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Topical human recombinant nerve growth factor for stage 1 Neurotrophic Keratitis: Retrospective case series of cenegermin treatment

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ABSTRACT

Purpose: To report on the management and effectiveness of treating patients with stage I Neurotrophic Keratitis using an 8-week course of topical recombinant human nerve growth factor (rhNGF, cenegermin).
Observations: In this retrospective case series, punctate epithelial erosions (PEE), best corrected visual acuity (BCVA) and corneal sensation were followed and documented from 2 to 12 months in patients treated as per the standard of care. Clinical outcomes including changes in PEEs, corneal sensation and BCVA are reported. Most patients also had preexisting thyroid disease.
Conclusions: All patients had clinically significant improvements in PEE, and corneal sensation. Three of the four patients had a significant improvement in BCVA, one patient had no change in their pre-treatment visual acuity (BCVA 20/20) The four patients studied also reported decreased photophobia and improvements in their quality of life. This case series provides real-world evidence of the safety and efficacy of cenegermin treatment of stage I NK for all four patients.

1. Introduction

Neurotrophic keratitis (NK), a rare eye disorder that affects the cornea, is a degenerative disease of the corneal epithelium characterized by decreased corneal sensitivity and poor corneal healing. Having NK can make the cornea more vulnerable to damage and decreases reflex tearing. Epithelial breakdown can result in ulceration, infection, melting, and perforation secondary to poor healing.[1–3] Any condition or disorder that affects corneal nerves can cause NK. Since the cornea has no blood vessels, it relies on nutrients in tears and neuromediators released by corneal nerves for trophic support. Neurotrophic keratitis causes a decrease in reflex tears, and as corneal sensation decreases, less tears are produced in response to corneal stimuli. This can lead to the corneal epithelium drying out and eventually breaking down.[4]

Multiple ocular and systemic diseases may lead to NK, however there is one common cause: damage to the trigeminal nerve (Cranial nerve V), which is the main nerve that innervates the cornea. When the nerves in the cornea are damaged this causes reduced sensitivity of the cornea and can lead to NK.[5] The most common triggers include herpetic keratitis, chemical burns, corneal/ocular surgery, chronic contact lens use and prolonged use of topical medications. Intracranial anomalies such as acoustic neuroma, meningioma and aneurysms may compress the trigeminal nerve or ganglion causing corneal sensitivity to be compromised. Another common etiology of NK is diabetes mellitus. Chronic uncontrolled diabetes patients can develop neuropathy involving the lower extremities, which similarly can occur in the cornea leading to sensory loss.[6] More recently, it has been determined that chronic dry eye disease (DED) disease can also cause corneal nerve damage since eye lubrication and nourishment is reduced leading to corneal nerve damage.[7–9] In fact, any condition that can cause corneal damage may lead to NK symptoms including DED, exposure keratitis, limbal stem cell deficiency, surgical damage to the cornea, and Sjögren's syndrome.[4,7–10] A recently published retrospective study cites dry eye as the underlying cause of NK in 8/63 eyes (12.7%), including 2/63 eyes (3.2%) that were attributed to Sjögren's syndrome. Dry eye was the fourth most common etiology in this study.[7] Another recently published retrospective chart review cites severe DED as the underlying cause of NK in 3/32 eyes (9.4%). Dry eye was tied for the fourth most common etiology in this study: "The most common cause of NK in our patients was herpes simplex keratoplasty, followed by ocular surgery, neurosurgical trigeminal damage, and severe dry eye disease."[8] Another retrospective study cites chronic ocular surface disease as the underlying cause of NK in 62/354

Abbreviations: rhNGF, human recombinant nerve growth factor; NK, neurotrophic keratitis.

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eyes (17.5%), of which 3/354 eyes (0.8%) were attributed to Sjögren's syndrome.[9] Finally, a review by Labetoulle et al. suggests that advanced DED may result in loss of neuronal endings, often as a consequence of inflammation, which may eventually evolve into NK.[10] The degree of sensory loss, duration of the condition and the presence of pre-existing ocular surface disease are all prognostic indicators for NK.[10]

