



Resolution of a neurotrophic keratopathy associated hypopyon with cenegermin

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ABSTRACT

Purpose: We present a novel case of a neurotrophic keratopathy associated inflammatory hypopyon that resolved after initiation of therapy with cenegermin (Oxervate; Dompe, Milan, Italy), a recombinant human nerve growth factor (rhNGF). This finding illustrates the potential of cenegermin in advanced inflammatory neurotrophic disease.

Observations: A 60-year-old female with a history of herpes zoster keratitis was evaluated in our clinic for stage 2 neurotrophic keratopathy. One month later, she presented emergently with a large epithelial defect, infiltrate, and hypopyon. Three separate sets of corneal cultures returned negative. She was treated with oral antivirals and aggressive topical antibiotics with no clinical improvement. Given the presumed diagnosis of stage 3 neurotrophic keratopathy with a sterile hypopyon, she was started on cenegermin 6 times daily for 8 weeks in the absence of a corticosteroid. By 2 weeks after starting cenegermin, the epithelial defect, infiltrate, and hypopyon sizes had improved. Within 4 weeks of starting cenegermin, the hypopyon had clinically resolved. The patient was subsequently started on topical corticosteroid drops for the last 4 weeks of cenegermin therapy. Examination at the conclusion of 8 weeks of cenegermin treatment revealed a closed epithelium and minimal scar. Best-corrected visual acuity with contact lens overrefraction was 20/70. Over the course of 7 months of continued follow-up, the cornea remained epithelialized without recurrent corneal infiltration or hypopyon.

Conclusions and importance: While cenegermin has been previously shown to be an effective treatment for neurotrophic keratopathy associated epithelial defects, resolution of a neurotrophic keratopathy associated inflammatory hypopyon with cenegermin is novel.

1. Introduction

The cornea has the greatest innervation density of any tissue in the human body, and corneal nerves play a key role in epithelial cell proliferation, migration, adhesion, and differentiation through the release of various neuropeptides.¹ The corneal epithelium, in return, releases neurotrophic molecules that stimulate nerve survival.² As a result, damage to corneal nerves results in deteriorating trophic properties and subsequent epithelial breakdown.² This condition is known as neurotrophic keratopathy. Common causes of neurotrophic keratopathy include herpetic disease, chemical injuries, trauma, prior corneal surgery, and chronic topical medications. Neurotrophic keratopathy is typically classified into three stages: early epithelial breakdown (stage 1), persistent epithelial defects (stage 2), and corneal ulceration (stage 3). Stage 3 disease may be complicated by progression to corneal

perforation, and rarely a sterile hypopyon may be present in the anterior chamber.³

Cenegermin is a recombinant human nerve growth factor (rhNGF), and under the tradename Oxervate (Dompe, Milan, Italy) was approved for the treatment of neurotrophic keratopathy in 2018 in the United States. The REPARO II trial evaluated safety and efficacy in 156 patients randomized to rhNGF 10 µg/ml, 20 µg/ml, or vehicle. In this study, the cenegermin groups demonstrated a significantly higher proportion of complete epithelial healing compared to placebo both at 4 and 8 weeks with an excellent safety profile.⁴

In this case report, we present the case of neurotrophic keratopathy associated hypopyon that resolved after treatment with cenegermin in the absence of a corticosteroid. This novel finding demonstrates the potential of cenegermin in advanced inflammatory neurotrophic disease.

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2. Case report

A 60-year-old female presented for evaluation of occasional redness and blurry vision in the right eye. She denied any medical history or systemic medications. Her past ocular history was notable for herpes zoster keratitis two years prior to presentation with resulting neurotrophic keratopathy. On initial evaluation, her best-corrected visual acuity (BCVA) was 20/30 in the right eye and 20/20 in the left eye. Intraocular pressure (IOP) was 20 mmHg in the right eye. Examination of the right cornea demonstrated a chronic non-healing epithelial defect and early stromal haze. She had decreased corneal sensation demonstrated using a cotton-tipped applicator. The patient was using loteprednol twice a week, preservative free tears 4–6 times daily, and valacyclovir 500 mg daily. At this visit, options were discussed including cenegermin for stage 2 neurotrophic keratopathy, which the patient wished to further consider prior to initiating.

