Neurotrophic Keratopathy Treated with Topical Recombinant Human Nerve Growth Factor (Cenegermin): Case Series Study with Long-Term Follow-Up

Salvador García-Delpech\textsuperscript{a}  Patricia Udaondo\textsuperscript{a}  
Alex Samir Fernández-Santodomingo\textsuperscript{a}  Damian García-Teillard\textsuperscript{b}

\textsuperscript{a}Aiken Ophthalmology Clinic, Aiken Foundation, and Service of Ophthalmology, Hospital Universitari i Politècnico La Fe, Valencia, Spain; \textsuperscript{b}Service of Ophthalmology, Hospital Punta de Europa, Algeciras, Spain

Keywords
Neurotrophic keratopathy · Recombinant human nerve growth factor · Cenegermin

Abstract
The authors report the use of topical recombinant human nerve growth factor cenegermin 0.02% in 5 patients diagnosed with neurotrophic keratopathy (NK) in a real-life setting. These 5 patients affected with stage II and III NK mainly of herpetic cause received cenegermin six times daily for 8 weeks. It was initiated upon refractoriness to prior conventional topical treatment. Visual acuity, corneal sensitivity test at four corneal quadrants, fluorescein staining, OC,T and photography were performed weekly during 9 weeks of follow-up from the completion of treatment. At the ninth week of follow-up, corneal sensitivity improvement and healing of corneal ulcers were found in all patients. No adverse events were reported, and no corneal ulcer recurrence was observed over a 4-year follow-up period. Cenegermin should be used in combination with conventional therapy for advanced NK, as it is an effective treatment for healing corneal ulcers, improving the corneal surface homeostasis and avoiding surgery.
Introduction

Neurotrophic keratopathy (NK) is a rare degenerative corneal disease, classified as orphan disease (ORPHA137596), caused by impaired corneal innervation, with an estimated prevalence of less than 5/10,000, affecting 6% of herpetic keratitis cases, 12.8% of herpes zoster keratitis cases, and 2.8% of patients who underwent surgical procedures for trigeminal neuralgia [1]. However, in patients with corneal ulcers, the percentage of cases of NK is relatively high, between 13% and 27% [2]. The disease can result in serious loss of visual acuity (VA) or even blindness and poses substantial diagnostic and treatment challenges to ophthalmologists. Alterations in corneal nerves lead to impairment of sensory and trophic function, with breakdown of the corneal epithelium, affecting health and integrity of the tear film, epithelium, and stroma [3, 4]. Damage at any level of the trigeminal nerve, from the trigeminal nucleus to the corneal nerve endings, may cause the development of NK. Common causes identified include herpetic infection, intracranial lesion, neurosurgery procedures, trauma, corneal dystrophy, diabetes, dry eye disease, or anterior eye surgery involving nerve transection. However, the relationship between the underlying etiology and the severity of clinical outcome of NK in terms of restoration of corneal sensitivity remains unclear [1].

Clinically, three stages of NK have been established [3, 5]: stage I or mild is characterized by superficial punctate epitheliopathy, tear film alteration, and reduced or absent sensitivity in one or more quadrants; stage II or moderate is characterized by the presence of a persistent epithelial defect associated with a variable degree of corneal hypoesthesia or anesthesia; and stage III or severe is characterized by stromal defects with ulceration or frank perforation together with corneal hypoesthesia or anesthesia. Early diagnosis, severity-based treatment [6], and careful monitoring of patients with NK are mandatory to achieve epithelial healing and prevent progression of corneal damage especially since worsening of NK is frequently asymptomatic.

Cenegermin 0.002% ophthalmic solution (Oxervate™, Dompé Farmaceutici SpA, Milan, Italy), which contains recombinant human nerve growth factor, is the first approved topical medication for the treatment of NK in the USA since August 22, 2018, and for the treatment of moderate or severe NK in the European Union since July 20, 2017. Cenegermin is a recombinant human nerve growth factor produced by Escherichia coli that has shown efficacy and safety in promoting healing of corneal ulcers in patients with NK associated with persistent epithelial defects and improvements in other relevant endpoints, such as VA, corneal sensitivity, and disease progression [7]. The efficacy of cenegermin in NK demonstrated in clinical trials [8–10] has been confirmed by real-world descriptions of individual cases especially related to the pediatric use of the drug in children with rare congenital diseases [11–14] as well as in adult patients [15–23]. Here, we report the long-term results of 5 adult patients with NK treated successfully with cenegermin and followed for over a period of 4 years after healing of corneal ulcers.

