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Neurotrophic keratopathy: Clinical presentation and effects of cenegermin

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ABSTRACT

Purpose: To report on 4 patients (3 adults, 1 child) with neurotrophic keratopathy (NK) treated with cenegermin 20 μg/ml (Oxervate®), a recombinant human nerve growth factor (rhNGF), which was authorized by the European Medicines Agency for the treatment of neurotrophic keratopathy stage 2 and stage 3 of Mackie Classification in patients over 18 years of age.

Observations: Three patients with neurotrophic keratopathy stage 2 and 1 patient with neurotrophic keratopathy stage 3, who were treated with cenegermin eye drops 6 times daily for 8 weeks, were observed. Two patients suffered from herpetic keratitis and 2 patients from neurotrophic keratopathy secondary to orbital radiation. In addition to closure of epithelial defects, an increase of corneal sensitivity and improvement of visual acuity has been shown in all treated patients at the end of therapy. One patient reported on neuralgic pain as a side effect. The corneal epithelium remained closed during the follow-up period of 11 weeks, 31 and 32 months after cessation of therapy in 3 patients, respectively. In one patient, corneal erosion recurred 4 weeks after completion of treatment due to recurrent HSV keratitis, which resolved after therapy adjustment and the corneal epithelium remained closed for 35 weeks.

Conclusion: The cases presented suggest that treatment with cenegermin 20 μg/ml not only promotes corneal epithelial wound healing, but also significantly improves corneal sensitivity and visual acuity with minor side effects in adults and children.

1. Introduction

The cornea is the most densely innervated tissue in the human body.[1] Damage to the trigeminal nerve plexus from the nucleus to the corneal nerve endings by various ocular and systemic diseases can cause neurotrophic keratopathy (NK).[2] The disease is characterized by corneal hypoesthesia or anesthesia and, thus, often by a discrepancy between the clinical picture and the patient's symptoms. Therefore, the diagnosis of NK is often the first obstacle and has to be made carefully based on the patient's clinical history, neurological examination and precise ocular examination, including slit-lamp microscopy, fluorescein staining, corneal sensitivity testing, tear film quantification.[3] So far, the current therapeutic management and monitoring of NK patients have a supportive character and are based on the severity of the disease (Mackie classification 1995)[4] aiming to promote corneal epithelial healing and to prevent disease progression.[3] The most common treatment methods include conservative treatment, such as application of preservative-free artificial tears, therapeutic contact lenses, cyclosporine eye drops, poly (carboxymethylglucosesulfate) eye drops, and autologous serum eye drops. Further therapeutic options for severe NK cases are minimally invasive procedures, e.g., tarsorraphy, induction of ptosis by botulinum toxin A, amniotic membrane transplantation (AMT) or surgical interventions, such as conjunctival flap cover surgery and corneal grafting.[5–9] Recent research on NK has been focused on novel medical treatment strategies promoting wound healing and restoring corneal sensitivity and visual acuity.[3]

Corneal epithelial homeostasis is synchronized by oxygen, catecholamines, cytokines, electrolytes, extracellular matrix molecules, neuropeptides, nutrients, vitamins and growth factors, including nerve growth factor (NGF), some of which can be modulated by environmental factors.[1,10–12] Among neurotrophic growth factors, NGF was historically the first one and was discovered by Rita Levi-Montalcini in the early 1950s.[13,14] NGF binds to two types of receptors, the low-affinity receptor, p75NTR, and the high-affinity receptor, TrkA. Its function includes stimulation of nerve fiber development and survival, trophic support for injured neurons as well as proliferation, migration and differentiation of epithelial cells. Therefore, NGF is indispensable for immune modulation, maintenance of corneal sensitivity, corneal trophism

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and, thus, ocular surface integrity.[2,5,15]