The concentration of multiple growth factors and neuromodulators that are responsible for maintaining a healthy ocular surface is reduced when the density of sub-basal corneal nerves decreases.[11] The ocular tear film plays a crucial role in maintaining both the corneal and conjunctival integrity, protecting against microbial challenge, thus preserving visual acuity.[11] Significant international research efforts are focused on understanding composition and regulation of the preocular tear film. In the Tear Film & Ocular Surface Society (TFOS) Dry Eye Workshop (DEWS) II Patient summary report, DED is defined as the following: "Dry eye is a multifactorial disease of the ocular surface characterized by a loss of homeostasis of the tear film, and accompanied by ocular symptoms, in which tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play etiological roles".[12] Chronic inflammation seen in DED can lead to damage in corneal sensory nerves ultimately leading to progression to NK.[7–9] The frequencies for the etiologies of NK in the recent studies cited[7–10] are generally in line with what was observed in the pivotal trials of neurotrophic growth factors to treat Stage 2 and 3 NK. There were 17/156 eyes (10.9%) in the REPARO clinical trial[13] and 6/48 eyes (12.5%) in the US clinical trial[14] that had dry eye disease listed as the underlying cause of NK.

Based on severity, NK can be divided into three stages based on the Mackie classification. Stage 1 - punctate epithelial erosions; Stage 2 - persistent epithelial defects; Stage 3 - corneal ulcers, melting and perforation. Work up for patients with NK should include a complete medical and surgical history, a review of medications, and an ocular examination. While reaching the clinical diagnosis is typically made without difficulty, the management of neurotrophic keratopathy can be quite challenging.[1–3,6]

The goal of treating patients with NK is to stop the disease from progressing and reverse the corneal pathology seen clinically. The most effective preventative strategy is to identify patients with NK as soon as possible to prevent progression of the disease. Although conventional therapy for stage 1 NK may provide temporary healing, the objective is to prevent epithelial breakdown, mostly by discontinuing toxic topical medications, administering lubricating agents such as preservative-free artificial tears and autologous serum drops, or insertion of an amniotic membrane device.[1] The aim of stage 2 and 3 therapies is to facilitate corneal healing and prevent corneal melting and perforation; procedures may include induced ptosis using botulinum, tarsorrhaphy, conjunctival flap, and amniotic membrane transplantation to restore ocular surface integrity. Consequently, these procedures often result in poor vision. Up until recently, these conventional treatments did not address the underlying problem of corneal anesthesia and do not provide a permanent cure.[6]

There is substantial evidence to support the use of neurotrophic growth factors to treat NK to re-establish corneal homeostasis, corneal integrity, and re-innervation of the corneal nerves.[5,15,16] Cenegermin (OXERVATE™) is a topical recombinant Human Nerve Growth Factor (rhNGF) that was approved for the treatment of NK in the US in August 20, 18.[13,14,18] In the REPARO[13] and US pivotal trials,[14]10.9% and 12.5% respectively had DED listed as the underlying cause of stage 2 and 3 NK in the clinical trial participants. Therefore, the clinical data that the FDA used to evaluate for the approval of cenegermin was based on patients with Stage 2 and 3 NK.[13,14] However, cenegermin is approved for all stages of NK.[16,17] There have been several reports that have confirmed good outcomes for the clinical application of cenegermin in Stage 2 and 3 NK.[18–21] Published literature on the use of cenegermin in adult patients with Stage 1 NK is limited. The case series, detailed in this report, demonstrates the efficacy of cenegermin for the treatment of stage 1 NK of various etiologies (DED, Sjögren's Syndrome, previous ocular surgery, herpetic keratitis). For example, the patient described in case number 1 has severe DED, which is the most likely underlying cause for his NK.

To the best of our knowledge, this is first published case series report of patients with adult stage 1 NK treated with cenegermin.

The aim of our retrospective case series report is to provide information on the clinical utility of cenegermin in stabilizing the ocular surface in patients with Stage I NK.

2. Methods

2.1. Cases and retrospective collation of data

All patients were followed in the clinic on a regular basis and were previously treated as per the standard of care based on the type and severity of their DED. The date range for the patient cases included in this report was from January 2019 through July 2020. Assessments included evaluating corneal sensation, quality of vision as assessed via best corrected visual acuity (BCVA) using Snellen acuity, symptoms of DED, tear break up time, use of artificial tears, and punctate epithelial erosions (PEE).

Baseline signs and symptoms were established prior to initiating cenegermin treatment. Consideration for inclusion in this retrospective case series report included reduced or absent corneal sensation, diagnosis of Stage I NK, and clinical progression despite maximal conservative (nonsurgical) treatment to the ocular surface at baseline.

