FDA-Approved Therapy for Neurotrophic Keratitis

Oxervate (cenegermin-bkbj) ophthalmic solution 0.002% (20 mcg/mL), a recombinant human nerve growth factor, is the first FDA-approved pharmacologic treatment that targets the root pathogenesis of neurotrophic keratitis.¹

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Expert Case Studies in Managing Neurotrophic Keratitis

The content from this supplement was derived from a roundtable discussion at the 2019 American Academy of Ophthalmology’s annual meeting in San Francisco. The panelists practice primarily in clinics that receive a high number of referrals for a number of cornea-related issues, including neurotrophic keratitis. All panelists are paid participants.

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**Eric D. Donnenfeld, MD**: Neurotrophic keratitis is one of the most difficult diseases that ophthalmologists manage. It can lead to significant ocular morbidity, and until recently, it represented a longstanding unmet need.

The following discussion by a panel of leading cornea specialists describes this sight-threatening disease, its etiologies, and how to diagnose it. The panelists also share their experiences with cenegermin bkbj 0.002% (20 mcg/ mL) ophthalmic solution (Oxervate, Dompé), the first medication approved by the FDA to treat neurotrophic keratitis.

**DEFINITION & PREVALENCE**

**Dr. Donnenfeld**: Dr. Sheppard, what is neurotrophic keratitis?

**John D. Sheppard, MD, MMSc, FACS**: Neurotrophic keratitis is a degenerative disease characterized by denervation of the cornea from a variety of causes, most commonly herpetic infection. It results in loss of corneal sensitivity, corneal epithelium breakdown, topographic irregularity with compromised visual function, poor corneal healing, and, if left unchecked, eventual development of corneal ulceration, melting, and perforation.

**Dr. Donnenfeld**: Dr. Majmudar, what is your experience with neurotrophic keratitis in your practice?

**Parag Majmudar, MD**: Neurotrophic keratitis is classified as a rare disease, with an estimated prevalence of 65,000 patients in the United States. As a tertiary care practice that focuses on corneal health, historically, we have struggled with how to treat these eyes, not only in the acute phase but also how to rehabilitate them in the long-term.

**Dr. Donnenfeld**: Dr. Desai, what is your experience with neurotrophic keratitis?

**Neel R. Desai, MD**: We also serve as a tertiary care center, so most patients who have neurotrophic keratitis are referred to us by other physicians. Unfortunately, we often see them after they’ve had persistent epithelial defects (PEDs) associated with neurotrophic keratitis for weeks, if not months. Typically, they’ve been treated with multiple therapies without success, and they’ve developed scarring and deep set denervation. This underscores the importance of educating our colleagues that we now have a therapy that targets the underlying pathogenesis.
**Ocular**
- Infections (eg, post-herpes)
- Ocular surgery (eg, post-laser vision correction)
- Contact lens wear
- Chemical and physical burns
- Abuse of topical anesthetics
- Drug toxicity
- Chronic ocular surface injury

**Central Nervous System**
- Post-neurosurgical procedures
- Stroke
- Neoplasm
- Aneurysms
- Degenerative disorders of the CNS
- Parkinsonism

**Genetic**
- Riley-Day syndrome
- Goldenhar-Gorlin syndrome
- Mobius syndrome
- Familial corneal hypoesthesia

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

Figure 1. A whole host of etiologies ultimately lead to neurotrophic keratitis.5,7

Dr. Donnenfeld: Do you consider neurotrophic keratitis a rare disease?

Dr. Desai: In my practice, it is a fairly common disease state that is the end of a pathway for unresponsive ocular surface inflammation and disease.1 I believe it is underdiagnosed because corneal sensitivity is not tested routinely in most general practices.5

Dr. Donnenfeld: Dr. Galor, what is your perception of the prevalence of neurotrophic keratitis?

Anat Galor, MD, MSPH: Prevalence estimates depend on our definitions and how well we’re screening for a disease. If we test corneal sensitivity in every patient who has ocular surface disease and other risk factors for neurotrophic keratitis, we will have a different prevalence estimate than if we focus only on stage 2 (moderate) or stage 3 (severe) disease.