Cenegermin (Oxervate®) has been authorized by the European Medicines Agency, the U.S. Food and Drug Administration, and other health authorities for the topical treatment of NK. The eye drops contain 20 μg/ml of cenegermin, a recombinant human nerve growth factor (rhNGF) being produced in the bacterium Escherichia coli. The recommended application frequency is 6 drops per day for 8 weeks. Two randomized clinical trials, NGF0212 and NGF0214, have shown a higher percentage of patients with complete healing of the corneal epithelium after 8 weeks of topical treatment with cenegermin 20 μg/ml compared to vehicle in patients ≥18 years. In contrast, only tendency to improvement of best corrected visual acuity (BCVA) and corneal sensitivity was observed in patients treated with cenegermin 20 μg/ml compared to vehicle.[16,17] However, in both trials, sample size calculations were made for the primary endpoint, which was the corneal healing rate after 8 weeks of treatment, and not to detect differences in secondary endpoints, such as BCVA and corneal sensitivity. Hence, more clinical data regarding the effect of cenegermin 20 μg/ml on BCVA and corneal sensitivity are needed.

The purpose of this case series was to determine the effects of cenegermin on corneal epithelial wound healing, corneal sensitivity, and visual acuity and to determine any adverse effects in 3 adults and 1 child.

1.1. Case reports

We describe 3 patients with NK stage 2 and 1 patient with NK stage 3 of Mackie's Classification, who were treated with cenegermin (Oxervate®) eye drops 6 times daily for 8 weeks. We documented the slit lamp microscopy findings and BCVA. Because corneal hypoesthesia or anesthesia is the indispensable criterion for the diagnosis of NK,[5] we performed semiquantitative measurement of the corneal sensitivity with a Cochet-Bonnet aesthesiometer (CBA) before, during, and after treatment. First, the central area was measured, then the peripheral segments. The CBA is based on the principle of axially transmitted pressure to the corneal surface by a nylon monofilament of defined diameter, but variable length. Depending on the length of the nylon monofilament, which is controlled by the forefinger, the patient's subjective reaction is observed. With decreasing length of the monofilament, the pressure transmitted to the corneal surface increases from 11 mm/grms up to 200 mm/grms. A scale on the CBA instrument indicates the length of the nylon monofilament. The value of 0.5, corresponding to a filament length of 5 mm, indicates the highest grade of hypoesthesia whereas the value of 6.0, corresponding to a filament length of 60 mm, represents the highest grade of corneal sensitivity.[5,18] Some patients were treated with autologous serum eye drops, which are prepared at the Transfusion Center of the University Medical Center Mainz. For this purpose, the patient's own blood is donated. After complete coagulation, it is centrifuged and the autologous serum eye drops are obtained from the supernatant. This is an undiluted product without the addition of antibiotics. After preparation, they are frozen and stored at l-20 °C in individual vials for daily use. The shelf life is 16 weeks. After thawing or opening, the ophthalmic vials may only be used for 24 hours to prevent contamination. The whole blood donation samples are tested for seroprevalence of hepatitis B and C, HIV 1/2 and syphilis, and a sterile control is performed as for any homologous donation. If patients had a history of AMT, it was fixed to the adjacent episclera with four interrupted sutures and to the conjunctiva with a continuous 10.0 vicryl suture in all cases. A bandage contact lens (20 mm diameter) was placed on the eye for the following 4 weeks.

1.1.1. Patient 1

A 62-year-old woman had been diagnosed with NK stage 1 on the right eye in 2013. NK was a result of multiple orbital radiations in 2010 due to orbital metastasis of breast cancer, which had been diagnosed in 2000. Despite intensive local therapy including preservative-free artificial tears, cyclosporine 1 mg/ml (Ikervis®) eye drops, poly(carboxymethylglucosesulfate) (Cacicol®) eye drops, autologous serum eye drops, as well as one AMT, the corneal surface deteriorated and developed a therapy resistant corneal erosion compatible with NK stage 2 in 2018. Hence, treatment with cenegermin 20 μg/ml eye drops 6 times per day for 8 weeks was initiated and accompanied by treatment with preservative-free artificial tears. After cessation of therapy, the corneal epithelial defect healed, corneal sensitivity improved and BCVA increased from 20/80 to 20/60. The clinical presentation was stable in all follow-up visits including the last one, 11 weeks after treatment cessation (Fig. 1). Later, this patient passed away during follow-up period.