2.2. NK treatment of patents as per the standard of care

Cenegermin-bkbj ophthalmic solution 0.002% (rhNGF 20 mcg/mL) [US package insert,[22] was prescribed and supplied by Dompé, Milan, Italy]. All patients described in this retrospective case series viewed the instructional video provided by Dompé and were instructed by clinic staff and the lead investigator on administration of the drops before initiating cenegermin treatment. The patients were subsequently observed instilling their first set of drops in the office (since drops come from a vial). The cenegermin drops were self-administered at 6 drops/day with at least 2-to-3-hour internals over 8 weeks as described in both the training and the package insert instructions.[20,22]

Assessing corneal sensitivity is essential to confirm the diagnosis of NK and to determine the severity of corneal nerve damage. Accepted methods of evaluating corneal sensitivity can be either quantitative (using a cotton thread or dental tape) or qualitative (corneal aesthesiometer, commonly used for research purposes). In general clinicians tend to use a qualitative method to make this assessment in the clinic.

The current case series is a retrospective review where corneal sensation was measured before and after the course of treatment using non-minted dental tape in the central and peripheral cornea, and was recorded as present, reduced, or absent.

For all patient cases detailed in this report, the patients were treated in both their right (OD) and left (OS) eyes; OU means both eyes – except in Case 2 for which only the left eye (OS) was treated, as the right eye (OD) was unaffected (Table 1).

2.3. Fluorescein eye staining, images and grading

Punctate epithelial erosions (PEE) representing epithelial loss were assessed using a fluorescein strip under cobalt blue light and a Wratten #12 filter. Photos were taken to objectively evaluate PEE before and after treatment with cenegermin. Images at baseline and post treatment were clinically evaluated and graded using the National Eye Institute/Industry (NEI) grading scale,[23] that divides cornea images into five areas assigning values from 0 (no staining) to 3 (intense staining) for each area, based on the intensity and distribution of the punctate staining up to 15 points per corneal eye image (Table 2).

Table 1
Stage 1 NK case summary of adverse events (AEs), follow-up and treatment outcomes.

Case Number	Affected Eye(s)	History, Baseline Signs & Symptoms	AEs during Treatment	Follow-Up Period and Comments	BVCA Before (baseline) and After Treatment
Case 1	Both eyes (OU)	LASIK, Sjögren's disease with no ocular or visual complaints; reduction in corneal sensation in left eye (OS); right eye (OD) had normal sensation.	Both eyes felt "tender" during treatment and resolved after treatment was completed	6 and 9 months: follow-up with clinically significant PEE improvements; stopped needing artificial tears after treatment (made her own tears) and had reduced photophobia	20/20 both eyes before and after treatment
Case 2	Only left eye (OS) was treated, as right eye was unaffected	Photophobia, and poor-quality vision; absent corneal sensation in all four quadrants of left eye (OS)	No AEs in either eye	2 and 6 months: follow-up; improved vision, & PEE, more comfortable with less photophobia;	Left Eye Before: 20/400 OS After: 20/70 OS
Case 3	Both eyes (OU)	DED, Sjögren's, HSV keratitis, in both eyes (OU), Brainstem stroke	Mild periorbital achiness during treatment in both eyes	4, 5 and 16 months: follow-up; complete corneal healing was maintained. At 16 months developed significant recurrent PEE with left eye (OS) affected more than the right (OD that required cryopreserved amniotic membrane and 2nd course of cenegermin started Feb 2022	Right and Left Eyes Before: 20/80 OD, 20/300 OS After: 20/50 OD and 20/100 OS
Case 4	Both eyes (OU)	DED and keratitis	"Uncomfortable soreness in both eye sockets" Described almost like a pressure headache, sensation	2 and 12 months: follow-up; significant improvement in PEE, corneal sensation, and less mucous production after treatment	Both Eyes, OU Before: 20/50 After: 20/20 After: 20/20 in both eyes

Description of the case series summarizing the treated eyes, baseline symptoms, any adverse events and follow-up with post treatment outcomes. OD, right eye, OS, left eye, OU, both eyes.

2.4. Statistical analyses and graphing

The NEI scores were averaged for all NK affected eyes and a two-tailed paired T test was run using the Microsoft Excel program comparing baseline (pre) and the longest post treatment duration (last visit; post) NEI scores. The pre- and post-treatment mean NEI scores were graphed using the Excel program.

