride. There is also evidence that tea tree oil, which is sometimes recommended for treating *Demodex* infestation, can be toxic to meibomian glands.[39]

What is your approach to patients with severe DED whom I call "incompletely treated"? These are individuals who have tried multiple therapies without sufficient response.

Dr Hamrah: I look carefully at their past treatments. If something was not used appropriately or given an adequate trial, I might reintroduce it. I routinely prescribe a combination anti-inflammatory regimen that includes a steroid for these patients, and I maintain the steroid at a low dose after an initial more intensive period of treatment.

When patients are complaining of ocular pain, we use an anesthetic challenge to evaluate the origin of the pain. Complete relief of pain after application of the numbing drop suggests the cause is from the eye, whereas no relief or partial relief indicates a central neuropathic component. In the latter situations, we prescribe an oral neuromodulator and then go to blood-derived products or test for NK and other comorbidities that may explain the patient's signs and symptoms.

Dr Gupta: I agree that it is very important to thoroughly review the treatments tried already because patients often do not give medications a fair trial and expect they can be adequately treated with a single therapy.

I like to start a topical steroid when I see patients who have not responded to a previous intense regimen because I expect it should provide benefit quickly. In addition, I layer therapies. I tell my patients that if we get enough drops in a bucket, there will be enough water that they should start to feel better. I also test corneal sensation to check for NK when I see complex patients such as this because my experience is that they often have mixed NK and DED.

Dr Toyos: As my practice is a tertiary referral center, the patients we see have already been on multiple treatments, including treatments for inflammation. Therefore, we also use systemic interventions for inflammation control, including fish oil supplements and low-dose naltrexone, and, in addition to topical therapies, we even put patients on a vegan diet for a short while to reset the gut microbiome.[40-42]

Is there anything about this patient's presentation and history that would raise your suspicion for corneal nerve damage and NK?

Dr Gupta: The chronicity of the problem is a red flag, together with the complexity of her disease.

Dr Hamrah: I agree that her failure to respond to multiple treatments is a warning sign together with the severity of her disease. As Dr Gupta said, patients with ocular surface disease can have multiple comorbid conditions with a dry component, NK, and pain.[43] Therefore, it is important to focus not only on 1 of those diseases, but to try to understand everything that is contributing to the phenotype.

Nerve Dysfunction and Dry Eye Disease

As recognized in the revised definition of DED developed by the Tear Film and Ocular Surface Society Dry Eye Workshop II, neurosensory abnormalities play an etiologic role in DED.[44] The underlying pathway may be understood according to the fact that corneal nerve function stimulates tear production and blinking and is essential for maintaining ocular surface homeostasis.[2,45] Nerve dysfunction also explains symptoms of DED because DED-related inflammation leads to sensitization and abnormal activity of corneal nerves that manifests with pain and allodynia. In addition, increasing ocular surface damage in DED leaves corneal nerves exposed, increasing their susceptibility to damage from inflammation and setting up a vicious cycle that perpetuates progression of corneal and neuronal damage with eventual loss of corneal sensation.

Case 2 Continued

Four years later, the patient had decreased corneal sensitivity in all 5 zones of the cornea when tested with a cotton wisp and 10+ ocular surface staining (National Eye Institute) OU, including centrally. She was enrolled in the NGF0118 clinical trial and was assigned to receive cenegermin 20 µg/mL 3 times daily. Her SANDE scores at baseline were 96 for symptom frequency and 95 for severity. She reported improvement in both eyes at 1 month. At her final visit at 10 months, her SANDE frequency and severity scores were 40 and 43, respectively. She described herself as "much improved" and not using any dry eye treatments.

The patient returned again after 2 years, requesting IPL and cenegermin. She reported not using any drops for DED since her last visit and having undergone blepharoplasty OU and a temporal brow lift elsewhere without any dryness postoperatively. She started cenegermin 6 times daily for 8 weeks and then received a second IPL treatment series. When seen 3 months later, the patient reported obtaining almost immediate relief after starting cenegermin and said that she felt the second course was more effective than the first but caused more lid tenderness. She also reported using artificial tears and oral cetirizine for allergies and was advised to switch to a topical antihistamine.

