Review Article

Neurotrophic keratopathy: Update in diagnosis and management

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The cornea is the most densely sensory innervated tissue in the body. Sensory corneal nerves are essential to maintain ocular surface homeostasis and are involved in the blink reflex, tear production, and the release of trophic factors that are key in the wound healing process. Compromise of corneal sensory nerves leads to neurotrophic keratopathy (NK), an uncommon degenerative disorder that may lead to corneal epithelial breakdown, ulceration, corneal opacification, and even perforation. Management of this condition is difficult and visual disability often ensues in affected patients. While treatment has been traditionally focused in promoting epithelial healing, the past decade has seen a breakthrough in new medical and surgical therapies geared toward promoting corneal reinnervation. This review presents a comprehensive update on NK, focusing on current as well as potential new strategies for its diagnosis and management.

Key words: Cornea, corneal nerves, neurotization, neurotrophic keratopathy, NGF

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Out of all tissues in the human body, the cornea is the most heavily innervated structure, with a 300–600 fold higher concentration of nerves than the skin.[1] Corneal innervation consists predominantly of sensory nerves which respond to various stimuli such as touch, pain, and temperature.[2] Sensory nerves take origin at the trigeminal ganglion, and their projections travel alongside the branches of the trigeminal nerve to reach the corneal epithelium.[2,3] The sub-basal nerve plexus (SBNP), entrenched deep in the corneal epithelium, is the most important landmark for corneal innervation as most of the nerve fibers concentrate here.[4] From SBNP, intraepithelial nerve endings branch upward to connect with the corneal epithelial cells (CEs).[5] Nerve endings lose their myelin sheath to allow proper corneal transparency and use basal epithelial cells as their Schwann cell surrogates.[5] Both neural and epithelial cells produce growth factors that act on each other to maintain ocular surface homeostasis.[5]

The integrity of the corneal nerves is essential for preserving its anatomical structure, mitigating injury, and ensuring overall health of the ocular surface. Proper innervation of the cornea is also responsible for reflex blinking and lacrimation to prevent corneal damage.[4] Corneal homeostasis is maintained through growth factor receptor signaling. Corneal nerves release trophic factors and neuromodulators such as brain-derived neurotrophic factor, substance P (SP), calcitonin-related peptide (CGRP), acetylcholine, and vasoactive intestinal peptide.[2] Of these, SP and CGRP are the ones most intimately associated with maintaining the health of CEs.[2] SP has been identified as an important contributor to corneal wound healing, tissue repair, and regeneration.[2,6] CEs, in turn, synthetize and release nerve growth factor (NGF), epidermal growth factor (EGF), and insulin-derived growth factor (IGF) among others which trigger signaling pathways that promote neurite growth, differentiation, and survival.[2,6,7] NGF has been shown to induce CE proliferation and healing.[2,6,8] NGF also promotes limbal stem cell (LSC) proliferation [Fig. 1].[8] Disruption of this trophic factor crosstalk between corneal neural cells and CEs results in alterations in the ocular surface and delayed wound healing.[9]

Neurotrophic Keratopathy (NK) is a rare neurodegenerative disease of the cornea caused by damage to the trigeminal nerve and its associated branches. It is characterized by decreased or absent corneal sensation.[10] An absence or reduction in corneal innervation reduces the availability of trophic factors, resulting in impaired metabolism, survivability, and regeneration of CEs.[10] With injury to the nerves, corneal sensation, blinking reflex, and ability to produce tears are also negatively affected.[10] Epithelial breakdown is common and can lead to devastating complications including ulceration, infection, melting,

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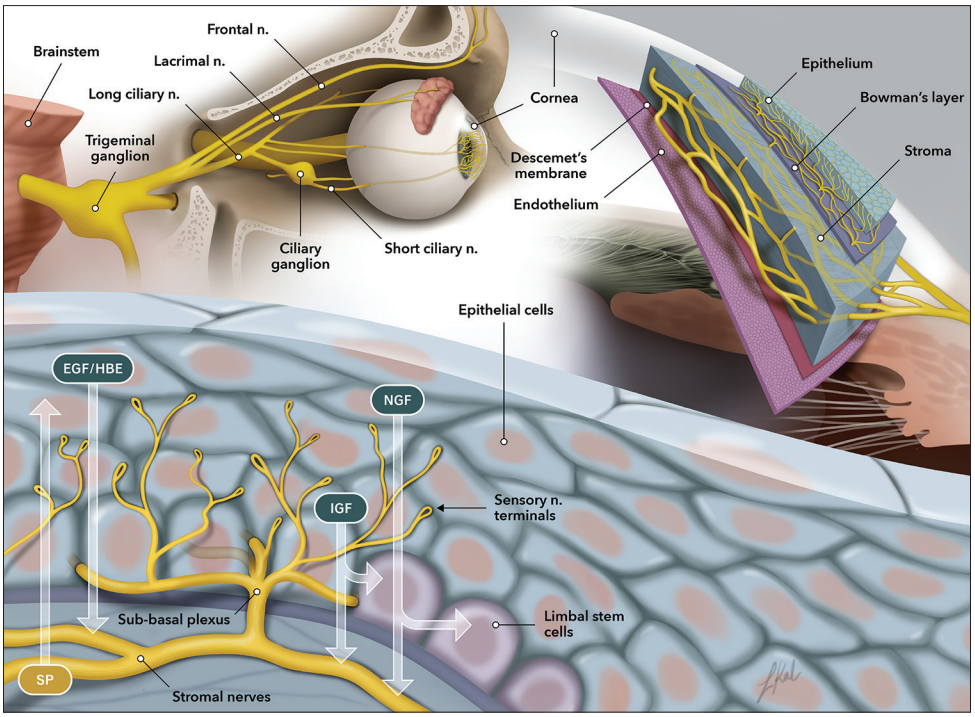

Figure 1: Corneal innervation and growth factor expression. Illustration showing corneal innervation anatomy by the ophthalmic branch of the trigeminal nerve (V1). The trigeminal nerve branches enter the cornea at the level of the stroma and generate smaller branches that form SBNP beneath the corneal epithelium. From this plexus, branches move upward to innervate corneal epithelial cells. The neural cells and the corneal epithelial cells express and secrete growth factors that act on each other to maintain corneal health and homeostasis. Schematic representation of some of the main mediators of corneal epithelial homeostasis is also shown. Neurotrophic factors like SP and BDNF are released by nerve terminals and act on corneal epithelial cells promoting cell proliferation and migration. Growth factors including NGF, EGF, HBE, and IGF are produced by corneal epithelial cells and act in a paracrine manner inducing neuronal cell survival and growth. Some of these growth factors also stimulate limbal stem cell proliferation. BDNF = brain-derived growth factor, EGF = epidermal growth factor, HBE = heparin-bound EGF, IGF = insulin growth factor, NGF = nerve growth factor, SBNP = sub-basal nerve plexus, SP = substance P

and perforation secondary to impaired healing.[11] This article aims to provide a comprehensive update on the diagnosis, clinical classification, and management of NK, with a particular focus on the therapeutic strategies. It also highlights emerging treatment modalities that target corneal reinnervation and discusses the implications for improving patient outcomes in this challenging condition.