Approximately 1 month after her initial evaluation, the patient presented to the emergency room with cloudy vision, photophobia, and aching in the right eye. Her visual acuity was counting fingers and IOP was 10 mmHg. Examination demonstrated 2+ conjunctival injection, and corneal evaluation revealed a 3.0 × 6.5 mm epi defect with a 2.4 × 4.6 mm underlying infiltrate. The inferior aspect of the infiltrate was associated with approximately 50% thinning and surrounding edema was present. Two additional <0.5 mm nasal infiltrates were also noted. A 1.6 mm hypopyon was also present (Fig. 1). Corneal cultures were taken, and the patient was started on fortified cefazolin and tobramycin hourly, cyclopentolate twice daily, erythromycin ointment four times daily, and valacyclovir 1 g three times daily. Corticosteroids were discontinued due to the large epithelial defect and possible underlying infection.

Over the ensuing 7 weeks, the epithelial defect and infiltrate failed to improve; fortified antibiotics were switched to moxifloxacin every 2 hours and erythromycin ointment was increased to hourly, and the patient remained on this regimen for over two weeks without clinical improvement. The corneal cultures returned negative, and two additional corneal re-cultures also returned negative. A presumed diagnosis was made of sterile inflammatory infiltrate and hypopyon secondary to herpes zoster keratitis. Given no response to the aforementioned treatment and the presence of stage 3 neurotrophic keratopathy, we started the patient on cenegermin 6 times daily for 8 weeks. She continued prophylactic moxifloxacin four times daily, erythromycin ointment nightly, cyclopentolate twice daily, and valacyclovir 1 g three times daily while using cenegermin. The patient was monitored twice weekly

after starting cenegermin. Importantly, corticosteroids were not initiated at this time due to the size of the epithelial defect.

By 2 weeks after starting cenegermin, the epithelial defect and infiltrate had improved, and the hypopyon had decreased in size to 1.0 mm. Within 4 weeks, the infiltrate measured 1.0 × 2.0 mm, less than half its original size, and the hypopyon was no longer visible (Fig. 2). By this point, the epithelial defect had nearly resolved, and prednisolone acetate 1% twice a daily was started, which was gradually increased to four times daily over the next 2 weeks. At the conclusion of 8 weeks of cenegermin therapy, the epithelium had healed and left behind a 1.0 × 1.0 mm scar. Patchy posterior synechiae were noted, but the exam was otherwise unremarkable (Fig. 3). Hard contact lens overrefraction revealed a BCVA of 20/70. Prednisolone acetate 1% was gradually tapered, and other topical medications discontinued. The patient was maintained on valacyclovir 1 g daily, as well as frequent preservative-free artificial tears. After 7 months of follow-up, the cornea had remained epithelialized without recurrent inflammation.

3. Discussion

In this case report, we illustrate resolution of a sterile hypopyon with rhNGF in a patient with a history of herpes zoster keratitis and resulting neurotrophic keratopathy. In this case, the large epithelial defect presented a clinical challenge; due to concerns that topical corticosteroids may delay epithelial healing, they were held until the epithelial defect was nearly resolved. The added corticosteroid at this later point further reduced inflammation and scar formation.

There are several possible mechanisms for resolution of this hypopyon with rhNGF. The inflammatory response of the corneal epithelium against offenders has been well-described. Epithelial injury results in the release of leukocyte chemotactic factors, which introduces inflammatory cells to the corneal stroma.^{5,6} Clinically, inflammatory cells in the anterior chamber may also be noted. Hence, closure of the epithelial defect may have been the primary etiology for resolution of this patient's hypopyon after initiating rhNGF.