1.1.2. Patient 2

A 60-year-old woman with a history of recurrent herpes simplex virus (HSV) keratitis since 2016 in the left eye, was first diagnosed with NK stage 3 in August 2018 due to a large, recurrent central corneal ulcer. It persisted despite treatment with AMT only 7 weeks before. Until then, she was treated with preservative-free artificial tears, lubricant ointments, ganciclovir ophthalmic gel (Virgan®) 3 times per day, corticosteroid eye drops 2 times per day and aciclovir tablets 400 mg 5 times per day. Furthermore, poly(carboxymethylglucosesulfate) (Cacicol®) and cyclosporin 1 mg/ml (Ikervis®) eye drops have been applied in the past. With regard to the corneal state, a local therapy with cenegermin 20 μg/ml eye drops was initiated 6 times per day for 8 weeks with an additional continuing therapy with preservative-free artificial tears, ofloxacin eye drops 4 times, ganciclovir ophthalmic gel 3 times and aciclovir tablets 400 mg 5 times per day. Corticosteroid eye drops were paused. During treatment, the patient reported on neuralgic pain and was treated with pregabalin 100 mg 2 times daily. At cessation of cenegermin 20 μg/ml therapy, the corneal epithelial defect was closed, corneal sensitivity improved and BCVA increased from 20/80 to 20/40. The following therapy was ganciclovir ophthalmic gel 2 times and aciclovir tablets 400 mg 2 times per day as well as artificial tears.

However, thirteen weeks post-treatment, epithelial edema without an accompanying epithelial defect occurred around the epithelial closure line, which could be stained with fluorescein, and was most likely due to the onset of reactivation of HSV keratitis. In the past, epithelial edema had often been the first clinical sign of incipient reactivation. Therefore, therapy was intensified and responded well to ganciclovir ophthalmic gel (Virgan®) 5 times, corticosteroid eye drops 2 times and aciclovir tablets 400 mg 5 times per day. After 2 weeks, the epithelial edema had resolved, and the corneal epithelium remained closed for 32 months under the current therapy with artificial tears and gel. After fitting scleral contact lenses and with stable clinical findings, BCVA increased to 20/25 (Fig. 2).

1.1.3. Patient 3

An 81-year-old man with a history of 3 penetrating keratoplasties (PK) and 6 AMTs in the past 21 months due to corneal perforations caused by HSV keratitis since 2016 was presented to us with a new corneal erosion in the graft on the right eye. It occurred 7 weeks after the last combined PK and AMT and was followed by the diagnosis of NK stage 2 in September 2018. Therapy with cenegermin 20 μg/ml eye drops 6 times per day for 8 weeks was initiated in addition to the continuing therapy with corticosteroid eye drops 4 times per day, ofloxacin eye drops 4 times and ganciclovir ophthalmic gel 2 times per day as well as systemic therapy with valaciclovir 1 g 2 times and mycophenolate mofetil 1 g 2 times per day. Autologous serum eye drops were paused during treatment. At cessation of therapy, the corneal epithelial defect has healed, corneal sensitivity improved and BCVA increased from 20/200 to 20/80. However, 4 weeks after treatment completion, a corneal erosion recurred due to recurrent HSV keratitiss. A therapy with autologous serum eye drops, therapeutic contact lenses, corticosteroid eye drops 4 times, moxifloxacin eye drops 3 times, ganciclovir ophthalmic gel 3 times and valaciclovir 1g as well as