Etiology

Any condition that causes damage to the trigeminal nerve either centrally or peripherally can cause NK, including surgical trauma, congenital conditions, central nervous system pathologies, systemic disease, and chemical injury [Table 1].[10,12,13] NK has an incidence rate of ≤5:10,000 individuals in the general population.[12]

The most common cause of NK is herpetic infection due to herpes simplex virus (HSV) and varicella zoster virus (VZV).[14] HSV-1 remains widespread, seroprevalence estimates suggesting that approximately 50% of the U.S. population is infected, while global estimates indicate that HSV-2 affects 11.3% of individuals aged 15-49 years, amounting to over 400 million people worldwide.[15,16] Herpes-induced nerve degeneration notably afflicts corneal SBNP, leading to sensory loss.[12] Altered corneal sensation persists even after the keratitis has resolved, and is typically more profound in VZV infections.[12] Confocal microscopy studies have shown reduced nerve density, total nerve count, and main trunks in eyes with herpetic keratitis compared to unaffected eyes and a decrease in corneal sensation was significantly correlated to the extent of damage.[17] Incidence rates of NK after herpetic eye disease exhibit variability across studies, ranging from 6% to 27% for HSV infection and around 25% for VZV.[12]

Damage to the trigeminal pathway by intracranial lesions, stroke, or neurosurgical procedures is typically pre-ganglionic or ganglionic, and thus does not affect the density of SBNP.[10,18] In contrast, corneal surgery can damage distant corneal nerve causing Wallerian degeneration and subsequent corneal insensitivity to the respective region.[10] Nerves in the affected area gradually regenerate, but corneal sensitivity may not be corrected fully.[10] Studies have shown that corneal sensation returns to preoperative values within 1–2 years after refractive surgery and 4–8 months post-cataract surgery.[19,20] However, nerve fiber density and branching can still be abnormal decades after penetrating keratoplasty (PKP).[21,22] Other ocular procedures that cause NK include extensive laser photocoagulation due to damage to the long ciliary nerves.[23]

Congenital causes of NK are rare and may be associated with other systemic manifestations.[24] Riley–Day syndrome is an autosomal recessive disorder causing autonomic neuropathy and demyelination of corneal nerves.[9] It is associated with corneal ulcerations in up to 50% of patients.[25]

Table 1: Etiologies of neurotrophic keratopathy

Etiology	Characteristics
Herpetic infection	• Herpes simplex virus • Varicella zoster virus

Surgical trauma	• Neurosurgical procedures
	• Ocular procedures
	  • Laser-assisted *in situ* keratomileusis
	  • Photorefractive keratectomy
	  • Keratoplasty
	  • Cataract surgery
	  • Laser photocoagulation

Congenital conditions	• Congenital corneal anesthesia • Hereditary sensory autonomic neuropathy • Riley–Day syndrome • Gorlin syndrome • Mobius syndrome • Congenital insensitivity to pain with anhidrosis
Neoplasms and CNS causes	• Intracranial tumors • Ischemic stroke • Aneurysm
Systemic diseases	• Diabetes • Multiple sclerosis • Sjogren syndrome • Amyloidosis
Iatrogenic	• Benzalkonium chloride • Topical anesthetics • Topical medications • Glaucoma drugs • Contact lenses • Chemical burns • Antipsychotics • Antihistamines • Chemotherapy drugs

CNS=central nervous system

Diabetic peripheral neuropathy is a microvascular disease that produces a loss of myelinated nerve fibers, Wallerian degeneration, and decreased nerve fiber production.[26] Studies have found decreased corneal sensation correlates with progression of peripheral neuropathy in diabetic patients, suggesting keratopathy is a manifestation of peripheral neuropathy.[26]

Chronic medical therapy for glaucoma may result in decreased corneal sensation, especially when topical beta-adrenergic antagonists are used.[27,28] This adverse event is largely thought to be secondary to benzalkonium chloride (BAK), a commonly used preservative in ophthalmic eye drops that has been shown to induce corneal neurotoxicity.[29]

Clinical Features and Staging

The primary clinical feature of NK is a painless cornea with reduced or null sensation.[30] In most cases, NK is an asymptomatic disease with progressively worsening ocular signs despite minimal symptoms.[31] This makes the disease particularly challenging as patients can experience disease progression for months or years without seeking medical attention.[31] Common symptoms include redness, dry eye, eye fatigue, photophobia, and reduced visual acuity.[31] Patients with advanced disease may experience severe vision loss and blindness due to corneal scarring, neovascularization, and corneal perforation.[31]

The Mackie[32] classification for NK has been a standard practice for clinicians in the past few decades and consists of three stages. Stage 1 is primarily marked by hyperplasia and irregularities in the corneal epithelium such as punctate keratopathy.[32] Most cases of NK are identified at stage 1.[12,32] Stage 2 is characterized by persistent corneal epithelial defects (PCED) with smooth or rolled edges.[32] PCED are typically located in the upper cornea due to impaired healing.[32] Descemet membrane folds may be present along with stromal swelling.[32] In rare cases, anterior chamber inflammation can occur, sometimes with hypopyon.[12,32] Swelling of the epithelium can contribute to the enlargement of PCED.[12,32] In stage 3, there is stromal involvement with corneal ulceration.[32] As the corneal injury worsens and involves the stroma, it can result in corneal melting and eventually lead to perforation.[32]

The Neurotrophic Keratopathy Study Group (NKSG) convened to propose an updated definition and staging system for NK.[11] The NKSG classification consists of a new six-step staging system to be used to guide treatment options [Fig. 2].[11]

Diagnosis

Diagnosis of NK is largely clinical. Most patients do not complain of ocular surface symptoms; however, some patients may experience neuropathic pain.[30] A comprehensive medical and surgical history should be performed with an emphasis on corneal and neurosurgical procedures, diabetes, and herpetic infections, as well as topical medication and contact lens use.[12]