Case Presentation

In this case series, we included five consecutive patients with a unilateral corneal lesion treated with cenegermin eye drops between April and November 2018, due to NK and refractoriness to prior conventional topical treatment, such as antiviral medication, anti-inflammatory drugs, antibiotics, artificial tears, or lubrication solutions. All patients were diagnosed and treated at a single ophthalmological center in Valencia, Spain, and their data were analyzed retrospectively. All clinical procedures were performed in accordance with
good clinical practices and adhered to the tenets of the Declaration of Helsinki concerning human subjects. All participants provided written informed consent for the protection of anonymity and use of nonidentifiable data for scientific purposes. For the aim of the study, the patients’ medical records were reviewed and data recorded during scheduled clinical visits are here summarized. The study was based on chart review and was exempted from approval of the Institutional Ethics Committee.

Five adult patients affected with stage II and III NK received cenegermin 0.002% ophthalmic solution (Oxervate™) six times daily for 8 weeks. The classification of Dua et al. [3] adapted from the Mackie classification [5] was used and included stage I or mild NK (epithelial changes only without epithelial defect), stage II or moderate (epithelial defect without stromal defect), and stage III or severe (stromal involvement). Treatment with cenegermin was initiated upon refractoriness to prior conventional topical treatments. The disease was unilateral in all patients (left eye in 4, right eye in 1). All patients underwent the following ophthalmologic examinations: noncontact slit lamp biomicroscopy; best corrected visual acuity (BCVA); Schirmer test without topical anesthesia; tonometry; corneal fluorescein staining; corneal sensitivity testing; and anterior segmental optical coherence tomography. Measurement of corneal sensitivity in five corneal zones (central and four quadrants) was performed before any invasive study using a sterile wisp of gauze and defined on a 0–3 scale, in which 0: no sensation, 1: sensation when touching with a thick stretch, 2: sensation when touching with a middle stretch, and 3: sensation when touching with a thin stretch (one filament) (Fig. 1). Results are expressed as the score reached with respect to score 3 (maximum sensation) (e.g., 1/3 means sensation when touching with a thick stretch/thin stretch). Therapeutic objectives with the use of cenegermin included healing of corneal ulcer, improvement of VA and corneal sensitivity, and avoidance of surgery. Complete corneal healing was defined as reestablishment of fully intact corneal epithelium.

Patient 1 was a 45-year-old woman with a history of long-standing herpetic keratitis refractoriness to previous topical treatment. Presenting complaints were foreign body sensation and vision loss. The BCVA was 0.2 decimal. The Schirmer test score was 12 mm/5 min. The initial diagnosis was NK stage II in the left eye with neovascularization, inflammation, corneal ulcer, and positive corneal fluorescein staining (Fig. 2). The corneal sensitivity was 0/3 central and three quadrants and 2/3 nasal region. After 3 weeks of treatment with cenegermin, corneal sensitivity improved to 1/3 in all quadrants (except for the nasal region), and after 6 weeks, corneal fluorescein staining showed complete corneal healing, BCVA improved to 0.4 decimal, and there was an increase in corneal neovascularization and decreased inflammation. No recurrence was observed during a follow-up of 4 years.

Patient 2 was a 43-year-old woman with NK caused by herpetic keratouveitis. The initial diagnosis was NK stage II in the left eye. Ophthalmologic examination disclosed a paracentral leukoma with an underlying epithelial defect and associated neovessels. Main findings were BCVA of 0.6 decimal, corneal sensitivity 0/3 in all five corneal zones, punctate erosion, and positive corneal fluorescein staining. After 3 weeks of treatment with cenegermin, sensitivity
improved to 1/3 in all corneal zones, punctate epithelial erosions disappeared, and there was an improvement of inflammatory signs. Fluorescein staining showed healing of the corneal ulcer (Fig. 3). No ulcer recurrence was observed during a 4-year follow-up.
Patient 3 was a 63-year-old man with idiopathic NK who presented with a central corneal ulcer and positive corneal fluorescein staining in the left eye. The initial diagnosis was NK stage III. The BCVA was 0.1 decimal in the left eye (amblyopia, right eye) and corneal sensitivity 1/3 in all corneal zones. After 15 days of treatment with cenegermin, subjective sensitivity and eye discomfort improved, and after 9 weeks, sensitivity improved to 2/3 in all corneal zones and complete healing of the ulcer was observed with slight epithelial punctate erosions. No recurrence of NK was observed during a 4-year follow-up period.