Alternatively, nerve growth factor (NGF) directly may play a role in modifying inflammatory responses. NGF has shown to display regulatory effects in various inflammatory conditions, including multiple sclerosis and colitis.⁷ NGF also plays an immune-modulatory and cytoprotective role in the cornea, and topical administration has been previously shown to promote allograft survival after corneal transplantation with decreased expression of proinflammatory cytokines (IFN-gamma, TNF-alpha).⁸ The corneal epithelium responds to potential offenders via

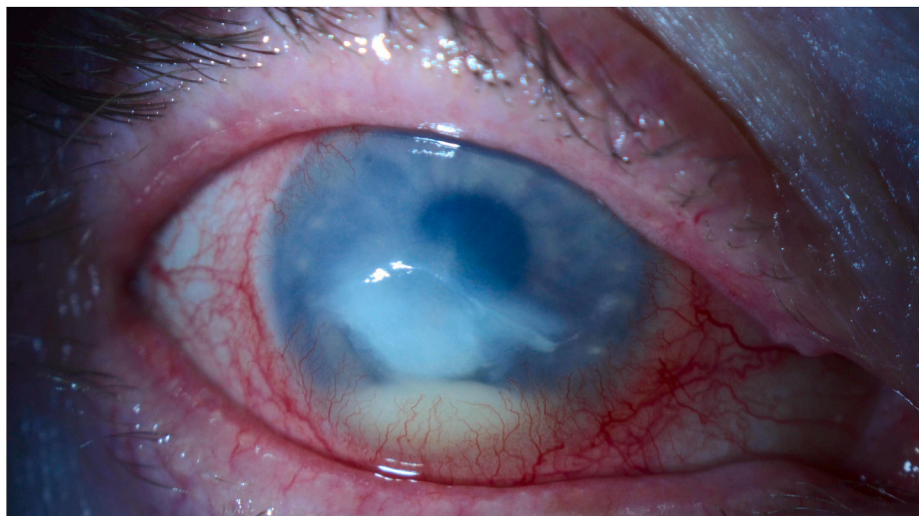


Fig. 1. Photograph of the right eye demonstrating large epithelial defect with underlying infiltrate and hypopyon. Two additional pinpoint infiltrates are present adjacent to the nasal limbus.

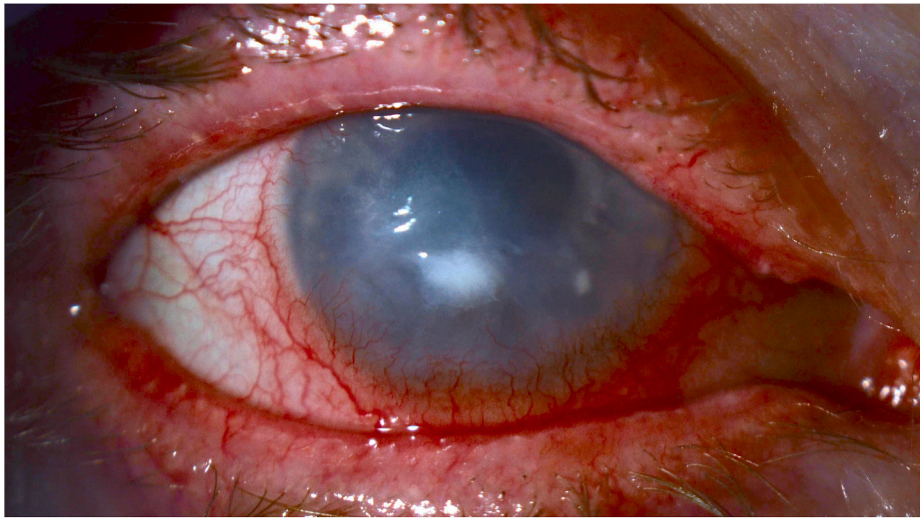


Fig. 2. After 4 weeks of treatment with cenergermin, the infiltrate was less than half of its original size and hypopyon was no longer clinically visible.