Ocular examination

A complete ocular examination including eyelids to detect entropion, ectropion, and trichiasis which can cause similar findings to NK is important. In addition, lagophthalmos associated with seventh cranial neurotization (CN) palsy may worsen NK by causing exposure keratopathy.[33] Assessment of blinking frequency and tear production gives insight into the quality of innervation.[12] Conjunctival injection can signal the presence of inflammation in the ocular surface.[12] Presence of keratopathy in its different stages is detected during slit-lamp examination. Fluorescein staining aids in diagnosis by enhanced visualization of corneal epithelial erosions and defects.[34] Fluorescein and lissamine green dyes are also useful in detecting other signs of eye dryness, such as tear meniscus height, tear breakup time, and conjunctival erosions.[34] The presence of corneal scarring and neovascularization can give insight into previous injury or infections.[10,33] Similarly, patchy atrophy of the iris can be a sign of previous herpetic infection.[10] To classify the severity of NK and monitor for its progression, corneal changes should be noted for location and quantified.[33]

Trigeminal nerve damage may be associated with other CN involvement, and therefore, testing CN V within the context of other CN function can help identify the cause of NK and potential associated conditions.[12] Presence of seventh or eighth CN palsy may suggest trigeminal nerve damage from an acoustic neuroma or its surgical removal.[33] Involvement

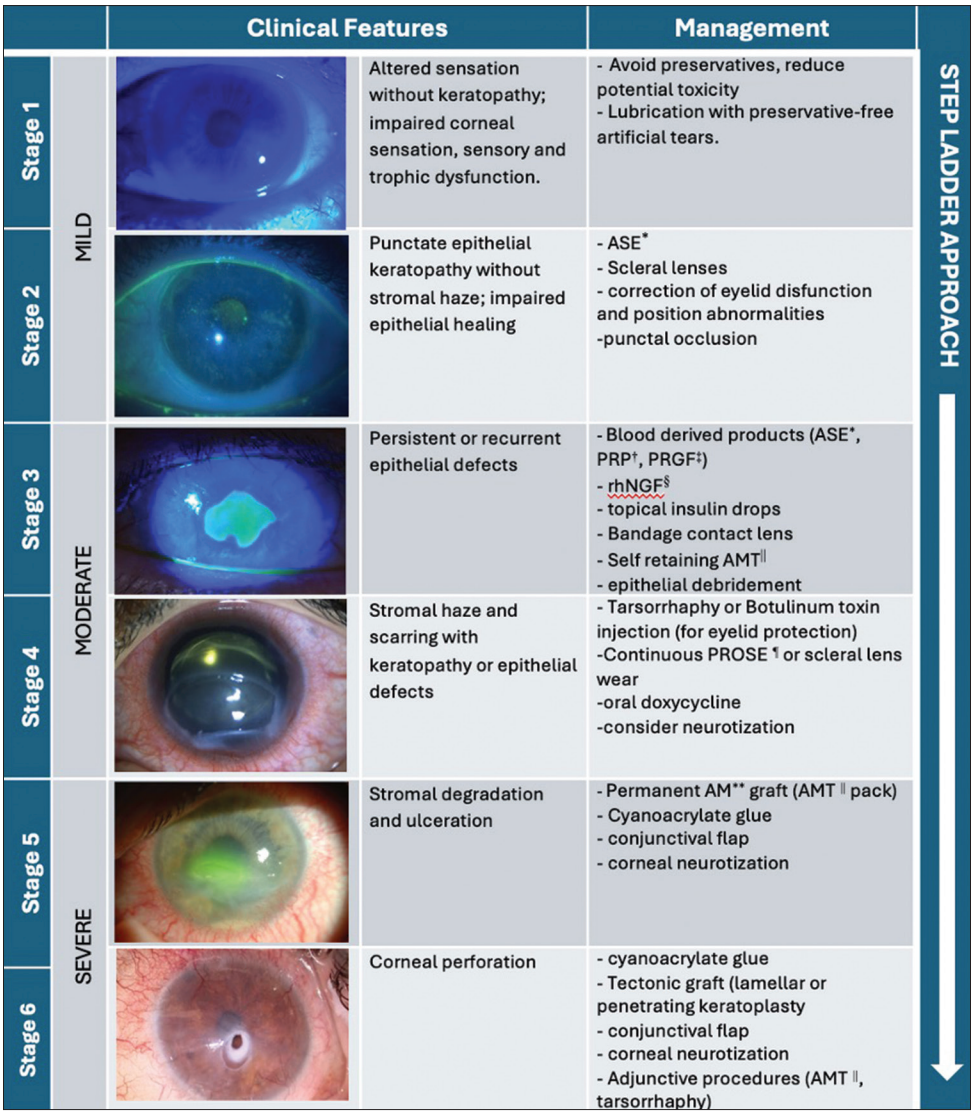

Figure 2: Neurotrophic Keratitis Study Group classification and suggested treatments according to disease stage. This six-stage classification considers the presence of corneal haze, and it is further categorized into mild, moderate, and severe. *Autologous Serum Eye Drops; †Platelet Rich Plasma; ‡Plasma Rich in Growth Factors; §Recombinant Human Nerve Growth Factor; ‖Amniotic Membrane Transplantation; ¶Prosthetic Replacement of the Ocular Surface Ecosystem; **Amniotic Membrane

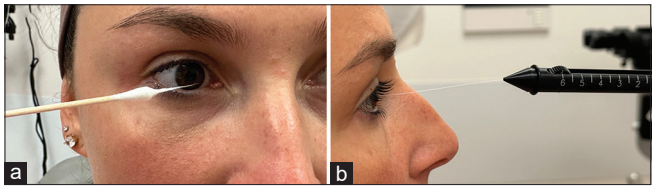

Figure 3: Measurement of corneal sensation. (a) Cotton filament is used to test corneal sensation by touching the cornea in the four different quadrants. (b) Cochet-Bonnet esthesiometer is used to test corneal sensation. The filament is shortened by 0.5 cm until a blink reflex is elicited

of third, fourth, fifth, and sixth CNs suggests aneurysm or cavernous sinus pathology.[33]

Corneal sensitivity assessment

Altered sensitivity is considered a pathognomonic finding for NK.[12] Testing corneal sensitivity should be performed in all patients suspected of NK and those presenting with recurrent or PECD to determine the extent of innervation loss.[12] Both corneas should always be tested and compared. A cotton filament can be used to test sensation by touching the cornea in the four different quadrants and observing if a blink reflex can be elicited [Fig. 3a]. It is best to approach the cornea from the side while performing the test. The response for each quadrant is recorded as normal, reduced, or absent. This method does not allow for accurate quantification of corneal sensation. However, it is readily available to be used in most settings.