Dr. Donnenfeld: Early intervention in the management of neurotrophic keratitis is the key to preserving healthy stroma before scarring develops.2,6 With that in mind, let’s discuss what causes neurotrophic keratitis.

**CAUSES OF NEUROTROPHIC KERATITIS**

Dr. Donnenfeld: The causes of neurotrophic keratitis are typically divided into four groups: ocular, systemic, genetic, and central nervous system (Figure 1).4

Let’s first discuss the ocular causes of neurotrophic keratitis.

Dr. Galor: Chronic ocular surface inflammation is a frequently overlooked cause of neurotrophic keratitis.5 This is because corneal nerve function has been somewhat overlooked when assessing patients with ocular surface diseases.5 So, we need to think about nerves and assess corneal nerve function in at-risk individuals, such as individuals using chronic glaucoma medications.4

Dr. Donnenfeld: Dr. Desai, what’s the most common cause of neurotrophic keratitis in your practice?

Dr. Desai: It’s a three-way tie. Post herpetic disease is quite common. I also see neurotrophic keratitis in patients who have chronic ocular surface inflammation from topical medications that contain benzalkonium chloride. This leads me to the third group: patients with end-stage ocular surface disease. Their corneas have been chronically inflamed. They used to complain to their doctors about their symptoms, but eventually they stopped complaining as their corneas became denervated. I would add that I think we are largely under-recognizing and under-diagnosing the neurotrophic keratitis caused by chronic ocular surface disease in general.5

Dr. Donnenfeld: The most common causes of neurotrophic keratitis are herpes simplex and herpes zoster viral infections.2,5 While herpes simplex is a significant problem, herpes zoster is devastating, as it can cause almost complete corneal denervation.2,5 These are the most difficult cases that I manage in my practice. Any type of surgical intervention has associated complications, so rehabilitating these corneas is imperative.2

Let’s discuss the systemic causes of neurotrophic keratitis. How big an issue is diabetes in neurotrophic keratitis?

Dr. Desai: Diabetes, particularly type 2 diabetes, is on the rise, and it is a significant contributing systemic factor.4

Dr. Majmudar: I believe diabetes is under-recognized as a cause of neurotrophic keratitis.

Dr. Donnenfeld: Among genetic causes, Riley-Day syndrome, or familial dysautonomia, is highly associated with neurotrophic keratitis.5,7 Dr. Sheppard, have you managed any patients who have Riley-Day syndrome?

Dr. Sheppard: Yes, but rarely. These children generally begin their journey with a pediatric ophthalmology referral and receive standard dry eye therapy, which is not adequate. Management can be difficult. Patients don’t have symptoms and they don’t complain, because there’s basically no corneal
innervation. The parents don’t cooperate because their kids look and feel fine. It’s a multifaceted challenge.

**Dr. Donnenfeld:** Among the many possible causes for neurotrophic keratitis related to the central nervous system, the cases I see most frequently are post-neurosurgical procedures, particularly parotid tumors.

**INSIGHTS ON DIAGNOSIS**

**Dr. Donnenfeld:** Dr. Majmudar, how do you assess and diagnose neurotrophic keratitis?

**Dr. Majmudar:** We start with a thorough history to identify risk factors, particularly prior infection, surgery, trauma, or systemic disease. It takes some detective work to piece together the full picture. Once we have a proper history, my physical examination focuses on the ocular surface, looking at the epithelium and testing corneal sensitivity. Although there are several methods for testing corneal sensitivity—some that are qualitative and some that are quantitative—most clinicians rely on a qualitative assessment using a cotton-tipped swab or dental floss to determine absence or presence of sensation.

**Dr. Sheppard:** The astute clinician recognizes the never-blinking or bug-eyed rarely blinking neurotrophic keratitis patient immediately upon walking into the examination. Normally, someone blinking 10 times per minute and sleeping 6 hours per night will blink more than 10,000 times a day. This rate is markedly reduced in patients with neurotrophic keratitis.

Another sign is when proparacaine or fluorescein is instilled. Typically, these drops burn or sting, but when specifically asked, patients with neurotrophic keratitis usually say they do not feel a thing.