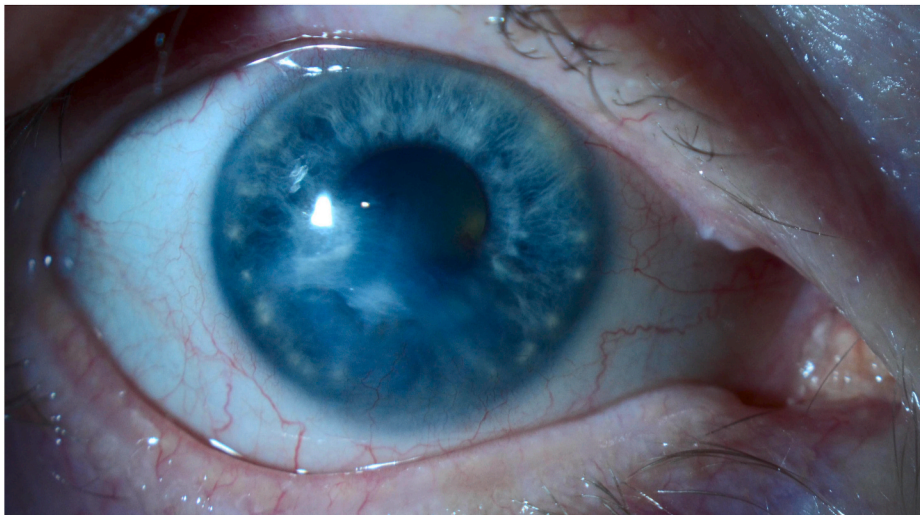


Fig. 3. After 8 weeks of treatment with cenergermin, a small scar was present. Best-corrected visual acuity with hard contact lens overrefraction was 20/70.

residential Toll-like receptors (TLRs), a family of molecules that play a critical role in recognizing microbial pathogens. Excessive TLR-related responses may lead to advanced inflammatory cell infiltration of the cornea and resulting vision-threatening fibrosis.⁹ TLR3 has been identified as the primary corneal mediator against viral infection, and triggers the activation of reactive oxygen species, NF- κ B, and interferons.^{10,11} NGF inhibits TLR3-induced NF- κ B activation, reactive oxygen species overexpression, and suppresses various downstream proinflammatory cytokines.¹¹ Given that clinical experience with cenergermin is still limited, this case highlights that the medication may be a promising therapeutic agent with utility in conditions having a significant inflammatory component.

Conventional therapy for neurotrophic keratopathy depends on stage of disease. Management of stage 1 typically involves aggressive lubrication with preservative-free artificial tears or autologous serum tears, and may also include punctal occlusion. In more advanced stages (stages 2 or 3), surgical intervention with tarsorrhaphy, amniotic membrane transplantation, and conjunctival flap may be indicated to restore the integrity of the ocular surface. In our patient, amniotic membrane transplantation (either sutured or self-retaining) was considered, however the presence of a sizeable hypopyon supported the need for more advanced therapy. Unfortunately, most conventional

medical and surgical treatments for neurotrophic keratopathy do not tackle the underlying pathology of corneal anesthesia, and therefore do not provide a permanent solution. On the other hand, cenergermin does address this fundamental issue.

Limitations of this case report include limited follow-up (7 months), lack of quantitative corneal esthesiometry measurements during clinical evaluations, and the confounding effect of a topical corticosteroid drop that was started four weeks after cenergermin. However, as described above, the hypopyon had clinically resolved prior to initiation of a corticosteroid.

4. Conclusions

In conclusion, we presented a case in which a neurotrophic keratopathy associated sterile hypopyon resolved after initiation of treatment with cenergermin, which is a novel finding. Cenergermin may have significant potential in advanced inflammatory neurotrophic disease. Further research is needed to better elucidate mechanisms of action and potential future clinical applications.

Patient consent

Written consent for publication was obtained from the patient whose data is presented in this case report.

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Authorship

All authors attest that they meet the current ICMJE criteria for Authorship.

Declaration of competing interest

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