New and Emerging Treatments for Neurotrophic Keratitis

Also known as neurotrophic keratopathy, neurotrophic keratitis (NK) is a rare, degenerative corneal disease caused by diminishing trigeminal innervation. It can lead to epithelial breakdown and to problems with healing, and it may ultimately cause ulceration, melting, and perforation.[1]

"The biggest problem is not recognizing neurotrophic keratitis early enough," said Rahul S. Tonk, MD, MBA, at Bascom Palmer Eye Institute in Miami. "The patient may sit for weeks before referral and lose epithelium and even stroma, affecting the optics of the eye for a lifetime."

Today, the goals of treatment are not only to support the ocular surface but also to repair damage to corneal nerves and restore corneal sensation, said Dr. Tonk. Both pathways are currently seeing interesting developments, which is fortunate, he said, especially given that NK is an orphan condition.

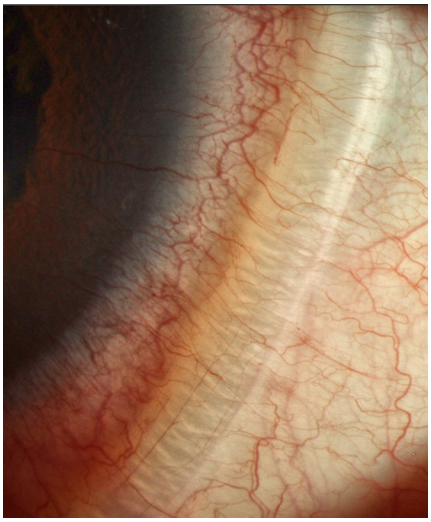
Oxervate

In 2018, the FDA approved cenegermin (Oxervate) for stages 1, 2, and 3 NK (see "Staging," next page). Made by Italian-based Dompé Pharmaceuticals, the novel eyedrop is the first to contain recombinant human nerve growth factor.[2]

Clinical trials. The FDA approval followed two randomized, controlled, multicenter trials of 151 patients with NK. "The primary outcome with Oxervate studies has been epithelial healing," said Asim Ali, MD, FRCS(C), at the University of Toronto. In these two trials, 70% of patients achieved complete corneal healing compared with 28% without cenegermin, and 80% of those who healed remained free of disease at one year.[3,4]

Study challenges. Aside from recruitment roadblocks due to a small patient pool, there have been a few challenges with NK clinical trials, said Sajjad Ahmad, FRCOphth, PhD, at Moorfields Eye Hospital in London. For example, earlier trials in the United Kingdom didn't last long enough to show whether healing is sustained, he said. "In addition, patients with NK are diverse. A stage 2 NK patient with diabetes and some sensation might have a very different outcome than someone with a neurosurgical lesion to the fifth cranial nerve and no sensation whatsoever. When studies aren't comparable, we need to consider all these kinds of factors."

Mechanism of action. Cenegermin is a recombinant form of human nerve growth factor, an endogenous protein that influences the differentiation and maintenance of neurons, helping to support corneal innervation and integrity in the anterior segment of the eye, said Dr. Tonk. But the success of nerve growth factors to regrow nerves depends on whether nerves are present nearby for recruitment, said Dr. Ali. Without this proximity, he said, "the restoration of sensation may not be one of the outcomes."



POST-OP. *A fascicle under the conjunctiva one month after corneal neurotization.*

Variable responses. The variability in response to cenegermin is incompletely understood, said Dr. Tonk. "Some patients respond well, some partially, and others not at all. And after finishing the treatment course, some patients relapse, which may depend upon the underlying cause." In real practice, what do things look like a year or two out? "It appears that most who have a beneficial response initially will hold that response," he said, "as long as they are followed closely and supported with supplemental treatments, such as lubricants, serum tears, topical anti-inflammatories, or amniotic membrane."

Protocols. The treatment protocol

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in clinical trials has been administration of eyedrops six times a day for eight weeks. In practice, the course may depend on response, said Dr. Tonk. "In the event of a partial or incomplete response, some doctors choose to repeat the treatment course, although insurance coverage can be a challenge."