Patient 4 was a 38-year-old woman with NK secondary to radiation therapy of a parotid gland tumor. She also presented with Sjögren's syndrome. The initial diagnosis was NK stage III of the right eye. There was a corneal ulcer, generalized punctate erosions, and corneal sensitivity 0/3 in all quadrants. After 3 weeks of treatment with cenegermin, complete corneal healing was achieved and sensitivity improved to 1/3 in all quadrants. No ulcer recurrence occurred during a follow-up of 4 years.

Patient 5 was a 52-year-old man with NK caused by herpetic keratitis. The initial diagnosis was NK stage II of the left eye. The corneal sensitivity was 0/3 in all zones and there were leukomas after repeated ulcers and reduced corneal paracentral thickness. After 3 weeks of treatment with cenegermin, eye discomfort improved, sensitivity was 1/3 in all zones, and fluorescein staining of leukomas was minimal. Complete healing of the ulcer was shown after treatment with cenegermin (Fig. 4). Recurrence of the ulcer was not observed during a 4-year follow-up period.

In all patients, the use of lubricant solutions for ocular dryness in the form of ocular drops 4–6 times/day with hyaluronic acid was maintained. In cases #3 and #4, in addition to lubricant solutions, they were treated with cyclosporine 0.1% (Ikervis®) one drop at night. All patients were satisfied with treatment and no adverse events were reported.

**Discussion**

In the present case series study of five adult patients with NK, therapy with cenegermin was associated with stromal and epithelial healing and improvement of corneal sensations. At the ninth week of follow-up, corneal sensitivity improvement and healing of corneal ulcers were found in all patients. No recurrence of corneal ulcer was documented over a 4-year follow-up period.

Cenegermin has been demonstrated to be safe and effective in the treatment of NK based on conducted regulatory trials [8–10]. However, in a review of the literature, the number of publications of the use of this drug in the management of adult patients with NK in daily
practice is still limited. Habibi et al. [21] reported 2 cases of NK after laser-assisted in situ keratomileusis surgery treated with an 8-week course of cenegermin, with improvement in VA, corneal sensitivity, and ocular surface staining, but the clinical signs and symptoms regressed 1 month after finishing treatment. The authors suggest that lower dosing and/or lower concentration over a longer period of treatment may be considered for post-LASIK patients with NK without persistent epithelial defect. Alhajraf et al. [20] reported a case of NK that presented as a ring-shape corneal ulcer in a patient with history of intravitreal ranibizumab injection for diabetic macular edema, initially misdiagnosed as acanthamoeba keratitis and unresponsive to anti-amoebic therapy; treatment with cenegermin led to reduction of ring and stromal opacities with closing of the epithelial defect. Pocobelli et al. [17] reported the first case of treatment with cenegermin for NK recurrence following optical penetrating keratoplasty. In the 3 cases of corneal ulcers due to NK treated with cenegermin, reported by Di Zazzo et al. [22], the cause of NK was herpetic keratitis in 2 patients and immune keratitis in one, and all patients healed within 8 weeks therapy with cenegermin. Zwingelberg et al. [19] reported the use of cenegermin in 11 patients with NK stages II and III, with epithelial healing and improvement in vision and corneal sensitivity after 18 months. Bruscolini et al. [23] evaluated 18 patients with NK treated with cenegermin and reported recurrences in 4 patients: within the first 12 months in three and within the first 36 months in one. Follow-up data at 4 years was available in 9 of the 18 patients, and all were free of recurrences.

Other treatment modalities reported for patients with NK with satisfactory results showing corneal defect/ulcer resolution include a combination of the neurotransmitter substance P and insulin-like growth factor 1 (IGF-1) [24, 25], topical insulin in cases of refractory NK stages II and III [26], and eye drops of autologous serum [27] and plasma rich in growth factors [28]. None of these options, however, are addressed to the main problem of inhibition of corneal sensitivity. Cenegermin improves corneal sensitivity in association with increase of sub-basal nerve density, diameter, and number of nerve branches, which indicates improvement in structure and function of corneal nerves [4]. Also, cenegermin acts directly on corneal epithelial cells to stimulate their growth and survival, maintains limbal epithelial stem cell potential, and binds receptors on lacrimal glands to promote tear production [7]. Recently, corneal neurotization has been proposed for severe NK [29, 30]. This procedure involves the transposition of a healthy donor nerve along the limbal circumference to re-establish corneal sensation and trophic function, which can be performed either by directly transposing the supraorbital nerve or by using a sural nerve interponate [29]. However, before adoption of this technique, a comparison of corneal neurotization with noninterventional therapies, such as cenegermin, is needed. However, the cost itself of cenegermin represents a major obstacle to the use of the drops in clinical practice.