**Dr. Donnenfeld:** A corneal sensitivity test is essential to confirm a diagnosis of neurotrophic keratitis. Some practices use anesthesiometer, while others use more low-tech methods. Dr. Sheppard, tell us about your technique for using a cotton-tipped swab.

**Dr. Sheppard:** First, a reminder. When you plan to test a patient’s corneal sensitivity, alert your staff to schedule a ‘no touch’ visit to ensure the patient will not receive any eye drops before sensitivity testing. In my experience, even an IOP check 1 hour or less prior to testing can compromise your examination. That said, I use an alcohol wipe, some sterile cotton-tipped swabs, and sterilized jewelers forceps. The compressed forceps pull out a wisp of cotton, which I twist with an alcohol-cleaned fingertip. I touch the unaffected eye with the cotton wisp first—I don’t want to touch a herpetic eye and then touch the other eye—and I note the response, watching carefully for the aforementioned lid and globe signs of sensation. I then touch the affected eye, often in quadrants because herpetic denervation does not necessarily involve the entire cornea. I then ask the patient, ‘If that’s a dollar’s worth of sensation [in the good eye], how much sensation is this [in the bad eye]?’ Sometimes you just have to decide yourself, so I use a semi-quantitative percentage of normal scale for my patients.

**Dr. Donnenfeld:** I also use a cotton wisp. I hold the eye open with one hand and hold the cotton wisp with the other hand. I approach the eye from the side so the patient can’t see the cotton wisp as it approaches the eye.

**Dr. Majmudar:** I believe you use a slightly different technique.

**Dr. Majmudar:** When I’m teaching residents, I find they immediately want to instill a combination topical fluorescein-anesthetic to stain the cornea, which would prevent us from assessing corneal sensitivity. My preferred technique is to wet a fluorescein strip with saline and gently touch the corneal surface with the tip, thereby eliciting a response from the patient in each eye. I can then immediately touch the strip to the conjunctiva. This method shows if there’s a difference in sensitivity between the eyes and also allows me to stain the ocular surface in a more time-efficient manner.

**Dr. Donnenfeld:** Dr. Desai, how do you perform corneal sensitivity testing in your practice?

**Dr. Desai:** Because we see most of our patients on referral, our workup technicians follow specific protocols. For example, if I’m seeing a patient for a pupillary abnormality, an anterior segment tumor, or a lens malposition, our technicians don’t dilate the pupil. Similarly, if I’m seeing a patient for suspected neurotrophic keratitis or a PED, our technicians test sensitivity with the esthesiometer before instilling any drops.

**Dr. Donnenfeld:** Dr. Galor, I understand you use dental floss to test corneal sensitivity.

**Dr. Galor:** We use dental floss to assess corneal sensitivity because the length and diameter of the dental floss can be easily standardized, and standardization is key. We gently touch the central cornea and qualitatively assess response to touch as: 4 hypersensitive, 3 normal, 2 decreased, and...
absent. While the scale is qualitative, we have found it to be easy to use and reproducible.

**Dr. Desai:** Do you test corneal sensitivity every time you suspect neurotrophic keratitis?

**Dr. Galor:** As part of my standard work-up, any patient who is referred to me with ocular surface disease, who is not responding to traditional therapies, will undergo corneal sensitivity testing.

### KEY SIGNS AND STAGING GUIDANCE

**Dr. Donnenfeld:** Most of us who work in consultative practices are seeing patients for second or third opinions, and they've already been treated by other physicians. Often, they'll be using medications to which they're not responding. The knee-jerk reaction is to change the medications, but that's almost never the right answer. Here's a pearl based on my experience: Suspicion of neurotrophic keratitis should be raised in patients who have not responded to traditional therapies. As mentioned before, loss of corneal sensitivity is key to diagnosing neurotrophic keratitis.²

**Dr. Galor:** I consider any punctate epithelial keratitis (PEK) as stage 1.⁴ Stage 2 involves a nonhealing corneal epithelial defect, and stage 3 is characterized by epithelial and stromal loss.³ In my practice, stage 1 is common. My goal is to diagnose and treat the disease early to prevent it from advancing to stages 2 and 3.