3. Case series descriptions and findings

3.1. Case 1

A 62-year-old white female with a history of laser-assisted in situ keratomileusis (LASIK), and Sjögren's disease was referred by her optometrist for severe keratitis. She had no ocular or visual complaints. Previous treatments included lifitegrast ophthalmic solution 5%, re-esterified omega-3 supplementation, and thermal pulsation. Current treatment included preservative-free artificial tears 4–5 times/day, and her past medical history was significant for hypothyroidism. A baseline examination demonstrated uncorrected vision of 20/20 in each eye, severe diffuse PEEs as seen using fluorescein, moderate conjunctival staining (lissamine green), and well-healed and centered LASIK flaps. She had a tear break-up time of 1 second OD/OS, Schirmer scores of 2 mm OD and 2 mm OS with diminished corneal sensation OU were also noted. The patient had no dry eye symptoms, as addressed using a SPEED questionnaire and history. She was diagnosed with Stage 1 NK and was treated with an 8-week course of cenegermin (6 drops/day) OU. Two weeks post treatment, the patient subjectively reported better quality vision in both eyes and less need for artificial tears use (Table 1). She had clinically significant improvement in PEE (Table 2) and corneal sensation post treatment, which continued through 6- and 9-months of follow-up (Table 1 and Fig. 1).

Table 2
Corneal fluorescein PEE staining grading using the National Eye Institute (NEI) scale before and after cenegermin treatment in indicated eye(s).

Case Number	Cenegermin (rhNGF) Treatment Frequency	NEI Score		
		OD	OS	Mean
Case 1	Baseline	15	13	14
	6 months after rhNGF initiation	4	5	4.5
	9 months after rhNGF initiation	2	2	2
Case 2	Baseline	not treated	15	15
	2 months after rhNGF initiation	not treated	5	5
	6 months after rhNGF initiation	not treated	4	4
Case 3	Baseline	8	15	11.5
	4 months after rhNGF initiation	8	10	9
	5 months after rhNGF initiation	3	6	4.5
Case 4	Baseline	6	14	10
	2 months after rhNGF initiation	6	6	6
	12 months after rhNGF initiation	2	2	2

NEI scores and mean scores for Cases 1–4 pre- and post-cenegermin treatment in the indicated eye. A two-tailed paired T test was done comparing baseline and the longest post treatment duration (last visit) NEI scores. The T test P value is $P = 0.004$, demonstrating that the scores are significantly different. OD, right eye, OS, left eye.

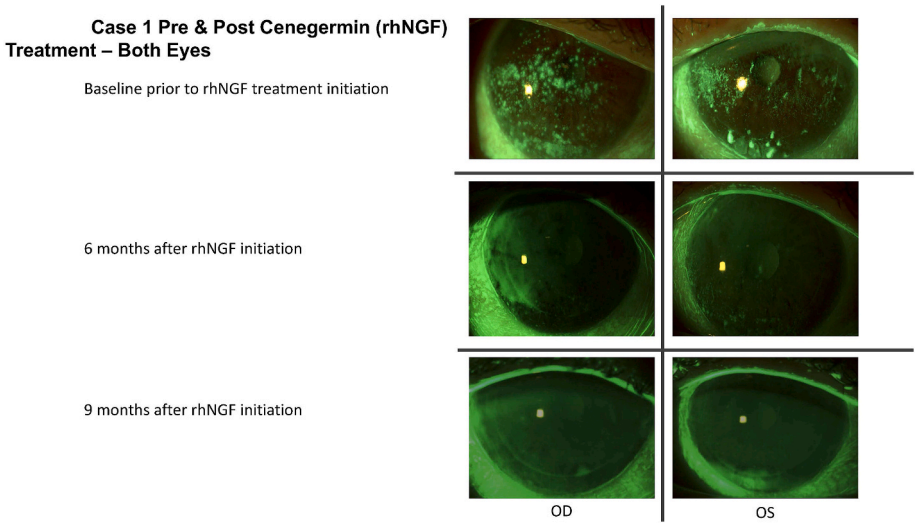

Fig. 1. Case 1 Top panel row: right and left eyes at baseline. Middle panel row: post 6 months following initiation of 8-week cenegermin 20 μg/ml treatment for right and left eyes. Bottom panel row: 9 months after starting treatment.