Cost. Despite best efforts, sometimes there are delays between prescribing Oxervate and getting the drop into patients' hands, said Dr. Tonk. Cost and coverage remain challenging. He recommends that physicians and patients take advantage of Dompé Connect to Care, which provides comprehensive support services such as benefits verification and financial resources. His approach is to "get the ball rolling" early with Oxervate preauthorization while utilizing supplemental NK therapies to bridge the gap.

Side effects and follow-up. Although Dr. Tonk has seen few side effects in his patients, several have experienced sharp ocular pain that is relieved by topical anesthetics as their nerves regenerate. Other possible side effects include ocular hyperemia, eye inflammation, and increased lacrimation.[2] "Continue to follow patients over time for their neurotrophic disease as well as for pain and other side effects," he said.

Corneal Neurotization

Used primarily for stage 2 and 3 NK, corneal neurotization is a surgical procedure to restore innervation to the cornea when sensation has been partially or completely lost, said Dr. Ali, adding that there is some controversy about exactly how it works.

Mechanism of action. "There appears to be a dual mechanism of action with corneal neurotization," said Dr. Tonk. "First, the grafted sensory nerves may directly improve corneal sensation. Second, the grafted nerves secrete substance P, calcitonin gene–related peptide, and the like, which promote corneal epithelial proliferation and healing."

Evolving surgical approaches. Although first described in 1972, corneal neurotization was introduced in 2009.[5] "Performed by plastic surgeons, the early approach involved an invasive technique, requiring a large incision," said Dr. Ali. "Today, we use a much smaller incision in the brow or elsewhere on the face, whether performing a nerve transfer or a nerve autograft or allograft." A variety of approaches are currently being developed or investigated.

The nerve transfer is from a functioning sensory nerve on the face, either from the supraorbital, supratrochlear, infraorbital, or great auricular nerve, he said. The nerve graft connects functioning sensory nerves in the face to the cornea. Choice of approach considers the donor nerve sensory function, proximity to the recipient cornea, and surgeon's preference, among other factors.[6]

Using a technique his group pioneered, Dr. Ali and team first map out facial sensation and plan use of donor nerves. Then he harvests the sural nerve from the calf and isolates and assesses the facial donor nerves.[7] "We pass the nerve graft ipsilaterally or contralaterally underneath the brow into the subconjunctival space, exiting near the limbus," he said. "The nerve graft is then split into individual fascicles that travel into the peripheral cornea, connecting the cornea to the donor nerve."

Challenges. Dr. Ali has performed about 30 of these procedures so far, with many in children who have congenital corneal anesthesia, where it's more challenging to get a map of reliable donor nerves. "It's usually much more straightforward in acquired situations where there are known, healthy donor nerves, and it's easier to map out and plan the surgery."

However, he said, abnormal anatomy —either in the eye or the face—may complicate this process. In addition, previous surgery to the face may make it difficult to find nerves or to pass them around the face. And previous retinal, glaucoma, or strabismus surgery, for example, may cause scarring of the conjunctiva and lead to challenges when attempting to cover the nerves.

Procedural tips. "This is a long and technically complex surgery," said Dr. Ali. "You need a few of these under your belt to be proficient. Depending on the approach, you may need more than one surgeon to perform the surgery with you." When first starting out, work with someone who has previously performed the surgery, said Dr. Ali. "Pick an adult patient who has an acquired cause of corneal anesthesia, especially unilateral involvement and without any prior history of ocular surgery or facial surgery."

What to expect. Whether using a nerve graft or nerve transfer, outcomes appear to be similar, said Dr. Ali. "However, there isn't good evidence comparing techniques head-to-head. Studies have not been randomized and the patient groups have varied in terms of stage of disease, patient age, and

Staging

As you look for NK, it's important to note that it has several stages.

Stage 1 NK may simply look like severe dry eye, said Dr. Tonk, except that it doesn't often respond to lubricant drops alone. "Clues that you are dealing with NK include a diffuse pattern of punctate keratopathy and a swollen, irregular epithelium, all of which can be responsible for several lines of decreased vision."