**Dr. Donnenfeld:** Dr. Sheppard, what are the characteristics of a PED in neurotrophic keratitis? What should we be looking for?

**Dr. Sheppard:** First, I look for signs of a healed defect, such as negative pooled staining, the classic epithelial suture lines where migrating surface cells finally meet, or subepithelial haze, remembering that most PEDs are central.²⁵

Most patients have unilateral disease. A patient with diabetes or with neurodegenerative disease may have bilateral neurotrophic keratitis, although one eye may have more advanced disease.³ A persistent stage 2 epithelial defect leaves the intact nonreflective Bowman’s membrane exposed.⁴

The classic deficient leading edge shows immobile, scrolled, opaquely apoptotic heaped-up epithelium. The epithelium is trying to heal, but it bunches up on itself. In chronic PEDs, associated neovascularization, scarring, and stromal haze will be prognostic of continued decline.²

Stage 3 lesions also reveal stromal thinning, in addition to stage 2 findings.⁵

**Dr. Donnenfeld:** Dr. Desai, in stage 1 mild neurotrophic keratitis, what do stromal scarring and corneal neovascularization tell us about the chronicity of the disease?

**Dr. Desai:** Corneal neovascularization indicates a chronic inflammatory state.² Even though we classify that as stage 1 mild,³ typically these patients are treated conservatively. This is reminiscent of our thinking 15 years ago when the DEWS report recommended immunomodulatory therapy only for stage 4 end-stage severe dry eye.⁵,⁸ We now universally understand this is not what we want to do.

**Dr. Galor:** To me, the goal is to keep the disease at stage 1. Once it advances to stage 2, there can be visual consequences.²

**Dr. Donnenfeld:** The important take-home message is that, if left untreated, even mild, stage 1 disease can result in significant vision loss.² Scarring and corneal neovascularization are signs that are consistent with vision compromise and chronicity of disease.² This is a disease where progression and vision compromise can potentially be prevented if treated appropriately and timely.² Once it advances to stage 2 and stage 3, it becomes much more difficult to treat and prevent possible vision loss.⁵

### TREATMENT CONSIDERATIONS

**Dr. Donnenfeld:** Treatments should be based on the degree of neurotrophic disease, the therapies that have already been tried, and the factors that lead to higher risk of vision loss.

**Dr. Majmudar:** What's your first-line therapy for mild neurotrophic keratitis?

**Dr. Majmudar:** Our first-line therapy will be tear replacement, discontinuing potentially toxic topical medications, and oral supplementation with omega-3 fatty acids. Topical steroids and systemic antibiotics may be indicated later, but in an early stage, we should focus on optimizing the ocular surface.²⁵

**Dr. Desai:** I would posit to my colleagues that many treatments—immunomodulatory therapy (lifitegrast and cyclosporine formulations, and steroids), serum eye drops, and systemic antibiotics such as doxycycline—should be
considered earlier in the process, to address any ocular surface associated diseases. I also consider amniotic membrane grafting useful at the present time, and I am optimistic about the potential for other biologics to help in the future.

Finally, I would use caution and perhaps not tie therapies so closely to staging. We want to treat early and treat the underlying issue. Hopefully, we can intervene sooner at the point of care and utilize nerve growth factor as a potential first- or second-line adjuvant.

Dr. Galor: I think about the underlying pathophysiology and the risk of disease progression, and then I tailor my therapy accordingly. I aggressively treat PEDs with strategies like amniotic membrane transplantation and autologous serum (Figure 2). If those therapies don’t work, I quickly move on. The key is to start early and not wait. If you wait, you can be left with visual consequences that you cannot reverse.

Dr. Donnenfeld: Disease modification is important, based not only on the risk of progression and the prognosis, but also on the visual potential of the eye. I am much more willing to consider a more aggressive approach to treatment for a patient who has a significant risk for disease progression and the potential for 20/20 visual acuity in an eye. We want to preserve vision and maintain the quality of the cornea in all patients.