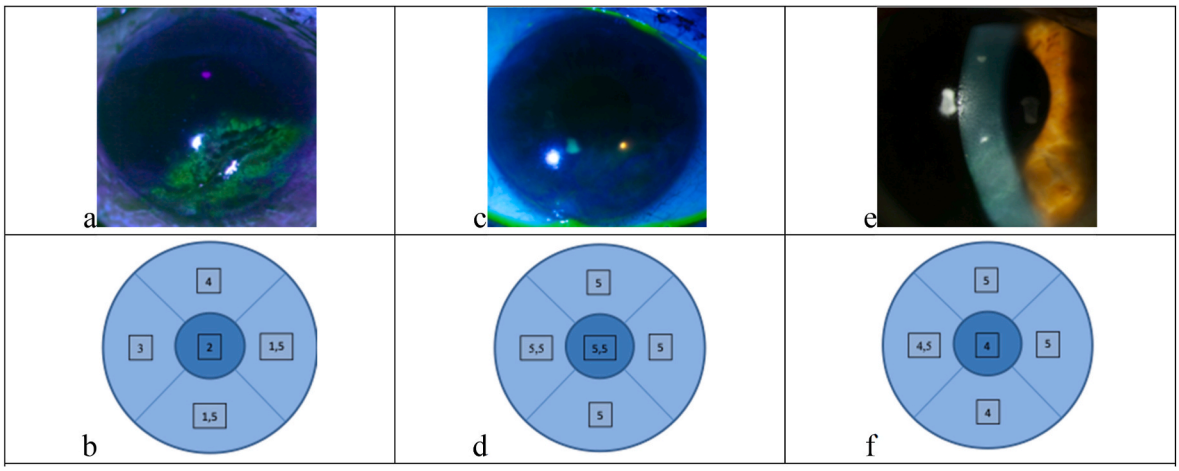

Fig. 1. (a) Neurotrophic keratopathy stage 2 of the right eye with an epithelial defect without stromal melting of the cornea at the start of therapy.(b) The related corneal sensitivity was reduced in all segments, especially in the area of the corneal defect.(c) After 8 weeks of cenegermin 20 µg/ml treatment, the corneal epithelium healed completely.(d) Corneal sensitivity increased in all segments.(e) Eleven weeks after completion of therapy, the condition of the corneal epithelium and(f) corneal sensitivity remained stable.

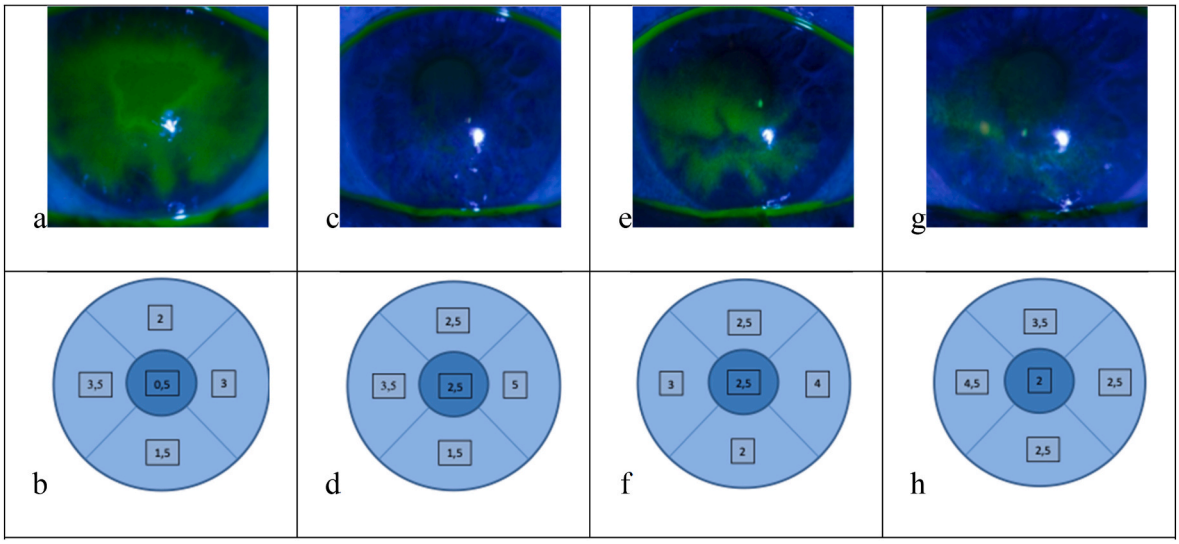

Fig. 2. a) Neurotrophic keratopathy stage 3 of the left eye with an epithelial defect with stromal melting and confluent fluorescein staining of the cornea at the start of therapy.(b) Corneal sensitivity was reduced in all areas, especially centrally.(c) After 8 weeks of cenegermin 20 µg/ml treatment, the corneal epithelium healed completely.(d) By then, corneal sensitivity had increased in all areas, especially centrally.(e) Thirteen weeks after completion of therapy, epithelial edema occurred without an accompanying epithelial defect, most likely due to a reactivation of herpes simplex virus keratitis.(f) However, corneal sensitivity remained nearly stable at that time.(g) Fifteen weeks after completion of therapy and adjustment of the virostatic and anti-inflammatory therapy, the epithelial edema has resolved and clinical state has stayed stable for the whole follow up period of 32 months post treatment. Some fluorescein staining remained in that area.(h) Improvement in corneal sensitivity after treatment with cenegermin 20 µg/ml endured since.

mycophenolate mofetil 1 g 2 times per day was initiated and corneal epithelium closure was achieved 14 weeks post-treatment and remained closed for 35 weeks (Fig. 3).