Cochet-Bonnet esthesiometer is traditionally considered the gold standard for ocular sensitivity tests.[35] It consists of a thin nylon monofilament with varying lengths that physically applies a spectrum of stimulus intensities at the cornea.[35] Testing typically starts with the filament set at 60 mm in length and is subsequently shortened by 5 mm until a blink reflex can be elicited or the patient manifests

feeling the filament [Fig. 3b]. The length of the filament at which the patient responds is recorded. Patients with normal corneal sensation can feel the filament at its maximum length of 60 mm.

Belmonte esthesiometer is a non-contact device that utilizes a jet of gas as stimulus for the cornea.[35] Noncontact devices such as Belmonte offer a reduced risk of corneal damage compared to contact methods.[36] This device can give information about different components of the corneal sensation, including mechanical, chemical, and thermal.[37]

A more novel esthesiometer called the Brill esthesiometer was approved by the US Food and Drug Administration in 2023.[36] This non-contact device is more portable than Belmonte and works by delivering ambient air as a stimulus to the cornea.[36] Brill comes equipped with a camera and small screen that allows the clinician to target specific areas of the cornea.[36] Brill also uses light-emitting diode light projections onto the cornea to allow for consistent distance between measurements.[36]

In vivo confocal microscopy

In vivo confocal microscopy (IVCM) is a non-invasive technique that can image the cornea at a cellular level to detect nerve and cell damage.[38] Using IVCM allows for an excellent identification of SBNP and the corneal epithelium.[8,38] With IVCM, loss of sub-basal nerve cells, as well as morphological changes in corneal nerves and epithelial cells can be visualized [Fig. 4].[38] Alterations in corneal nerve morphology in SBNP that can be observed with IVCM include nerve sprouting and thickening, reduced nerve fiber density, increased tortuosity, branching, reflectivity, neuromas, and beading.[39]

The utility of IVCM has also been proposed in many systemic conditions causing peripheral neuropathy, and there is well-established evidence for IVCM imaging of the corneal sub-basal plexus in diabetic peripheral neuropathy.[38] The ability to view histology in real time with IVCM also allows for monitoring inflammation and the regeneration of corneal nerves in response to treatment.[38]

Anterior segment optical coherence tomography

Anterior segment optical coherence tomography (ASOCT) is a non-contact imaging technique that allows for a high-resolution detailed analysis of fine anatomical structures of the eye.[40] Thinning of the corneal epithelium is a common finding in NK and can be identified and quantified with this imaging technique.[40] ASOCT can also detect edema in the cellular layers of the cornea and characterize stromal ulcers' size and depth.[40,41] It is particularly useful in preoperative planning and posttreatment evaluation of corneal health, as well as monitoring disease progression.[40]

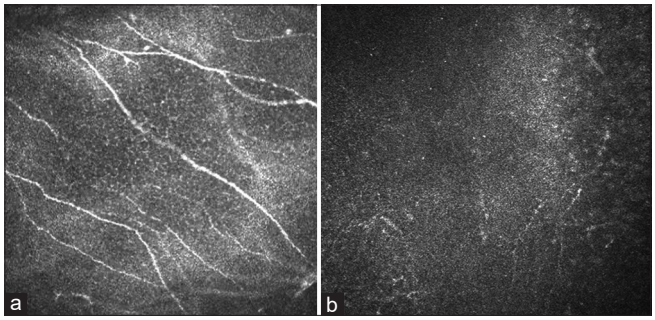

Figure 4: Confocal microscopy imaging of corneal nerves. Confocal imaging of a corneal sub-basal nerve plexus in a normal cornea (a) and in a cornea with neurotrophic keratopathy following herpes simplex infection (b)

Differential diagnosis

Several chronic diseases including dry eye syndrome, blepharitis, exposure keratopathy, drug toxicity, contact lens-related disorders, chemical injury, and LSC deficiency, among others, may also affect corneal sensitivity and coexist with NK.[31] When ulceration is present, a differential diagnosis with infectious and immune keratitis should always be considered.[33]

Treatment

Treatment of NK is difficult, and is traditionally mostly focused in promoting epithelial healing with the goal of interfering with disease progression.[31] In the past decade, significant advances in medical and surgical therapies geared toward promoting corneal reinnervation have been made. Therapies that address the underlying corneal nerve damage in NK have the potential to significantly improve disease stability and long-term prognosis. The type of treatment is typically dictated by disease stage and severity, and may include a combination of medical as well as surgical strategies.[31]

Medical therapy

Avoid iatrogenic ocular toxicity

Precipitating conditions and other factors that could be contributing to NK should be identified and addressed.[31] All preserved topical medications, particularly those containing BAK, should be discontinued whenever possible. Topical non-steroidal drugs are also associated with delayed epithelial healing and should be avoided.[12,31] Prolonged treatment regimens for glaucoma significantly elevate the risk of NK.[42] Changing to preservative-free formulations has shown to improve corneal nerve morphology in patients with glaucoma.[43]

Lubrication of the ocular surface

Treatment of stage 1 disease is primarily based on lubrication of the eye.[31] It is important for patients to apply ocular lubrication at a fixed schedule since early stages of NK may be asymptomatic.[31] Preservative-free artificial tears are preferred and are the first line of treatment for ocular surface disease (OSD) and NK. Besides providing lubrication and mechanical support, preservative-free artificial tears also help dilute inflammatory cytokines on the ocular surface and reduce osmolarity.[44] Similarly, amniotic membrane extract eye drops have been shown to improve clinical signs and symptoms of OSD, including NK.[45]

Blood-derived products

Blood-derived products contain many kinds of different biochemical components including several growth factors promoting epithelialization in a closer mechanism to natural tears.[46] They have shown efficacy in the treatment of PCED,

other forms of OSD, and NK.[47] Autologous options sourced from the patient's own peripheral blood or serum include autologous serum eye drops (ASE), platelet-rich plasma (PRP), and plasma rich in growth factors (PRGF).[47]

ASE are the most commonly used product and contain various neurotrophic factors including NGF, SP, and IGF-1, which are essential to corneal physiology, and have been shown to improve wound healing and corneal sensitivity in non-randomized uncontrolled studies of NK.[48] ASE can be used in concentrations between 20% and 100%, as there is no universally accepted protocol for their formulation.[49]

While autologous source is preferred in most cases, allogeneic peripheral blood serum and umbilical cord blood serum could be sourced from donors and used when autologous source is not possible or in cases in which the risk of introducing inflammatory cytokines with autologous source is high.[50] Previous research has found that umbilical cord serum contains higher levels of neurotrophic factors (SP, IGF-1, and NGF) than peripheral blood and tears and can be effective in improving epithelial healing and corneal sensitivity.[51]