Now, let’s discuss the first FDA-approved therapy for neurotrophic keratitis.

**Oxervate: Recombinant Human Nerve Growth Factor Targets the Root Pathogenesis of NK**

**INTRODUCING OXERVATE**

Dr. Donnenfeld: Oxervate (cenegermin-bkbj) ophthalmic solution 0.002% (20 mcg/mL) is the first FDA-approved application of a recombinant human nerve growth factor (rhNGF) as a drug or treatment. Oxervate was designated an orphan drug and a breakthrough therapy. It was given fast-track status and was approved under priority review by the FDA.

Cenegermin-bkbj, the active ingredient in Oxervate, is a recombinant human nerve growth factor (rhNGF) that is structurally identical to the human NGF protein made in ocular tissues (Figure 3). NGF is an endogenous protein involved in the differentiation and maintenance of neurons and is believed to support corneal integrity through three mechanisms: corneal innervation, tear secretion, and epithelial cell growth.

Oxervate is the first topical biologic medication approved in eye care and the first FDA-approved medication specifically indicated for neurotrophic keratitis. It is approved for use in patients 2 years of age and older.

Two clinical trials enrolled the largest combined population of neurotrophic keratitis patients ever examined in randomized controlled trials. In the REPARO (European) trial, 72% of patients receiving Oxervate, compared to 33.3% receiving vehicle, were completely healed at week 8. In the NGF0214 (US) trial, 65% of patients receiving Oxervate had complete corneal healing compared to 16.7%
of vehicle-treated patients. Complete corneal healing was defined as 0 mm staining in the lesion area and no persistent staining in the rest of the cornea.

The endpoint, complete corneal healing, is extraordinarily difficult to meet. You can have significant improvements and not have complete absence of staining.

Importantly, 80% of patients who achieved complete corneal healing in the REPARO (European) trial were still completely healed 48 weeks after one 8-week course of Oxervate (cenegermin-bkbj) ophthalmic solution 0.002% (20 mcg/mL).

As for side effects, the most common is eye pain following instillation (16%), and I make it a point to explain to my patients that they may experience eye pain, which is a key part of patient education. Other adverse reactions, occurring in 1% to 10% of patients, were corneal deposits, foreign body sensation, ocular hyperemia, ocular inflammation, and tearing. There was no evidence of systemic absorption or immunogenicity in clinical trials.

EVALUATING OXERVATE AS A TREATMENT OPTION

Dr. Donnenfeld: Dr. Sheppard, where does Oxervate fit within your current treatment options?

Dr. Sheppard: Early intervention creates a superior long-term picture for my patients. In the face of a frank and obvious diagnosis of any stage of neurotrophic keratitis in which the patient’s vision is threatened, I prescribe Oxervate, because I believe I’m targeting the underlying disease pathogenesis. Any patient who has neurotrophic keratitis deserves at least a consideration of Oxervate as a treatment option.

Dr. Donnenfeld: Dr. Galor, where does Oxervate fit in your treatment options?

Dr. Galor: If I am referred someone with stage 2 or 3 neurotrophic keratitis and the disease persists after we have tried other options, such as bandage contact lenses, autologous serum, and amniotic membranes, my next step is Oxervate.

Dr. Donnenfeld: Dr. Desai, how do you decide when to start treating with Oxervate?

Dr. Desai: I usually think in terms of risk stratification rather than the disease stage. I consider the risk of disease progression and the vision potential for a particular eye. I think we have enough personal experience to support earlier intervention with Oxervate.

Dr. Donnenfeld: I consider the answers to fundamental questions when deciding when to introduce Oxervate:
- What was the previous treatment and response?
- What is the corneal sensation?
- How severe is the disease?
- What is the visual potential for the affected eye?

Then I have a conversation with the patient, because patients should be part of the decision-making process. They need to be educated about the cause of the disease, their treatment options, and Oxervate’s role in managing the disease. At the end of the day, part of my job as the treating physician is to make a treatment recommendation. Generally, patients follow my recommendation.