**Conclusion**

In a case series of 5 patients with NK, treatment with cenegermin was effective and well tolerated in the healing of corneal ulcers with a trend of improvement of VA and corneal sensitivity. No corneal ulcer recurrence was observed over a follow-up period of 4 years. The present findings add evidence of the effectiveness of cenegermin for the treatment of NK in the real-life setting with long-lasting benefits.

**Acknowledgments**

The authors thank Marta Pulido, MD, for editing the manuscript and editorial assistance.
Statement of Ethics

Written informed consent was obtained from all patients for publication of the details of their medical cases and accompanying images. Ethical approval is not required for this study in accordance with national guidelines.

Conflict of Interest Statement

There are no potential conflicts.

Funding Sources

Funding support was provided by Dompé Farmaceutici SpA, Milan, Italy.

Author Contributions

Salvador García-Delpech: conceptualization and study design, care of the patients, data collection, and writing of the manuscript; Patricia Udaondo and Damian García-Teillard: care of the patients, data collection, and critical review of the manuscript for intellectual content; and Alex Samir Fernández-Santodomingo: review of the literature, care of the patients, data collection, and critical review of the manuscript for intellectual content. The final draft was approved by all authors.

Data Availability Statement

All data generated during the study are included in this article. Further inquiries can be directed to the corresponding author.

References

1. Sacchetti M, Lambiase A. Diagnosis and management of neurotrophic keratitis. Clin Ophthalmol. 2014 Mar 19; 8:571–9.
2. Roth M, Dierse S, Alder J, Holtmann C, Geerling G. Incidence, prevalence, and outcome of moderate to severe neurotrophic keratopathy in a German tertiary referral center from 2013 to 2017. Graefes Arch Clin Exp Ophthalmol. 2022 Jun; 260(6):1961–73.
3. Dua HS, Said DG, Messmer EM, Rolando M, Benitez-Del-Castillo JM, Hossain PN, et al. Neurotrophic keratopathy. Prog Retin Eye Res. 2018 Sep; 66:107–31.
4. Mastropasqua L, Lanzini M, Dua HS, D’Uffizi A, Di Nicola M, Calianno R, et al. In vivo evaluation of corneal nerves and epithelial healing after treatment with recombinant nerve growth factor for neurotrophic keratopathy. Am J Ophthalmol. 2020 Sep;217:278–86.
5. Mackie IA. Neuroparalytic keratitis. In: Fraunfelder F, Roy FH, Meyer SM, editors. Current ocular therapy. Philadelphia, PA, USA: WB Saunders; 1995. p. 452–4.
6. American Academy of Ophthalmology. EyeWiki. Neurotrophic keratitis. Available from: https://eyewiki.aao.org/Neurotrophic_Keratitis#Diagnostic_Procedures (Accessed January 25, 2022).
7. Sheha H, Tighe S, Hashem O, Hayashida Y. Update on cenegermin eye drops in the treatment of neurotrophic keratitis. Clin Ophthalmol. 2019 Oct 7;13:1973–80.
8. Ferrari MP, Mantelli F, Sacchetti M, Antonaniali MI, Cattani F, D’Anniballe G, et al. Safety and pharmacokinetics of escalating doses of human recombinant nerve growth factor eye drops in a double-masked, randomized clinical trial. BioDrugs. 2014 Jun;28(3):275–83.
Bonini S, Lambiase A, Rama P, Sinigaglia F, Allegritti M, Chao W, et al. Phase II randomized, double-masked, vehicle-controlled trial of recombinant human nerve growth factor for neurotrophic keratitis. Ophthalmology. 2018 Sep;125(9):1332–43.

Pflugfelder SC, Massaro-Giordano M, Perez VL, Hamrah P, Deng SX, Espandar L, et al. Topical recombinant human nerve growth factor (Cenegermin) for neurotrophic keratopathy: a multicenter randomized vehicle-controlled pivotal trial. Ophthalmology. 2020 Jan;127(1):14–26.

Fausto R, Cecuzzi R, Micheletti E, Clerici R, Riva I, Katsanos A, et al. A case report of pediatric neurotrophic keratopathy in pontine terminal cap dysplasia treated with cenegermin eye drops. Medicine. 2020 Jul 24;99(30):e20816.

Papadopoulos K, Besgen V, Sekundo W. Successful treatment of a pediatric neurotrophic keratitis with cenegermin. Cornea. 2021 Apr;40(4):516–8.