1.1.4. Patient 4

A 9-year-old girl with a congenital rhabdomyosarcoma of the right orbit, first diagnosed in 2015, was treated with chemotherapy and radiation of the right orbit. Consecutively, the corneal sssurface displayed a paracentral scar and keratokonjunctivitis. In 2018, a cataract surgery combined with anterior vitrectomy was performed due to a secondary cataract after radiation. Five months later, an epithelial defect, progressive corneal vascularization and reduced corneal sensitivity occurred compatible to NK stage 2. Corneal sensitivity was very difficult to examine with a Cochet-Bonnet aesthesiometer due to reduced compliance and was therefore tested with a cotton-tipped applicator. She was treated with preservative-free artificial tears, lubricant ointments, ofloxacin eye drops 4 times, occasionally with topical corticosteroid eye drops and ganciclovir ophthalmic gel. Due to lack of improvement and a negative HSV finding tested by a corneal smear by PCR, the antiviral therapy was stopped and an off-label therapy with cenegermin 20 µg/ml eye drops 6 times per day for 8 weeks was initiated, additionally to topical treatment with preservative-free artificial tears and lubricant ointments. Unlike the FDA, the EMA continues to allow the usage of cenegermin in Europe, including Germany, only for adults over 18 years of age. After an 8-week course of cenegermin 20 µg/ml treatment, the corneal epithelium was intact, corneal vascularization showed marginal regression, corneal sensitivity seemed to have increased slightly and BCVA improved from 20/50 to 20/40. At 31 months after treatment with cenegermin 20 µg/ml, corneal condition, corneal sensitivity and BCVA were stable (Fig. 4).