Dr. Sheppard: We’re talking about how far up the algorithm we move Oxervate therapy for neurotrophic keratitis, and we all agree that all patients are not the same. For me, it’s easier to move an FDA-approved product more proximal in my treatment algorithm than it is a non FDA-approved product, for example, serum tears or compounded amniotic membrane extract.

Dr. Donnenfeld: Agreed. Supporting the ocular surface with a dry eye therapy does not treat neurotrophic keratitis. It may make it better, but it doesn’t target the underlying cause.

With that in mind, let’s look at some real-world cases. Please note that the information presented in the following cases is for educational purposes only, and the diagnosis and treatment-related decisions described were at the discretion of the treating physicians.

CASE 1: STAGE 2 NEUROTROPHIC KERATITIS

Dr. Desai: This 75-year-old man was referred to me for what was presumed to be herpes simplex virus (HSV) keratitis but was actually herpes zoster virus (HZV) keratitis. The patient had been treated with topical and systemic antiviral agents for several months continuously before presentation. He had received several dehydrated amniotic membrane grafts.

At the patient’s initial visit, I diagnosed stage 2 neurotrophic keratitis with a chronic nonhealing epithelial defect and confirmed complete anesthesia of the affected eye through a corneal sensitivity test. This was a classic oval central corneal defect with heaped edges. I noted some mild corneal neovascularization peripherally and the onset of mild stromal scarring.

Based on the patient’s history, I modified his current medications. I stopped the topical medications that I believe contributed to the development of not only neurotrophic keratitis but also herpes zoster virus keratitis.
keratitis but also limbal stem cell toxicity. I continued a low-maintenance dose of oral acyclovir and initiated oral L-lysine, then prescribed autologous serum eye drops and applied multiple self-retaining cryopreserved amniotic membrane. All of these are appropriate treatment options for neurotrophic keratitis. \(^2,5,7\) This seemed to heal the corneal epithelium completely for a few weeks, but ultimately the ulcer would recur a few weeks to months later.

While this patient was in my care, Oxervate (cenegermin-bkbj) ophthalmic solution 0.002% (20 mcg/mL) was approved in the United States. I escalated therapy to the point of suturing on cryopreserved amniotic membrane and debriding the ulcer and its edges before applying amniotic membrane grafts until the patient could start Oxervate. This was a relatively good baseline because the photographs (Figure 4A) were taken about 2 weeks after I had removed the sutured cryopreserved amniotic membrane. There was a central defect with staining and some peripheral corneal neovascularization.

By week 2 of Oxervate therapy, the cornea had started to re-epithelialize, and at week 5 there was significant progress (Figure 4B). After completing the 8 weeks of therapy, re-epithelialization was complete. Although the epithelium was irregular at that time, the healing was sustained to present day. Post-treatment, the cornea was fully healed, and we avoided the dense scarring that I’d expected, given this patient’s history and course of therapy (Figure 4C).

In summary, at initial presentation, I thought this patient was on a path requiring a permanent tarsorrhaphy, and I’d have to abandon any hope of visual rehabilitation. Remarkably, we were able to turn it around in 8 weeks. I still see the patient from time to time post-cataract surgery, and the cornea remains healed.

**CASE 2: STAGE 2 NEUROTROPHIC KERATITIS**

Dr. Majmudar: I first saw this 79-year-old woman about 3 years ago upon referral by her primary care physician. She had a typical herpes zoster rash over the left side of her forehead and around the eyes. She had some mild ocular involvement with anterior chamber inflammation and mild PEK. She responded well to an antiviral medication and a topical steroid. Her visual acuity was good.

Two years later, she presented with a central corneal ulcer. Topical lubrication with drops and ointments had been tried with no success, and I was considering performing a tarsorrhaphy. While tarsorrhaphy can be effective, it does carry significant issues for patients in terms of cosmesis and comfort. \(^2\)

The patient had been using gabapentin for post-herpetic neuralgia. She was also using oral prednisone and oral valacyclovir, as well as topical polymyxin B sulfate and trimethoprim sulfate (Polytrim, Allergan) and neomycin.

Corneal sensitivity testing confirmed no sensation in the area of the epithelial defect. I diagnosed stage 2 neurotrophic keratitis and decided to treat with Oxervate.