PRP contains platelet-derived growth factor, transforming growth factor beta, and platelet factor IV, and it is also commonly used to promote wound healing in many other conditions outside the eye.[52] PRGF is an optimized formulation to promote tissue regeneration with similar properties to amniotic membrane, including bactericidal, anti-inflammatory, and antifibrotic activities.[53]

While several studies have demonstrated the efficacy of blood-derived products in the treatment of OSD and NK, some of their drawbacks include the risk of microbial contamination and infection, inconvenience for the patient, and the lack of standardized protocols for their preparation.[53]

Recombinant human nerve growth factor

Recombinant human nerve growth factor (rhNGF) is produced by *Escherichia coli* as a pro-peptide and binds to TrkA and p75 receptors to regulate growth, survival, and differentiation of neuronal cells.[54] It stimulates epithelial growth and survival, maintains LSC potential, binds to receptors in lacrimal glands to induce tear production, and promotes corneal reinnervation.[6,8] Cenegermin 0.002% (Oxervate™) is a topical rhNGF approved in the USA, Canada, Europe, Australia, and China for the treatment of stage 2 and 3 NK. Preservative-free 0.002% cenegermin comes in seven multi-dose vials; it is administered six times a day for a total of 8 weeks.[55] The REPARO trial that led to its US approval showed a statistically significant proportion of patients with complete corneal healing after a 4- to 8-week course of rhNGF treatment compared to placebo.[56] However, the study failed to show a statistically significant difference in corneal sensitivity between groups.[56] A multicenter, randomized, vehicle-controlled pivotal trial confirmed the efficacy of rhNGF in decreasing lesion size in patients with NK.[57] This study found that rhNGF reduces the progression and recurrence of NK, but failed to show improvement in corneal sensitivity. Safety and tolerability were also confirmed, and most common adverse events included pain, foreign body sensation, and tingling suggestive of nociceptor sensitization.[57] A recent multicenter, uncontrolled study suggested rhNGF may also be effective in treating stage 1 NK with possible improvement in corneal sensation.[58] Drug cost and limited insurance coverage continue to be barriers to more wide utilization of rhNGF. Interestingly, Fleeman *et al*.[59] evaluated the cost-effectiveness of rhNGF as part of a single technology appraisal for the National Institute of Health and Care Excellence in the UK and found the economic model flawed, concluding that there is not enough evidence to recommend its use within its marketing authorization for NK.

Insulin

Promising research suggests that topical insulin can also promote re-epithelization of the cornea and improve visual acuity during stage 2 or 3 NK.[60] Insulin is closely related to IGF produced by CEs. IGF is known to promote epithelial cell migration and proliferation, LSC differentiation, enhance wound closure, and regulate keratocyte organization network.[61-63] Insulin also enhances healing in CEs by transactivation of EGF receptor.[64] While it needs to be compounded, insulin offers a low-cost and accessible alternative with no reported side effects.[60] Concentrations vary from 1 to 25 U/mL, and one drop is administered four times daily. A randomized study in diabetic patients found that at lower concentrations insulin provided a higher therapeutic efficacy in wound healing, reducing inflammation, and corneal nerve regeneration.[65]

Metalloproteinase inhibitors

Metalloproteinases (MMPs) are proteolytic enzymes involved in an intricate signal transduction cascade that includes induction of many proinflammatory molecules. They have been found to be elevated in many inflammatory, traumatic, and infectious corneal conditions.[66] Elevated levels of MMPs influence tissue remodeling, epithelial migration, and vascular proliferation.[66] Although these enzymes are necessary for wound healing, their overexpression found in many ocular surface conditions including NK contributes to delayed epithelial healing and ulceration.[67] MMP inhibitors such as tetracyclines, ascorbate, and acetylcysteine can decrease the risk of corneal melt and ulceration by influencing collagen synthesis and decreasing degradation in patients with NK.[2,12] As an antibiotic class, tetracyclines are particularly useful in MMP inhibition, and oral doxycycline reduces the tear concentration of MMPs.[68] Oral vitamin C administration can potentially help in accelerating corneal epithelial healing and reducing corneal opacity by influencing collagen synthesis.[69] MMP inhibitors are commonly used as adjuvants in non-infectious ulcers and may potentially reduce the risk of progression of NK.[70]

Nicergoline

Nicergoline (Sermion; Pfizer, New York, NY, USA) is a semisynthetic ergoline derivative used for the treatment of dementia. It has multiple mechanisms of action including Phosphoinositide 3-Kinase/Protein Kinase B (AKT) pathway activation that results in increased SP and NGF levels and antioxidant activity.[71] When administered orally (30 mg daily for at least 2 weeks), it increases the concentration of NGF and SP in the cornea and has been proposed as an adjunctive therapy for NK.[72] In a study of 27 eyes with NK treated with

nicergoline, tear NGF levels were significantly higher and resulted in 85% of epithelial defects healed and improvement in mean corneal sensitivity and visual acuity.[72]

Contact lenses

With the goal of achieving epithelial integrity, thereby stabilizing corneal thinning and minimizing the risk of corneal perforation, the use of contact lenses can protect the cornea from abrasive eyelids, promoting epithelial healing and improving hydration of the desiccated ocular surface.[12] Soft contact lenses are readily available and very commonly used.

Scleral contact lenses also have a protective and therapeutic role in OSD. The lens can be worn daily or continuously under close observation. Continuous short-term wear of scleral contact lenses can be useful in the treatment of refractory epithelial defects [Fig. 5].[12,73] Once the surface is healed, daily scleral contact lens wear can protect the corneal epithelium from recurrent breakdown and contribute to maintaining ocular surface stability in patients with NK.[74] The secondary benefit of scleral lens therapy in patients with NK is an improvement in visual acuity by treating the irregular astigmatism from abnormal epithelium and scar tissue.[75] Furthermore, chronic corneal opacities have been shown to improve over time with daily long-term scleral lens therapy.[76]