Discussion

Dr Gupta: This patient had an autoimmune diagnosis underlying her DED. I think that in such a setting, clinicians might focus solely on the DED. This case is a good reminder to keep the diagnosis of NK in the back of our minds because it can be comorbid with DED.[43]

Dr Toyos: It is also noteworthy that the patient in this case did well for 2 years after completing cenegermin. That shows the potential for a sustained benefit after a course of cenegermin. I am looking forward to seeing the results from the phase 3 studies investigating cenegermin for severe SS-related DED.[31,32]

The idea has been raised that treatment with cenegermin could lead to migraine, but there has been no signal associating cenegermin with headache either in clinical trials or in my own experience. I think lid pain is a common adverse effect of cenegermin, but it is generally mild, rated by my patients as 2 to 4 on a scale of 0 to 10. The increased lid tenderness this patient experienced with her second vs first course of cenegermin may be related to the more frequent dosing schedule used in the second course—6 times daily vs 3. Ocular and lid pain among patients I enrolled in the phase 2 study usually lasted approximately 2 weeks

and never persisted beyond 4 weeks.[33] None of my patients requested treatment for pain relief or discontinued study participation because of the pain, although a few patients at other centers did.

When my clinical study patients reported lid tenderness,[33] I was excited for them because I felt it was an indication they were using cenegermin and not vehicle. It seems the tenderness generally begins after approximately 2 weeks and is thought to be a consequence of nerve regeneration.[46]

Dr Hamrah: I describe the phenomenon to my patients as "growing pains" and frame it as a positive development signaling that their nerves are growing back. I think this concept motivates treatment compliance.

Case 3: Patient With Stage 2 Neurotrophic Keratitis

From the Files of Preeya K. Gupta, MD

A 32-year-old woman with a 20-year history of type 1 diabetes presented with DED. She had ptosis surgery 3 months earlier and then developed lagophthalmos, resulting in exposure keratopathy (OD > OS). Treatment with punctal plug insertion and topical lubricants was ineffective. BCVA was 20/100, and corneal sensation was reduced by floss test. Slitlamp examination showed rough-looking corneal epithelium and a central epithelial defect with rolled edges **(Figure 7)**. The patient was diagnosed with stage 2 NK.

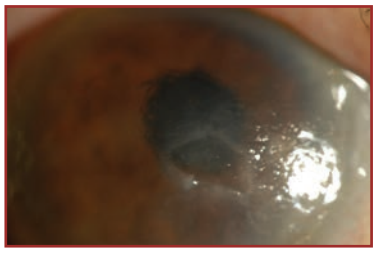

Figure 7. Slitlamp image of the patient in Case 3 with stage 2 neurotrophic keratitis shows a central epithelial defect with rolled edges

Discussion

Dr Gupta: I was prompted to check corneal sensation in this patient because of her longstanding history of diabetes. I also test corneal sensation in all patients with an epithelial defect unless I know it has an infectious etiology.

Dr Hamrah and I were members of an expert panel that developed consensus opinions on best practices for diagnosing and treating NK.[47] Our group identified certain patient characteristics that we strongly felt should prompt corneal sensitivity testing **(Table 3)**.[47] A painless newly observed epithelial defect of unknown etiology is one of these characteristics. With that in mind, I always consider concordance between signs and symptoms when deciding about testing corneal sensation. A patient who has a large epithelial defect but is asymptomatic is likely to have NK. A history of herpetic eye disease is another indication for testing, but because patients may not realize they had been diagnosed with an ocular herpetic infection, I ask if they were ever put on a longer course of pills or drops to treat a bright red painful eye. I also review the history for any diagnoses or procedures that can cause damage to the trigeminal nerve. I often test corneal sensitivity if I see limbal stem cell deficiency because some of its underlying conditions are also etiologies for NK.

How would you treat this patient?

Dr Hamrah: I like using amniotic membrane as initial treatment. I also use serum tears, but it takes time for the serum to arrive. If the defect does not heal, I might repeat the amniotic membrane or switch to cenegermin.