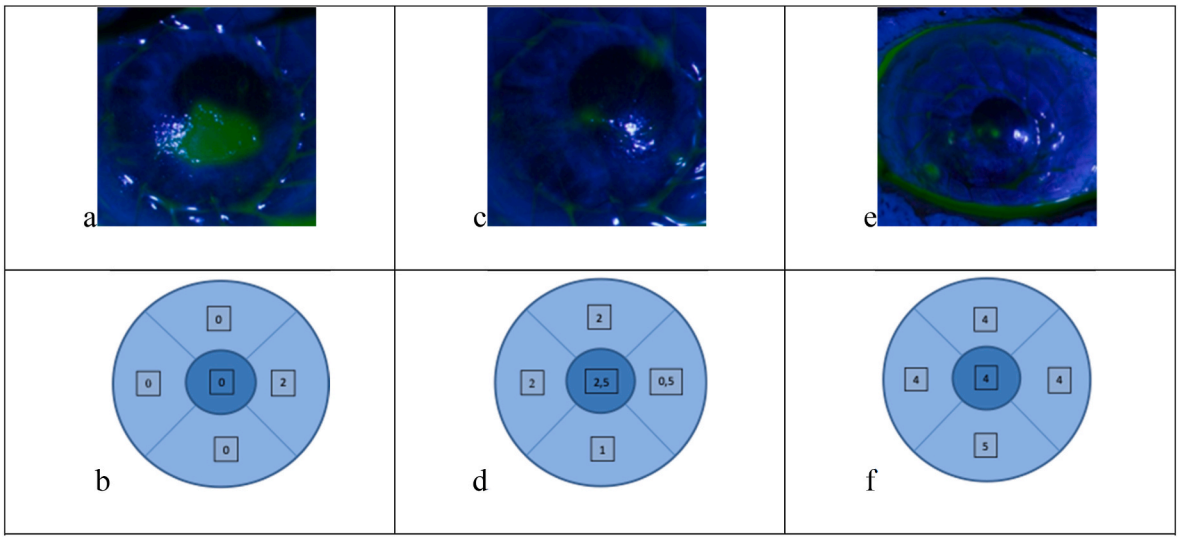

Fig. 3. (a) Neurotrophic keratopathy stage 2 of the right eye with an epithelial defect on the graft without stromal melting at the beginning of therapy.(b) The associated corneal sensitivity abolished in 4 segments and was greatly reduced in the nasal segment.(c) After 8 weeks of cenegermin treatment, the corneal epithelium completely healed.(d) Corneal sensitivity increased in all segments, even in previous anesthetic areas. Four weeks after completion of treatment, a corneal erosion reoccurred. After adjustment of virustatic, anti-inflammatory and immunosuppressive therapy, the corneal epithelium responded well to treatment.(e) 14 weeks after cenegermin treatment, the corneal epithelium had completely healed again with remaining fluorescein staining and stayed stable for 35 weeks post-treatment.(f) Improvement of corneal sensitivity after cenegermin treatment endured since.

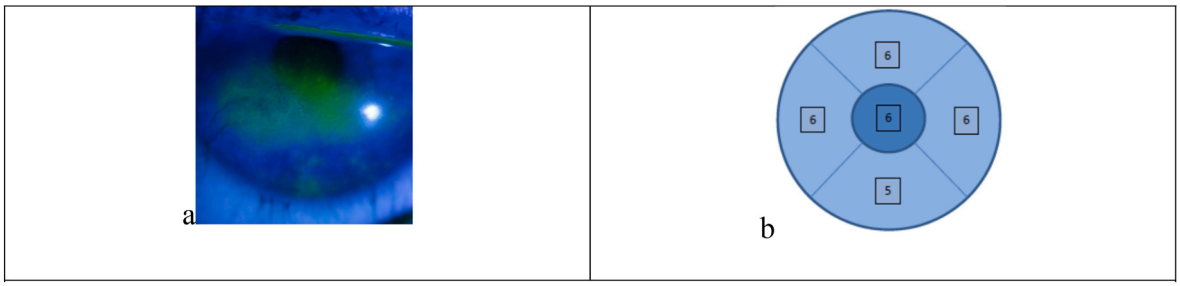

Fig. 4. Neurotrophic keratopathy stage 2 of the right eye of a 9-year old patient. The cornea displayed an epithelial defect, inferotemporal corneal vascularization and paracentral diffuse haze at the beginning of therapy (no photo documentation before treatment available due to reduced compliance).(a) After 8 weeks of cenegermin 20 μg/ml treatment, the corneal epithelium was completely closed while fluorescein staining persisted, vascularization had slightly receded and corneal sensitivity appeared to have increased.(b) After 29 weeks of cenegermin 20 μg/ml treatment, the corneal surface was stable. Corneal sensitivity improved. BCVA increased to 20/40. Corneal epithelium remained closed for 31 months post-treatment.

2. Conclusions

Neurotrophic keratopathy has dramatic consequences for the integrity of the corneal surface and hence for the integrity of the entire eye. We report on our first experience with cenegermin 20 μg/ml, a new authorized treatment for neurotrophic keratopathy. Two randomized clinical trials, NGF0212 and NGF0214, have reported a higher percentage of patients with complete healing of the corneal epithelium after 8 weeks of topical treatment with cenegermin 20 μg/ml compared to vehicle. Improvement of corneal sensitivity and BCVA, however, did not reach statistical significance in these studies compared to vehicle.[16,17]

Long-term results after cenegermin treatment are still missing. In the present report, corneal epithelialization persisted for the follow-up of 11 weeks, 31 and 32 months after cessation of therapy in 3 of 4 patients, respectively. In 1 patient, a corneal erosion recurred 4 weeks after cessation of cenegermin 20 μg/ml treatment, which was most likely due to a reactivation of HSV keratitis and the history of in total three penetrating keratoplasties.[19] The last keratoplasty was performed only 7 weeks before initiating the rhNGF treatment, leading to an overlap of the intensive local corticosteroid postoperative care and cenegermin 20 μg/ml treatment.

An increase in corneal sensitivity was observed in all cases immediately after cessation of therapy including the previously anesthetic corneal segments, which remained stable during the whole follow-up period, even in a case where corneal erosion had recurred. The results support the postulated increasing effect of cenegermin 20 μg/ml on corneal sensitivity.