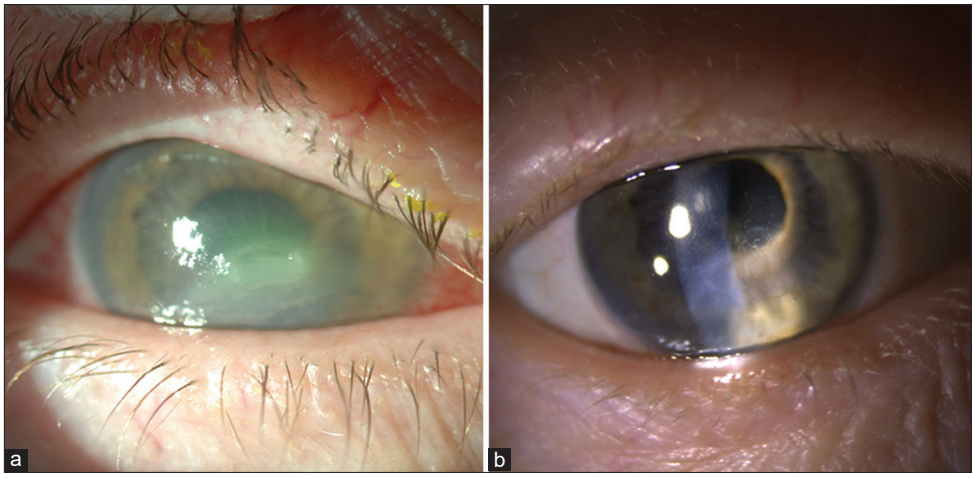

Figure 5: Treatment of neurotrophic keratopathy with scleral contact lens. Slit-lamp photographs of a patient with neurotrophic keratopathy due to diabetes. (a) Corneal involvement with ulceration and persistent epithelial defect that failed multiple treatments. (b) Ulcer and epithelial defect healed with continuous scleral lens wear. Patient was then transitioned to daily scleral contact lens wear. Image was taken 5 years after ulceration, demonstrating long-term stability

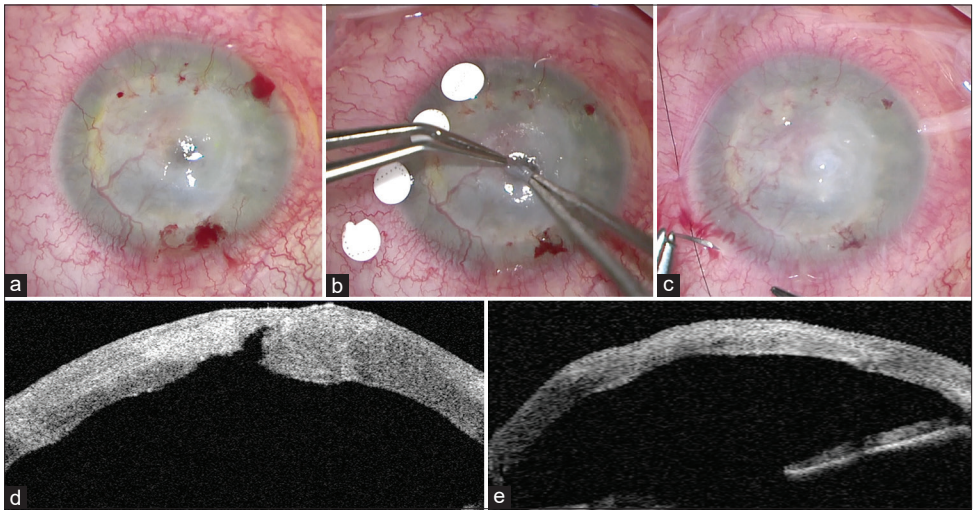

Figure 6: Treatment of stage 3 neurotrophic keratopathy with amniotic membrane transplantation in a patient with penetrating keratoplasty and history of herpes simplex infection. Failed penetrating keratoplasty with severe haze, neovascularization, and central corneal thinning with perforation (a). Perforation is treated with amniotic membrane pack and fibrin glue (b and c). (d) Preoperative ASOCT of the cornea showing stromal perforation. (e) ASOCT after perforation was repaired with amniotic membrane grafting. ASOCT = anterior segment optical coherence tomography

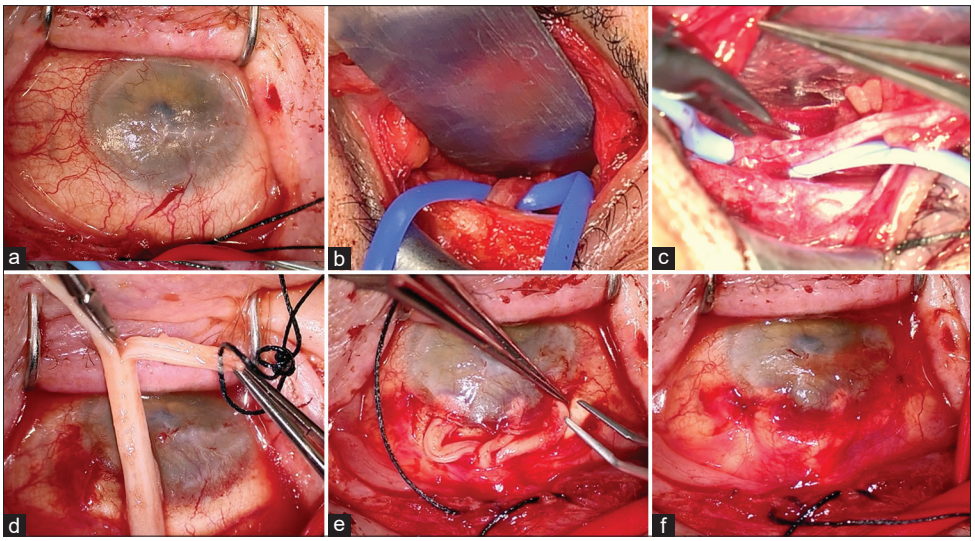

Figure 7: Corneal neurotization procedure. Neurotrophic keratopathy in a patient with history of herpes zoster. (a) Note advanced disease with significant inferior corneal opacification, thickened irregular epithelium, and vascularization. (b) Isolation of the infraorbital nerve. (c) End-to-side connection of the nerve graft to the infraorbital nerve. (d) Separation of nerve fascicles within the nerve sheath. (e) Fascicles are placed in the intrastromal scleral–corneal pocket. (f) Nerve graft is covered with conjunctiva utilizing fibrin glue to secure the tissue in place

Surgical therapy

Correction of eyelid dysfunction and position abnormalities should be considered early in the treatment of NK. *Punctal plugs* can help maintain corneal hydration, but should probably be avoided in the presence of active inflammation.[31,77] *Epithelial debridement* may be required when the epithelial defect develops thickened borders and becomes stagnant. In these cases, debridement may allow for better epithelial cell proliferation and migration across the defect.[78]