Pedrotti E, Bonetto J, Cozzini T, Fasolo A, Marchini G. Cenegermin in pediatric neurotrophic keratopathy. Cornea. 2019 Nov;38(11):1450–2.

Loto MG, Toro MO, Indemini PE, Fruttero C, Denina M, Dalmazzo C, et al. Pediatric use of recombinant human nerve growth factor 20 μg/mL eye drops (Cenegermin) for bilateral neurotrophic keratopathy in congenital corneal anesthesia. Cornea. 2021 Feb 1;40(2):228–31.

Ahuja AS, Bowden FW 3rd, Robben JL. A novel treatment for neurotrophic corneal ulcer using topical cenegermin (OXERVATE™) containing recombinant human nerve growth factor. Cureus. 2020 Nov 27;12(11):e11724.

Riva I, Micheletti E, Fausto R, Bruttini C, De Angelis G, Cecuzzi R, et al. Human recombinant nerve growth factor (Cenegermin) in a patient affected by primary congenital glaucoma with neurotrophic keratopathy. Eur J Ophthalmol. 2022 Jul;32(4):NP78–81.

Pocobelli A, Komaiha C, De Carlo L, Pocobelli G, Boni N, Colabello Gisoldi RAM. Role of topical cenegermin in management of a cornea transplant in a functionally monocular patient with neurotrophic keratitis and facial nerve palsy: a case report. Int Med Case Rep J. 2020 Nov 11;13:617–21.

Mandarà E, Brocca D, Pellegrini F, Interlandi E. Topical nerve growth factor for the treatment of neurotrophic keratopathy caused by Wallenberg syndrome. Cornea. 2022;41(5):647–8.

Zwingelberg SB, Bachmann BO, Cursiefen C. Real life data on efficacy and safety of topical NGF eye drops (Cenegermin). Klin Monbl Augenheilkd. 2020 Dec;237(12):1455–61.

Alhajraf K, Lin SR, Jacobs DS. A corneal ring ulcer. Am J Ophthalmol Case Rep. 2020 Aug 5;20:100856.

Habibi RN, Lee MD. Treatment of dry eye from laser-assisted in situ keratomileusis with recombinant human nerve growth factor (cenegermin). Cornea. 2021 Aug 1;40(8):1059–61.

Di Zazzo A, Varacalli G, Mori T, Coassin M. Long-term restoration of corneal sensitivity in neurotrophic keratopathy after rhNGF treatment. Eur J Ophthalmol. 2022 Jan;32(1):NP15–8.

Bruscolini A, Sacchetti M, Moramarco A, Albanese GM, Cerini A, Lambiase A. The long-term clinical efficacy of recombinant human nerve growth factor in the treatment of neurotrophic keratopathy [Abstract]. Invest Ophthalmol Vis Sci. 2021;62(8):728.

Yanai R, Nishida T, Chikama T, Morishige N, Yamada N, Sonoda KH. Potential new modes of treatment of neurotrophic keratopathy. Cornea. 2015 Nov;34(Suppl 11):S12–7.

Yanai R, Nishida T, Hatano M, Uchi SH, Yamada N, Kimura K. Role of the neurokinin-1 receptor in the promotion of corneal epithelial wound healing by the peptides FGLM-NH2 and SSSR in neurotrophic keratopathy. Invest Ophthalmol Vis Sci. 2020 Jul 1;61(8):29.

Soares RJDSM, Árêde C, Sousa Neves F, da Silva Fernandes J, Cunha Ferreira C, Sequeira J. Topical insulin-utility and results in refractory neurotrophic keratopathy in stages 2 and 3. Cornea. 2022;41(8):990–4.

Matsumoto Y, Dogru M, Goto E, Ohashi Y, Kojima T, Ishida R, et al. Autologous serum application in the treatment of neurotrophic keratopathy. Ophthalmology. 2004 Jun;111(6):1115–20.

Sanchez-Avila RM, Merayo-Lloves J, Riestra AC, Fernández-Vega Cueto L, Anítaa E, Begoña L, et al. Treatment of patients with neurotrophic keratitis stages 2 and 3 with plasma rich in growth factors (PRGF-Endoret) eye-drops. Int Ophthalmol. 2018 Jun;38(3):1193–204.

Lueke JN, Holtmann C, Besogol K, Geerling G. Corneal neurotization. Ophthalmologe. 2020 Mar;117(3):248–52.

Giannaccare G, Bolognesi F, Pellegrini M, Spina R, Allevi F, Marchetti C, et al. Corneal neurotization: a novel surgical procedure for neurotrophic keratopathy. Cornea. 2022 Apr;41(4):403–7.