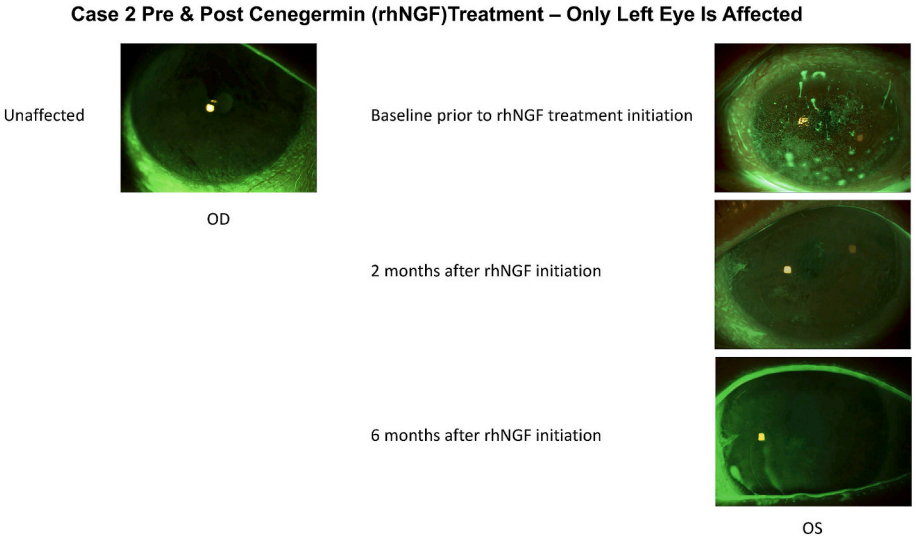

Fig. 2. Case 2 Only the left (OS) eye was affected with NK and treated. Top row shows OS at baseline before treatment. Middle row: 2 months after rhNGF treatment. Bottom row: 6 months after initiating treatment.

3.2. Case 2

A 74-year-old white female who has had multiple ocular surgeries in the left eye (OS) and was referred by a local retina service for evaluation and treatment of DED. Her past ocular history was significant for high myopia OU, retinal detachment repair, with three pars plana vitrectomies, cataract surgery with subsequent intraocular lens implant dislocation and a secondary anterior chamber intraocular lens implant, all involving the left eye. The patient's past medical history was significant for hypothyroid, hypertension and cluster migraines. On examination her best corrected visual acuity (BCVA) was 20/40 OD and 20/400 OS. She complained of photophobia, and poor-quality vision. In addition, she had diffused PEE (Table 1, Table 2, and Fig. 1), absent corneal sensation in all four quadrants OS, anterior segment demonstrated concomitant corneal filaments, reduced tear break-up time, and a well-centered anterior chamber intraocular lens implant. The tear film in her right eye appeared unremarkable with a tear meniscus height between 0.2 and 0.5 mm, and there was no corneal staining (Fig. 2) and normal corneal sensation (Table 1). Previous treatments included preservative-free tears, lubricating ointment at bedtime, re-esterified omega-3 supplementation, thermal pulsation, cyclosporine drops and cryopreserved amniotic membrane. Cenegermin therapy was recommended OS for her Stage 1 NK, as only the left eye was affected. At her post treatment visits at 2 and 6 months she reported being more comfortable with better vision and less photophobia. Her BCVA improved to 20/70 OS, and she had improved corneal sensation (reduced sensation temporally but present other quadrants), with significant reduction in PEE (Tables 1–2 and Fig. 2).

3.3. Case 3

A 67-year-old white female was referred by a rheumatologist 8 years previously for DED. She had an extensive past medical history and past ocular history significant for brainstem cerebral vascular accident, 4th nerve palsy, Sjögren's, Herpes Simplex Virus keratitis, chronic progressive external ophthalmoplegia (inherited, bilateral upper lid weakness, associated with cardiac problems, vertical diplopia) hypothyroid, allergies, cardiomyopathy, hypoglycemic syndrome, fibromyalgia, and