As severity of disease progresses, *amniotic membrane transplantation* (AMT) is an effective surgical treatment that can restore epithelization of eyes with NK.[12] The amniotic membrane is the innermost layer of the placenta.[12] Its biological properties with anti-inflammatory, anti-scarring, and anti-angiogenic activity support corneal health.[12] Many of these properties are mediated by growth factors within the membrane, such as NGF, keratinocyte growth factor, and hepatocyte growth factor, all of which promote corneal healing.[12] Several studies have shown the safety and efficacy of AMT for the treatment of NK.[79-81] Furthermore, AMT was shown to be more effective than autologous serum in patients with deep stromal ulcers caused by post-herpes NK and topical anesthetic abuse, and comparable in efficacy to tarsorrhaphy or bandage contact lens placement for refractory NK.[79,82]

Temporary or permanent tarsorrhaphy may be a surgical option for stage 2 or 3 patients who fail other treatments.[31,34] While it can sometimes be resisted by patients, it is highly effective with 90% of patients achieving full epithelialization.[83] Alternatively, botulinum toxin can be injected into the levator muscle inducing ptosis that lasts 3–6 months.[34] The goal of these procedures is to provide covering for the cornea that protects it from further damage against the environment or blinking lids.[34]

In more advanced disease with progressive ulceration, in particular cases with poor visual potential, *conjunctival flaps* are an excellent option to stabilize the ocular surface. They provide mechanical protection and isolate the cornea from proteolytic enzymes and proinflammatory mediators.[12] They provide a vascular supply to the cornea that results in protection against infection and ulceration and have been successfully used in the treatment of NK.[12]

Treatment of corneal perforation as one of the complications of NK is unfortunately often required in severe cases. *Cyanoacrylate glue* and *AMT packing with fibrin glue* [Fig. 6] can be used to treat small perforations.[12] Larger perforations may require tectonic corneal grafting.[12] *PKP or lamellar techniques* can be used in this instance, with high rate of persistent epithelial defects and recurrent corneal melts requiring adjunctive procedures such as tarsorrhaphy and AMT grafting.[12] Optical grafts for visual rehabilitation carry a poor prognosis with high risk of complications and, in fact, poor corneal sensation is considered a relative contraindication for PKP.[84]

Corneal neurotization is a surgical technique aimed at restoring corneal sensation and improving epithelial healing in NK patients [Fig. 7].[31] This technique addresses nerve loss directly by stimulating new nerve growth onto the cornea from nearby sensory nerves transferred to the perilimbal region. An intact donor sensory nerve can be transferred directly to the affected cornea or indirectly using an interpositional nerve graft, which can be harvested either as an autograft (e.g., sural nerve) or as a decellularized allograft.[85] Various techniques have been described, and donor nerves ipsilateral and contralateral to the affected cornea can be used, as well as end-to-end or end-to-side connections. The availability of a sensate site, the size of the donor nerve, the surgeon's experience, and the distance between the donor nerve and the cornea are important factors in deciding the surgical approach.

Table 2: Neurotrophic keratopathy treatment outcomes

Treatment	Study	Design	No. of eyes (*n*)	NK stage	Outcomes					Significant findings
					Follow-up (months)	Epithelial healing (%)	Time to heal	Rec. rate (%)	Adverse events	
rhNGF	Bonini *et al.* (2018)[56]	Phase II multicenter RCT	156	Stage 2: 76 Stage 3: 80	12–14	74%	4–8 weeks	<4	Pain, blurred vision	The REPARO study demonstrated rhNGF is a safe and effective treatment for moderate-to-severe NK. No change in corneal sensation
	Pflugfelder *et al.* (2020)[57]	Multicenter RCT	48	Stage 2: 33 Stage 3: 15	6	69.6%–65.2%	4–8 weeks	12.5	Pain, foreign body sensation, tingling	Confirmed safety and efficacy of rhNGF for NK. rhNGF treatment reduced the rate of recurrence and progression
PRP	Wróbel-Dudzińska *et al.* (2018)[52]	Prospective uncontrolled observational study	25	Stage 2: 12 Stage 3: 13	10	80%	9.2±2.85 weeks (mean)	None	None	Improved BCVA from 0.10±0.14 to 0.30±0.27 (P=0.001)
Insulin	Soares *et al.* (2022)[60]	Retrospective observational study	21	Stage 2: 11 Stage 3: 10	1.48	90%	18±9 days (stage 2), 29±11 days (stage 3)	9.5	None	90% of eyes achieved complete re-epithelialization within 7–45 days; significant improvement in BCVA
Insulin + substance P	Yamada *et al.* (2008)[63]	Prospective open study	26	Not spec.	~15.6 (mean)	73%	10.5 days	None		Significant resurfacing of epithelial defects
ASE	Matsumoto *et al.* (2004)[48]	Retrospective noncomparative case series	14	Stage 1: 2 Stage 2: 9 Stage 3: 3	15.6±10.8 (mean)	100%	17.1±8.0 days (mean)	None	None	BCVA improved by >2 lines in 78.6% of eyes. Significant increase in corneal sensitivity posttreatment
ASE versus AMT	Turkoglu *et al.* (2014)[79]	Retrospective	ASE: 20 AMT: 22	Neurotrophic corneal ulcer	ASE 6.7±2.05 AMT 6.8±3.9	ASE 70% AMT 72.7%	ASE: 22.1±8.0 days, AMT: 20.0±4.64 days	ASE: 10 AMT: 0	None	Both treatments were effective for neurotrophic corneal ulcers. AMT was more effective for deep ulcers
AMT versus rhNGF eye drops	Sacchetti *et al.* (2022)[80]	Multicenter retrospective observational study	AMT: 13 rhNGF: 23	AMT: 80% stage 3 rhNGF: 54% stage 3	12	AMT 86% rhNGF 96%	AMT: 4.7±3.7 weeks (mean) rhNGF: 4.5±2.2 weeks (mean)	AMT: 46 rhNGF: 13	None	Higher healing rate and lower recurrence with rhNGF compared to AMT; however, there was more advanced disease in AMT group. Further intervention needed in recurrence
AMT	Schuerch *et al.* (2020)[81]	Retrospective case series	149	Non-healing corneal ulcers	6	70%	21% <1 month 40% 1–3 months 9% 3–6 months	30	None	Neurotrophic ulcers had the highest success rate (93.3%). Thirty percent failure needing further intervention
PROSE scleral lens therapy	Chahal *et al.* (2017)[78]	Retrospective interventional case series	18	N/A	22.5	83%	Not spec.	11	Mild; mucus build up on the lens	Significantly improved BCVA (20/80 to 20/35), reduced corneal staining, and improved OSD index scores in patients with exposure keratopathy who failed conventional therapies

Contd...

Table 2: Contd...