Figure 4. Case 1. These photos were taken prior to Oxervate (A), at week 5 (B), and after week 8 (C).

Figure 5. Case 2. At baseline (A,B). After 8 weeks of treatment with Oxervate, the ocular surface was significantly improved (C,D,E).
At baseline (Figures 5A and 5B), the defect was paracentral with a well-demarcated edge and the typical heaped-up epithelium. In retrospect, I believe this patient was farther along the spectrum than I’d initially thought. She already had significant volume loss and was on the way to scarring.

After 8 weeks of treatment with Oxervate (cenegermin-bkbj) opthalmic solution 0.002% (20 mcg/mL), the ocular surface was significantly improved, although a small defect remained (Figures 5C, 5D, and 5E). Even though this would have been classified as a failure in the FDA trials, this outcome had a tremendous impact on the patient’s clinical condition at the completion of treatment, and symptomatically the patient felt much better. She has some corneal opacity, so there are lingering questions about visual rehabilitation.

CASE 3: STAGE 2 NEUROTROPHIC KERATITIS

Dr. Sheppard: An 8-year-old girl had been referred to me with significant primary eyelid disease with a history of staphylococcal hypersensitivity keratoconjunctivitis and likely herpetic infection in the left eye. She had been treated with cryopreserved sutureless amniotic membrane, hypochlorous acid eyelid scrubs, and artificial tears—the whole litany of therapies, including oral omega-3 supplements and low-dose topical steroids. The cornea of the left eye was completely anesthetized, and a diagnosis of neurotrophic keratitis was confirmed. Although the eyelids improved with earlier treatment, the cornea did not.

The patient developed recurrent nonhealing defects at this early stage 2 neurotrophic keratitis, and scarring began to develop paracentrally, as seen in baseline images (Figure 6A). Her visual acuity and glare were suboptimal, as her topographies revealed alarming irregular refractive errors.

To address her stage 2 neurotrophic keratitis, I started Oxervate along with oral azithromycin and oral valacyclovir.

After 4 weeks of Oxervate therapy (Figures 6B and 6C) the epithelial defects improved, and only mild PEK lingered. By 8 weeks (Figure 6D), in terms of stromal changes, the cornea appeared completely healed to all but the most vigorous scrutiny with a high-magnification slit lamp examination. The patient’s visual acuity at follow-up was 20/25.

INTEGRATING OXERVATE INTO PRACTICE

Dr. Donnenfeld: The key to treating neurotrophic keratitis is diagnosing it in the first place. An evaluation for neurotrophic keratitis should be considered for any patient with persistent PEK who has not responded to conservative therapy. Results from a simple corneal sensitivity test will change how we manage ocular surface disease.

Dr. Desai, how do you identify candidates for Oxervate?

Dr. Desai: When patients are referred to us with possible neurotrophic keratitis, we perform cornea sensitivity testing, evaluate risk factors in their clinical history, and then we risk-stratify—the goal being to prevent disease progression to more severe, debilitating stages. Oxervate is among our potential first- or second-line therapies for at-risk patients, regardless of the stage of neurotrophic keratitis.

Dr. Donnenfeld: How do you educate patients about using Oxervate?

Dr. Desai: We schedule a visit for the day a patient will receive the first dose of Oxervate, so we can demonstrate how to assemble it and use it. This routine helps us educate patients to ensure compliance with using the medication.

Dr. Donnenfeld: Dr. Sheppard, do you have any pearls of wisdom for integrating Oxervate?

Dr. Sheppard: Patients who also have red, irritated eyes, discharge, meibomian gland disease, ciliary flush, and poor eyelid closure should be treated for concomitant conditions before managing neurotrophic keratitis with Oxervate.

In my experience, some patients experience ocular discomfort.
Dr. Donnenfeld: Dr. Galor, how often do you see patients who are using Oxervate?

Dr. Galor: I tailor my follow-up to the clinical situation. In general, I see my patients with PEDs every 1 to 2 weeks.