Table 3. Patient Characteristics to Prompt Corneal Sensitivity Testing[47]

Strongly Recommended	May Be Considered
• Persistent epithelial defect that does not improve within 14 days • Painless, newly observed epithelial defect of unknown etiology • History of herpetic eye disease • History of procedures that might have damaged the trigeminal nerve or conditions that might have involved the trigeminal nerve • Pain in the affected eye and multiple, concurrent risk factors, such as persistent poorly controlled diabetes and either reduced blink or a history of corneal procedures	• Acquired limbal stem cell deficiency • Newly observed epithelial staining and persistent poorly controlled diabetes • Persistent poorly controlled diabetes and vision changes not ascribed to diabetic retinopathy or cataract (even in the absence of corneal findings)

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Dr Toyos: I would probably start with cenegermin. I generally do not use amniotic membrane for patients with chronic disease because I feel it does not last long enough.

Case 3 Continued

A self-retained cryopreserved amniotic membrane was placed on the eye, and paperwork for cenegermin was submitted. When the amniotic membrane was removed after 7 days, corneal staining had resolved, the cornea was clear, and uncorrected VA improved to 20/25. Because the NK resolved after treatment with the amniotic membrane, cenegermin was not used. Because of her risk for recurrence, the patient was asked to continue lubricants and tape her eyelid at night. She was also started on topical cyclosporine.

Dr Gupta: Gaining insurance approval for using cenegermin to treat stage 1 or even stage 2 NK can take time, depending on the patient's insurance. For patients with limited coverage, they can apply for reduced cost or funded therapy through a program available from the manufacturer.

Recommendations for ongoing management in this case highlight that, in addition to achieving corneal healing, treatment for NK should include a plan for maintaining epithelial integrity.

Case 4: Patient With History of Acoustic Neuroma Surgery

From the Files of Preeya K. Gupta, MD

A 70-year-old male was seen with declining vision. He had acoustic neuroma surgery 10 years earlier and had a posterior chamber intraocular lens. Examination showed 20/400 BCVA, central corneal haze, and irregular epithelium, with a 3 × 2 mm defect in the left eye **(Figure 8)**. He had limited response to previous treatment with topical preservative-free lubricants, punctal plugs, serum tears, and amniotic membrane. Testing with floss showed very reduced corneal sensation.

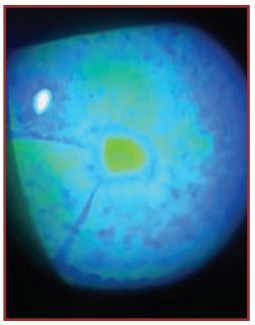

Figure 8. Slitlamp image of the patient in Case 4 after fluorescein instillation shows a 3 × 2 mm epithelial defect

Discussion

Dr Gupta: A patient with an active epithelial defect related to NK will not sense pain and, therefore, may not recognize the disease is worsening.[5] Because I have seen patients such as this being lost to follow-up and then later return unknowingly with a descemetocele or iris prolapsing through a perforated cornea, I feel I have to be aggressive with treatment. I would prescribe cenegermin for this patient.

Would you put another amniotic membrane on while the patient waits for the cenegermin?

Dr Toyos: I would not, but I might recommend IPL because I think there is great value in trying to restore natural tears. I also get patients off any topical drops if possible, especially anything that contains preservatives.

Dr Hamrah: I would put a second amniotic membrane on if the first one resulted in at least 50% improvement. Otherwise, I would order cenegermin. I tend not to use scleral lenses for NK because there are so many other good treatments. Scleral lenses temporarily improve vision, but they are palliative, do not address the underlying etiology, seal the eye off from trophic factors found in natural tears, and increase exposure to any inflammatory mediators that are present.[3,5,48]

Dr Toyos: We also try to stay away from scleral and contact lenses because of their potential complications.

Case 4 Continued

Cenegermin was started. Initial follow-up was by telephone because the patient presented early during the COVID-19 pandemic. He reported being much better and able to see out of the affected eye. When the patient was evaluated after completing the cenegermin, his BCVA had improved to 20/30. Because the cornea was at high risk of decompensating, treatment was continued with preservative-free lubricants, lubricant ointment, lifitegrast, and serum tears.

Discussion

Dr Gupta: Is there anything else that you would do to try to prevent recurrence of epithelial breakdown?