Treatment	Study	Design	No. of eyes (*n*)	NK stage	Outcomes					Significant findings
					Follow-up (months)	Epithelial healing (%)	Time to heal	Rec. rate (%)	Adverse events	
	Schornack *et al.* (2014)[75]	Retrospective case series	17	Not Spec.	38 (mean)	100%	1 day to 4 weeks	None	Microbial keratitis, corneal abrasion, epithelial defect	Scleral lenses were effective in protecting ocular surfaces, healing epithelial defect, and improving BCVA (from 20/120 to 20/40); epithelial defect healed in most NK cases
Corneal neurotization	Fogagnolo *et al.* (2020)[86]	Multicenter, interventional, prospective case series	26	Stage 1: 3 Stage 2: 10 Stage 3: 12	18.76 (mean)	100%	3.9±1.5 months	None	Mild, no major AE	NK healed in all patients; corneal sensitivity improved significantly (P<0.001), corneal neve fiber length detectable in all patients at 1 year
	Swanson *et al.* (2022)[92]	Meta-analysis	64	2.46 average stage	13	81% improvement in NK stage	9 months (time to reinnervation)	6	Hematoma, corneal neuroma, epithelial defect	Significant improvement in BCVA (70%), NK Mackie staging (81%), and corneal sensation (100%)

AMT=amniotic membrane transplantation, ASE=autologous serum eye drops, BCVA=best corrected visual acuity, NK=neurotrophic keratopathy, OSD=ocular surface disease, PROSE=prosthetic replacement of the ocular surface ecosystem, PRP=platelet rich plasma, RCT=randomized controlled trial, rhNGF=recombinant human nerve growth factor, AE= Adverse Effects

Both direct and indirect transfers have shown efficacy in improving NK within 6 months of surgery, and long-term outcomes appear similar between techniques.[86] Corneal sensation returns in about 80% of cases starting about 5–6 months, but it is not complete compared to the contralateral normal cornea.[87] There are some structural differences between normal and post-neurotization corneas, including a less-uniform distribution of nerve fibers, thinner axons, no restoration of the characteristic whorl pattern, and a larger number of myelinated fibers.[88]

Neurotization is indicated for patients with advanced disease who have not responded to conventional therapies.[31] Visual acuity often continues to be limited after CN due to pre-existing corneal scarring, and further studies are needed to evaluate its safety and efficacy in earlier stages of NK before permanent corneal opacity occurs. Younger age is correlated with faster and more complete recovery of corneal sensation.[89] In addition, CN has been shown successful in post-herpetic NK, with 78% showing resolution of corneal pathology.[90]

While CN shows promise in the treatment of NK by significantly improving corneal sensation, preventing further epithelial breakdown and enabling corneal healing, there are still many unanswered questions such as the long-term stability of corneal sensitivity, the most adequate timing for the procedure, and the potential use of adjuvant therapies like rhNGF to stimulate nerve growth.

Selecting among the various therapies depends on disease stage and availability, as there are no randomized studies comparing safety and efficacy of all these treatments. Di Zazzo *et al.*[91] performed a review of 35 studies and 667 eyes and found that treatment with rhNGF, ASE, and SP/IGF resulted in comparable resolution rates of epithelial defects in patients with NK. Among the treatments studied, AMT and NGF were associated with a faster healing time. NGF and SP/IGF were associated with lowest recurrence rate and required less surgical procedures.[91] However, the level of evidence among studies is highly variable, and while CN is the therapy most consistently associated with the return of corneal sensation, rhNGF is the only treatment with level 1 evidence supporting efficacy in randomized and controlled clinical trials for the treatment of NK [Table 2].[48,52,56,57,60,63,75,78-80,81,86,92]

Emerging therapies and clinical trials

The use of 0.05% cyclosporine A (CsA) eye drops for treating NK secondary to herpes simplex keratitis was studied in 15 eyes, all classified with stage 2 or 3 NK. A combination of CsA, bandage contact lenses, and ganciclovir ophthalmic gel resulted in 100% of patients achieving corneal healing and a low recurrence rate.[93]

Kanu *et al.*[94] developed a photocrosslinkable, chitosan-based hydrogel for sustained delivery of rhNGF to the ocular surface. The hydrogel was designed to enhance the efficacy and bioavailability of rhNGF, which can be a challenge with eye drops. The Az-Ch hydrogel demonstrated favorable physical properties, including optical transparency, biocompatibility, and the ability to release rhNGF gradually over 24 h while maintaining its biological activity.

RGN-259, a topical ophthalmic solution containing thymosin beta-4 (Tβ4), is being investigated in a Phase 3, multicenter, randomized, placebo-controlled trial for the treatment of NK. Tβ4 is a naturally occurring peptide that aids in tissue repair by promoting CE migration, proliferation, and wound healing. Initial results from preclinical and early clinical studies suggest that RGN-259 may help restore corneal sensitivity and accelerate epithelial healing in NK.[12,95]

Ongoing studies are currently evaluating the efficacy of AMT and rhNGF for the treatment of stage 1 NK. Since most literature supports their use for more severe stages, these studies aim to intervene before significant corneal degeneration occurs.[58,96] Results of the DFENDO study, a Phase IV multicenter, open-label clinical trial for the use of rhNGF in stage 1 NK, have been recently published suggesting efficacy in improving corneal sensitivity and visual acuity.[58]

Several novel drugs are in the pipeline currently undergoing investigation. The pigment epithelial-derived factor short peptide, BRM-424, is undergoing Phase II clinical trials for the treatment of NK (NCT05927428). The mechanism of action is proposed to involve activation of limbal corneal epithelial stem cells. Similarly, a Phase II multicenter trial to evaluate efficacy of NGF mimic, Udonitretag has finished enrolment but results have not been published yet (NCT04276558). Hepatocyte growth factor produced by mesenchymal cells regulates epithelial cell mitosis and inhibits fibrosis. CSB-001 is a 0.1% ophthalmic solution of human recombinant 5-amino acid deleted hepatocyte growth factor undergoing Phase II clinical trials for the treatment of stage 2 and 3 NK (NCT04909450). Finally, Olympia study is a Phase 2 randomized controlled trial evaluating the safety and efficacy of varenicline nasal spray for the treatment of stage 1 NK.[97]

Conclusion

NK is a challenging condition with the potential for permanent vision loss in affected patients. Significant advances have been made in the treatment of this disease, and now, medical and surgical treatments that promote corneal reinnervation are available. There are also several ongoing studies evaluating novel promising strategies that can expand the therapeutic options for NK. Further studies are needed to refine indications particularly related to both timing and disease stage for each therapeutic intervention and to understand their long-term outcomes.

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