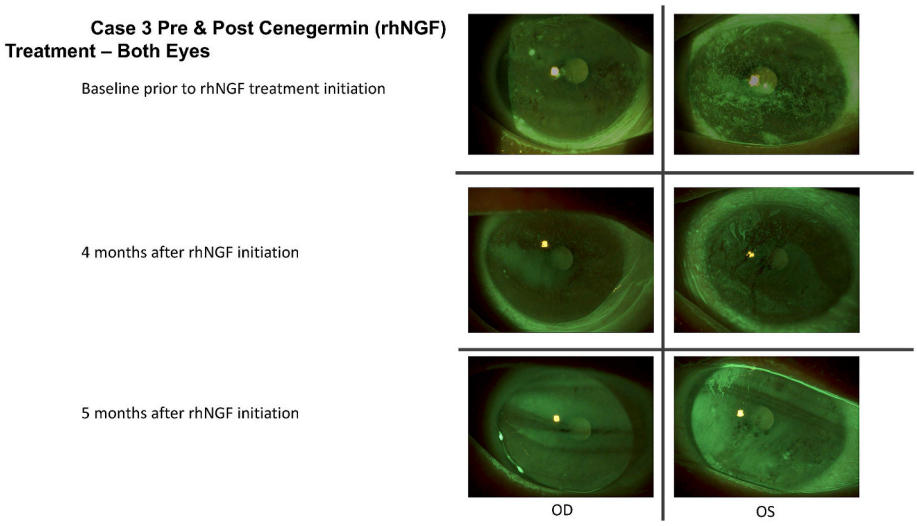

Fig. 3. Case 3 Top panel row: right and left eyes at baseline. Middle panel row: 4 months after initiating 8-weeks cenegermin 20 μg/ml treatment for right and left eyes. Bottom panel row: 5 months after initiating treatment.

non-Hodgkin's lymphoma. Treatments for her DED included punctal cautery, lifitegrast ophthalmic solution, 5%, cyclosporine ophthalmic emulsion 0.05%, azithromycin drops, re-esterified Omega-3 supplementation, cryopreserved amniotic membrane and topical dapsone. She complained of reduced vision resulting in frequent falls. Her baseline examination demonstrated BCVA of 20/80 OD and 20/300 OS, diffuse PEE OU (Fig. 3 and Table 2) with reduced corneal sensation OS > OD (Table 1). She received an 8-week course of cenegermin in both eyes after which her BCVA improved to 20/50 OD and 20/100 OS. She said her eyes were more comfortable and could open her eyes more frequently since initiating the cenegermin treatment. She also reported less frequent falling. Her post treatment follow-up visits at 4 and 5 months showed complete corneal healing was maintained (Tables 1–2 and Fig. 3).

3.4. Case 4

A 52-year-old white male with progressive worsening of signs and symptoms of DED since 2007. He has had keratitis since 2007. His past medical history included non-allergic vasomotor rhinitis (negative for Sjögren's). His baseline examination revealed a BCVA of 20/50 OU, severe, diffuse keratitis with the left eye having greater staining than the right eye (Fig. 4, Table 2). He had reduced corneal sensation in all 4 quadrants OU, moderate conjunctival injection, significant mucous formation, and severe photophobia (Table 1). Signs and symptoms (blurred vision) were worse in the left eye. He was unable to fulfill his work obligations and became severely depressed due to his debilitating dry eye condition. His previous treatments included cyclosporine ophthalmic emulsion 0.05%, lifitegrast ophthalmic solution, 5%, re-esterified Omega-3 supplementation, lid hygiene using topical hypochlorous acid, intermittent topical steroid and allergy drops, azithromycin 1% ophthalmic solution, punctual cauterization, autologous serum tears, compounded spironolactone and n-acetylcysteine drops, topical albumin drops, preservative-free tears, ointment, compounded topical tacrolimus, cryopreserved amniotic membrane, scleral contact lenses and moisture chamber goggles. After completing an 8-week course of cenegermin OU, his BCVA improved to 20/20 in each eye, with clinically significant improvement in corneal sensation and PEE as determined by the examiner (Fig. 4 and Tables 1–2). The patient reported significant improvement in his quality-of-life post treatment and was able to return to both work and social activities.