Dr Hamrah: As you mentioned earlier, it is important to have a plan that will help maintain the epithelial integrity after patients complete cenegermin because even though cenegermin promotes nerve regrowth, nerve density does not reach the level seen in healthy eyes.[49] For maintenance therapy, I like to use serum tears and other ocular surface treatments, which could include IPL or cyclosporine. I think it is much more cost effective to prevent recurrence using those modalities than to face the situation in which a patient needs another course of cenegermin. I also ask patients at high risk of recurrence to return for follow-up every 3 months.

Dr Toyos: Using something that will maintain corneal integrity is also important because we may not be able to eliminate the underlying etiology for NK.

Dr Gupta: Do you shorten the interval for follow-up for patients with certain etiologies of NK?

Dr Hamrah: Looking at a series of approximately 40 patients, we found that diabetes and use of glaucoma drops were associated with nonresponse. I follow patients with these histories more closely, especially because it can be challenging to get the glaucoma specialist to switch the patient to preservative-free medications. I also monitor patients with a history of herpetic keratitis more closely to make sure that their flare-ups are controlled. I see patients with a history of cranial neurosurgery with greater frequency because in my experience, they seem to worsen more quickly after finishing cenegermin.

Take-Home Messages

Corneal Nerves in Ocular Surface Health and Disease

- Corneal nerves have a critical role in maintaining ocular surface homeostasis
- Loss of corneal sensation is the underlying cause and diagnostic hallmark of NK
- Corneal nerve damage can factor into the pathophysiology of DED, its symptoms, and its progression
- Corneal nerve damage in eyes with ocular surface damage can manifest with either pain or absence of symptoms

Neurotrophic Keratitis Management

- The goals of treatment of NK are to prevent progression of corneal damage and to promote corneal healing
- There are multiple therapies from which to choose, but many provide only ocular surface protection and are just palliative
- Topical cenegermin aims to address the underlying etiology of NK and is safe and effective for promoting corneal healing
- Management to maintain corneal epithelial integrity is important after effective treatment of NK in patients at risk for recurrence

Evaluation and Management of Severe Dry Eye Disease

- Severe DED that is refractory to treatment may be related to improper treatment or an undiagnosed autoimmune disease, including SS
- Review how patients use their existing treatments
- Maintain an index of suspicion for SS and review the patient's personal and family history and extraocular signs and symptoms for relevant diagnostic clues that will guide the further workup
- There are a host of treatments to use in the management of severe DED
  - Topical cenegermin showed benefit for treating moderate to severe DED in a phase 2 study and is being evaluated for treatment of severe SS-related DED in phase 3 studies

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1. Which of the following is a function of corneal nerves in maintaining homeostasis of the ocular surface?
   a. Stimulation of tear production
   b. Trophic support to corneal epithelial cells
   c. Protection through reflex blinking response
   d. All the above

2. In which ocular surface disease can symptoms of pain resulting from changes in corneal nerve function be present?
   a. DED
   b. NK
   c. Both a and b
   d. Neither a nor b

3. What is the diagnostic hallmark of NK?
   a. Pain without stain
   b. Decreased corneal sensation
   c. Corneal epitheliopathy
   d. Tear hyperosmolarity

4. According to a recent consensus, which would be less likely to prompt corneal sensitivity testing to aid in the diagnosis of NK?
   a. Presence of an epithelial defect without pain
   b. Presence of new epithelial staining and poorly controlled diabetes
   c. Presence of pain, reduced blink, and poorly controlled diabetes
   d. History of herpetic eye disease

5. A patient who has been using generic topical timolol maleate for 9 years to treat glaucoma is diagnosed with stage 1 NK and MGD. First-line treatment can include:
   a. Switching to a preservative-free drop for intraocular pressure lowering
   b. IPL
   c. Cenegermin
   d. All the above

6. A patient is diagnosed with SS-related DED and stage 1 NK. His rheumatologist had prescribed oral cevimeline and oral hydroxychloroquine as treatments for his SS. He is started on preservative-free artificial tears, topical loteprednol, 0.5%, and cyclosporine, 0.05%, for DED management. Treatment for the NK might include all the following, EXCEPT:
   a. Bandage contact lens
   b. Cenegermin
   c. Autologous serum eye drops
   d. Asking the rheumatologist if the hydroxychloroquine can be changed to a different immunomodulatory agent