Two patients with HSV keratitis, a leading cause of NK,[20,21] needed adjunctive local and systemic virostatic therapy. Even so, they suffered from recurrence of HSV keratitis after cessation of rhNGF treatment. The 2nd patient showed an epithelial edema without an accompanying epithelial defect 13 weeks post-treatment and the 3rd patient showed a corneal erosion 4 weeks after treatment completion.

NK can be even more challenging in the pediatric population, especially in making an accurate diagnosis and decision of an adequate therapeutic strategy.[22] Corneal hypoesthesia or anesthesia is an obligatory clinical criterion for the diagnosis of NK. However, the measurement with a Cochet-Bonnet aesthesiometer is often difficult to perform in young children.[23] Although conservative treatment options are similar in adult and pediatric patients, the use of cenegermin 20 μg/ml in patients under 18 years of age is not approved by the EMA and requires further evaluation as only limited data is available for this patient

group and no major study has yet demonstrated the drug's efficacy in children. Surgical treatment should be performed with caution due to reduced compliance in the postoperative phase, risk of rejection in case of penetrating keratoplasty and high risk of amblyopia. We observed epithelial closure in a 9-year-old girl suffering from NK induced by orbital radiation after cenegermin 20 μg/ml treatment with a follow-up period of 31 months. Of note, corneal sensitivity and BCVA improved as well.

NK is considered as an orphan disease based on the estimated prevalence of 1–5/10.000 [3]. It is important to note the comparatively high cost of treating a rare disease with a recombinant human nerve growth factor. The total cost of 8 weeks of treatment with cenegermin 20 μg/ml in Germany is approximately 20.000€. This is about 25 times the cost of autologous serum eye drops for 16 weeks, 6 times the cost of an AMT, and 3 times the cost of PK in Germany. Although several studies[5,24,25] including our clinical findings have shown therapeutic efficacy, Oxervate® was surprisingly withdrawn from the German market in 2020 by the Federal joint Committee (G-BA) due to lack of sustainability, creating a new hurdle for the use of cenegermin. To date, there is no equivalent therapy to cenegermin, and the EMA continues to approve its' use for NK stage 2 and stage 3 of Mackie classification for adults over 18 years of age.

Therapeutic management of NK still remains challenging. The presented cases support the notion that apart from promoting corneal epithelial wound healing, cenegermin 20 μg/ml shows significant improvement in corneal sensitivity and in visual acuity with minor side effects. Moreover, our findings suggest that cenegermin 20 μg/ml is also effective in pediatric patients.

Patient consent

Consent to publish the case report was not obtained. This report does not contain any personal information that could lead to the identification of the patient.

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Intellectual property

We confirm that we have given due consideration to the protection of intellectual property associated with this work and that there are no impediments to publication, including the timing of publication, with respect to intellectual property. In so doing we confirm that we have followed the regulations of our institutions concerning intellectual property.

Research ethics

We further confirm that any aspect of the work covered in this manuscript that has involved human patients has been conducted with the ethical approval of all relevant bodies and that such approvals are acknowledged within the manuscript.

IRB approval was obtained (required for studies and series of 3 or more cases).

Written consent to publish potentially identifying information, such as details or the case and photographs, was obtained from the patient(s) or their legal guardian(s).

Authorship

The International Committee of Medical Journal Editors (ICMJE) recommends that authorship be based on the following four criteria:

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2. Drafting the work or revising it critically for important intellectual content; AND
3. Final approval of the version to be published; AND
4. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

All those designated as authors should meet all four criteria for authorship, and all who meet the four criteria should be identified as authors. For more information on authorship, please see http://www.icmje.org/recommendations/browse/roles-and-responsibilities/defining-the-role-of-authors-and-contributors.html#two.

All listed authors meet the ICMJE criteria.

We attest that all authors contributed significantly to the creation of this manuscript, each having fulfilled criteria as established by the ICMJE.

One or more listed authors do(es) not meet the ICMJE criteria.

We believe these individuals should be listed as authors because:

We confirm that the manuscript has been read and approved by all named authors.

We confirm that the order of authors listed in the manuscript has been approved by all named authors.

Declaration of competing interest

The following authors have no financial disclosures: JB, AG, NP, JP.

All authors attest that they met the current ICMJE criteria.

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