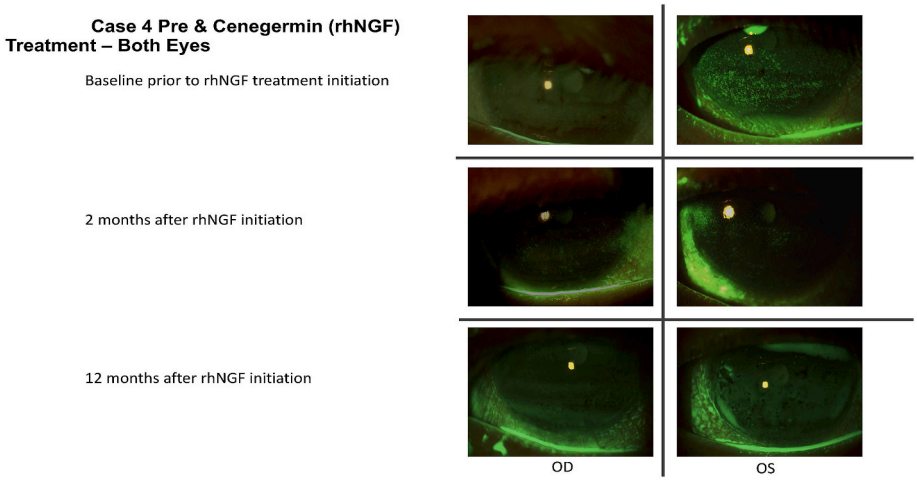

Fig. 4. Case 4 Top panel row: right and left eyes at baseline. Middle panel row: after completion of 8-weeks cenegermin 20 μg/ml treatment for right and left eyes. Bottom panel row: 12 months post treatment.

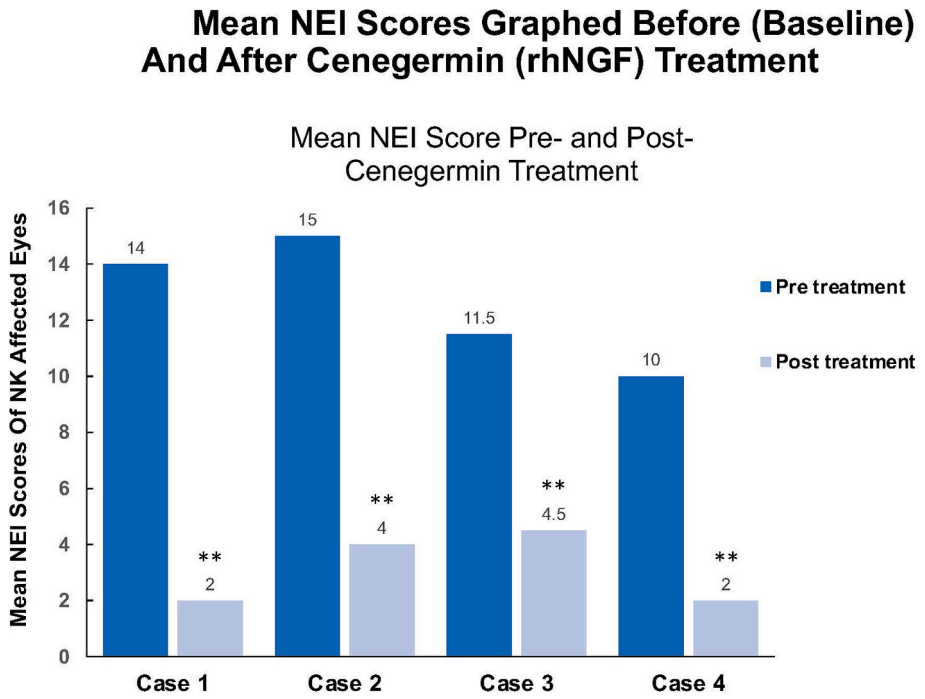

Fig. 5. Mean NEI Scores Graphed Before and After Final Cenegermin Treatment
Mean NEI scores of affected eyes for Cases 1–4 pre- and post-cenegermin treatment. Baseline (pre) and the longest post treatment duration (last visit; post) mean NEI score values are graphed from Table 2. **, P = 0.004, 2-tailed, paired T-test

3.5. Summary of case series data

The summary of the NEI scores can be seen in Table 2 and the bar graph illustrates the mean NEI scores at baseline (pre cenegermin treatment) versus the mean NEI scores post treatment (Fig. 5).

3.6. Adverse events

According to information detailed in the cenegermin package insert,[22] the most common adverse reactions with overall incidence of >5% are eye pain, ocular hyperemia, eye inflammation and increased lacrimation. Patients were informed of the possibility of adverse events and instructed to notify us if they were unable to tolerate treatment. Adverse events reported by patients during cenegermin treatment in our series were eye pain, achiness, tenderness, soreness, or headache sensation, which is believed to occur as the corneal nerves regenerate (Table 1). Corneal neovascularization was not observed in any of the patients.

4. Discussion

Loss of homeostasis and corneal sensation has a multitude of sequelae on the cornea, including visual complaints, increased risk of infection, keratitis and inflammation, corneal ulceration, and possible perforation. We are fortunate to live in an era where we have more treatment options for these patients with persistent keratitis. These include immunomodulators, topical steroids, nasal stimulation, cryopreserved amniotic membrane and scleral lenses to name a few. Additionally, repository corticotropin injections (Acthar® gel) is another treatment option for patients with severe, persistent keratitis. A study evaluating the efficacy of using repository corticotropin injection in patients with severe keratitis, demonstrated 50% of patients had improvements after corticotropin injections and patients experienced less discomfort.[24] Effective, topical treatments may be an easier and more accessible treatment for at home use for patients.