Stage 2 NK is associated with recurrent or persistent epithelial defects or delayed healing following epithelial scraping, said Dr. Tonk. These defects are often bordered by rolled, loose edges of swollen epithelium.

Stage 3 NK is characterized by a corneal ulcer wherein the stroma may melt or even perforate. Surgeons should investigate for melt when looking at any epithelial defect, said Dr. Tonk. This can be done easily with a thin, high-powered slit beam or by obtaining an anterior segment OCT scan. Even in the best case, melts are associated with corneal haze and irregular astigmatism and can limit final visual outcome.

outcomes being measured." Generally speaking, return of sensation takes more time than it does with Oxervate, he added.

Other Emerging Treatments

"It's exciting to see new options on the horizon for something that is essentially an orphan disease," said Dr. Ali. Some are being investigated for NK or are already in use outside the United States. Many of these may be used in combination with treatments that tackle the root cause of NK, said Dr. Tonk. "We have a number of emerging treatments designed to support the ocular surface and others to treat the root cause of NK itself."

Topical insulin. Although not yet widely used in the United States for NK, topical insulin has been used off label in the United Kingdom for patients who are "at the end of the road" and at risk of corneal melting or perforation, said Dr. Ahmad. The typical protocol is to use standard insulin diluted to a concentration of 1 unit per millilter, he said. "It's worth trying—and not just in those with diabetes—because it's safe, cheap, well-tested in millions as a systemic treatment, and it works in a subgroup of patients."

Although its mechanism of action is not confirmed, said Dr. Ahmad, insulin essentially acts as a mitogenic agent, likely via the insulin-like growth factor receptor. "We know that's important in epithelial proliferation and migration," he said.

Insulin-like growth factor. A drug currently in development, insulin-like growth factor likely works on the same receptors as insulin, and it induces cell migration, proliferation, differentiation, and survival, said Dr. Ahmad. "However, it needs to be made to clinical standards and be marketed, whereas insulin is cheap and already available."

PRGF-Endoret Technology. Autologous serum contains vitamin A, epidermal growth factor, and various anti-inflammatory and promitogenic growth factors and cytokines that help with epithelial healing, said Dr. Ahmad. Dr. Tonk agreed, adding that he also uses plasma rich in growth factors (PRGF), an emerging blood derivative eyedrop. "PRGF can be prepared from commercial kits, such as Endoret," he said, "which activates platelets and thereby releases a variety of growth factors and anti-inflammatory compounds in a far greater concentration than that found in circulating plasma." Further, the Endoret process removes pro-inflammatory leukocytes from its final product.

"We find PRGF useful for high-grade ocular surface disorders, persistent epithelial defects, and neurotrophic keratitis," said Dr. Tonk. "In addition to using the PRGF tears, we may suture the actual coagulant onto the ocular surface. This is similar to what's done with an amniotic membrane, but we have found it to be more potent."

DSAEK patch grafting. For cases in which the cornea is perforated, Dr. Ahmad and colleagues sometimes use a partial thickness corneal transplant to patch from the inside.[8] "This is a relatively novel approach that's not yet widely used," he said. (View a video of the DSAEK patch graft procedure, also known as mini-DSAEK, at aao.org/clinical-video/mini-dsaek-macro-corneal-perforations-2.)

Nerve Growth Factor Mimetics

The development of human nerve growth factor (NGF) mimetics is an area of growing interest and potential for NK patients.

"Unlike Oxervate, which is a recombinant version of nerve growth factor," said Dr. Tonk, "NGF mimetics are a kind of synthetic molecule meant to mimic the nerve growth factor. These are designed to bind NGF receptors with a high affinity and may be less costly than recombinant NGF."

Nicergoline, a drug used to treat dementia, especially in cases with vascular etiologies, is an example of an NGF drop in development,[1] said Dr. Ahmad.

The Italian company Recordati is also recruiting patients at 45 study sites in seven countries in North America and Europe for a phase 2 trial, said Dr. Tonk. They are looking at a new eyedrop called MT8 (udonitrectag) for stage 2 and stage 3 NK.

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