Dr. Donnenfeld: Many patients who have neurotrophic keratitis have concomitant diseases, such as diabetic eye disease and dry eye. How do you manage these other disease processes at the same time?

Dr. Galor: I want to set up the eye for success, and I think it’s important to use a stepladder approach. That’s why preservative-free artificial tears are important, not for treating the neurotrophic keratitis but for stabilizing the ocular surface. Treating inflammation is also important, perhaps with short-term corticosteroids and, longer term, with an anti-inflammatory agent. I always think about exposure and may consider a temporary or permanent tarsorrhaphy, depending on the situation.  

Dr. Donnenfeld: Patients who have neurotrophic keratitis, by definition, don’t have normal corneal sensation, so we can’t rely on symptoms to guide management. As I explain to patients, fluctuating or decreased vision is usually the only sign that the cornea may be breaking down. As with all diseases, the earlier we treat neurotrophic keratitis, particularly recurrences, the better the potential outcome. To me, declining vision in a patient who has neurotrophic keratitis is an ocular emergency. I want to see that patient as soon as possible.

Dr. Sheppard: The obvious must be respected. A significant plurality of these patients have herpetic disease, usually herpes simplex, so we must be certain they are compliant with an adequately absorbed dose of an antiviral.

CONCLUSION

Dr. Donnenfeld: Dr. Desai, based on your knowledge of this medication, what advice would you give to eye care practitioners who have not used Oxervate (cenegermin-bkbj) ophthalmic solution 0.002% (20 mcg/mL)?

Dr. Desai: I would encourage our colleagues to start thinking about neurotrophic keratitis early in their evaluations of patients with risk factors for this disease and incorporate corneal sensitivity testing into their routine. Use the resources Dompé makes available to facilitate patients’ access when prescribing Oxervate.

Dr. Donnenfeld: Neurotrophic keratitis is a difficult disease to manage. It requires a certain level of expertise, and you must use your entire team to develop a treatment plan that is seamless and effective. For those managing neurotrophic keratitis, Oxervate should be considered when evaluating appropriate treatment options. If you’re not comfortable managing this disease, then refer your patients to an experienced cornea specialist who is.

OXERVATE™ (cenegermin-bkbj) ophthalmic solution 0.002% is indicated for the treatment of neurotrophic keratitis.

WHAT IS OXERVATE™?
OXERVATE™ (cenegermin-bkbj) ophthalmic solution 0.002% is indicated for the treatment of neurotrophic keratitis.

DOSAGE FORMS AND STRENGTHS
Ophthalmic solution for topical use in the eye: cenegermin-bkbj 0.002% (20 mcg/mL) is a clear, colorless solution in a multiple-dose vial.

CONTRAINDICATIONS
None.

WARNINGS AND PRECAUTIONS
Use With Contact Lenses
Contact lenses should be removed before applying OXERVATE because the presence of a contact lens (either therapeutic or corrective) could theoretically limit the distribution of cenegermin-bkbj onto the area of the corneal lesion. Lenses may be reinserted 15 minutes after administration.

Eye Discomfort
OXERVATE may cause mild to moderate eye discomfort such as eye pain during treatment. The patient should be advised to contact their doctor if a more serious eye reaction occurs.

ADVERSE REACTIONS
Clinical Studies Experience
Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be compared directly to rates in the clinical studies of another drug and may not reflect the rates observed in practice.

In 2 clinical trials of patients with neurotrophic keratitis, a total of 101 patients received cenegermin-bkbj eye drops at 20 mcg/mL at a frequency of 6 times daily in the affected eye(s) for a duration of 8 weeks. The mean age of the population was 61 to 65 years of age (18 to 95).

The most common adverse reaction in clinical trials that occurred more frequently with OXERVATE was eye pain (16% of patients). Other adverse reactions included corneal deposits, foreign body sensation in the eye, ocular hyperemia (enlarged blood vessels in the white of the eye), swelling (inflammation) of the eye, and increase in tears (1%-10% of patients).

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For healthcare providers seeking educational resources on neurotrophic keratitis and OXERVATE for themselves and their patients, please visit the OXERVATE resource portal at OXERVATE.com/hcp/resources