The safety and efficacy of cenegermin 20 μg/ml drops have been successfully tested in clinical trials in adult patients with moderate (stage 2) and severe (stage 3) NK.[13,14] It is also important to assess the safety and efficacy of cenegermin in a real-world clinic setting and to determine whether cenegermin can achieve good clinical outcomes in patients with stage 1 NK.

Previously, NK treatment options have been limited to reducing signs and symptoms but have not directly targeted the underlying degeneration of corneal nerves. Cenegermin eye drops are the first and only topical ophthalmic biologic FDA-approved and represent the first human NGF used for any medicinal treatment in humans. Cenegermin is currently used as first-line treatment for NK stages 1–3, for patients with failed responses to conventional drug treatment. The data from the pivotal trials was based on patients with stage 2 and 3 NK.[13,14]

This is the first time, to our knowledge, that the real-world effectiveness of treating stage1 NK patients with cenegermin has been reported. All four patients were followed up and had improved outcomes that were retrospectively studied with reduced PEEs, as evidenced by improvement in corneal staining based on NEI score differences pre- and post-cenegermin treatment that were statistically significant (p = 0.004). The striking differences from baseline (pre-treatment) and the post-treatment NEI scores are visualized in the graphed data (Fig. 5), where the reduction of PEEs via NEI scores is clearly demonstrated. In addition, improvements were reported in qualitative corneal sensation and BCVA compared to baseline after being treated with an 8-week course of cenegermin. Three out of the four patients had an improvement in BCVA, and the other patient (Case 1) remained stable with BVCA 20/20. Since NK is characterized by progressive ocular surface changes caused by the loss of sensitivity from trigeminal damage,[25] treating Stage 1 NK early may have the potential to prevent progression to Stage 2/3 NK. More studies of cenegermin for Stage 1 NK are needed to confirm the ability to prevent progression.

5. Conclusions

Individuals with NK present unique clinical challenges because of their significant inability to perceive pain and a tendency of not

responding to standard therapies for ocular surface disease. This case series demonstrates that cenegermin treatment was effective in treating Stage 1 NK, with maintenance of long-term corneal healing in all four patients following a single 8-week course of therapy. Treatment was well-tolerated, and patients reported that it was easy to self-administer and led to improvements in their quality of life. Although cenegermin is indicated for all stages of NK,[22] data on the efficacy for stage 1 NK is limited. The data from this case series provides evidence and confirms that cenegermin is a viable treatment option to heal and protect the ocular surface in earlier stages of NK, and to prevent disease progression.

Patient consent

The retrospective study protocol and data collection format were reviewed by an appropriate Institutional Review Board (IRB). The IRB exemption was granted by Sterling IRB (Sterling, Atlanta, GA) and it was determined that the Category 4 Exemption (DHHS) applies — secondary research for which consent is not required. The IRB exemption was granted based on the study meeting the criteria: "Information, including information about the biospecimens, will be recorded in such a manner that the identity of the human subjects cannot readily be ascertained directly or through identifiers linked to the subjects, the investigator will not contact subjects, and the investigator will not reidentify subjects."

Written consent to publish this case series report has not been obtained from the patients, as this report does not contain any personal information that could lead to their identification.

Declaration of competing interest

ATE is a consultant and speaker for Dompé. She has grant support from Bausch & Lomb, AimMax Therapeutics, Inc. and Sylentis, S.A.U. She is a consultant/speaker for the following companies: Novartis, Allergan/Abbvie, AMO/J&J, Bausch & Lomb, Biotissue (C), Bruder (C), Dompé, EyePoint (C), Kala Pharmaceuticals, Imprimis (C), Kala Pharmaceuticals, OTX, Oyster Point, Physician Recommended Nutriceuticals (Chief Medical Officer), SightSciences (C), SUN Ophthalmics, Tarsus, Visus (C), Zeiss (C).

ATE is a Property Rights/Patent Holder for EpiGlare Tester (Hilco). JLW is a Novartis stockholder and consultant at Takeda.

All authors attest that they meet the current International Committee of Medical Journal Editors (ICMJE) criteria for authorship. Medical writing and editorial assistance were provided by ScienceDocs, Inc., Rancho Palos Verdes, CA.

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