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ORIGINAL RESEARCH

Management of Stage 1 Neurotrophic Keratopathy with Shelf-Stable, Cryopreserved Amniotic Membrane: A Retrospective Study

Alain M Bauza[1,2]

[1]Department of Ophthalmology, Santamaria Eye Center, Perth Amboy, NJ, USA; [2]Department of Ophthalmology, Freehold Ophthalmology, Freehold, NJ, USA

Correspondence: Alain M Bauza, Santamaria Eye Center, 104 Market Street, Perth Amboy, NJ, 08861, USA, Tel +1-732-826-5159, Email alainbauza@gmail.com

Purpose: To assess whether shelf-stable, cryopreserved amniotic membrane (CAM) can improve clinical signs and symptoms in patients with early-stage neurotrophic keratopathy (NK).

Methods: A multiple-center, retrospective study of patients with early-stage NK who failed prior conservative therapies and were subsequently treated with shelf-stable CAM and a 24-hour collagen shield. NK was defined as the presence of superficial punctate keratopathy in conjunction with reduced corneal sensitivity (Mackie stage 1) in the central corneal zone measured with a cotton-wisp. Tear break up time (TBUT), corneal staining, symptoms, best corrected visual acuity (BCVA), and corneal sensitivity were assessed at baseline, 1-week, 1-month, and 3-months.

Results: A total of 18 eyes of 13 patients met the eligibility criteria and were included for analysis. At baseline, the mean corneal staining score, TBUT, and BCVA logMAR were 1.69 ± 0.79, 3.1 ± 1.8 seconds, and 0.32 ± 0.19, respectively. At 10.5 ± 4.9 days, corneal staining, TBUT, and BCVA significantly improved. A total of 61.5% of eyes had no epitheliopathy and corneal sensitivity was normal in 9.1% of eyes. At 31.2 ± 10.8 days, corneal sensitivity was normal in 73.3% of eyes, and corneal staining scores, TBUT, and BCVA significantly improved. A total of 11 eyes (73.3%) had no epitheliopathy. At 14.7 ± 3.7 weeks, corneal sensitivity was normal in 61.5% of eyes. Corneal staining significantly improved to 0.43 ± 0.43 ($p < 0.001$), TBUT significantly improved to 6.5 ± 2.4 s ($p = 0.005$), and BCVA logMAR was 0.21 ± 0.24 ($p = 0.13$).

Conclusion: This exploratory retrospective study suggests that treatment with shelf-stable CAM may improve corneal epithelial integrity, visual acuity, and corneal sensitivity in patients with early-stage NK.

Keywords: amniotic membrane, cornea, corneal sensitivity, neurotrophic keratitis, ocular surface disease

Introduction

The cornea is the most densely innervated tissue in the human body, more than 300 to 600 times that of the skin.[1] Corneal nerves play a crucial role in maintaining homeostasis of the ocular surface by triggering blinking and tearing reflexes as well as providing trophic support to the avascular cornea by releasing nutrients and trophic factors.[2] As a result, damage to the corneal nerves reduces sensory input, diminishes these protective reflexes, and impairs corneal epithelial wound healing.[3,4] This pathological state can lead to neurotrophic keratopathy (NK), which is a degenerative disease of the cornea that is characterized by breakdown of the corneal epithelium and reduced corneal sensitivity due to impaired corneal innervation. NK is commonly classified by the extent of corneal damage using the Mackie grading scale:[5] ocular surface abnormalities and superficial punctate keratopathy (stage 1), persistent epithelial defect (stage 2), and corneal ulceration with stromal involvement (stage 3). Common causes and risk factors of NK include herpetic infection, diabetes, ocular surgery, severe dry eye disease, chronic use of preserved topical medications, and neurosurgical procedures.[6–8] While NK has been largely considered a rare orphan disease, emerging evidence suggests that early-stage NK is more prevalent than historically reported.[6,9–12] Reduced corneal sensitivity, which is a hallmark of NK, has

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been observed in 19.7% of eyes with superficial punctate keratopathy.[12] Furthermore, an estimated 58% of dry eye patients who present for cataract consultation have co-existing NK.[10] Prompt treatment is imperative in these patients in order to halt disease progression and ultimately preserve vision.

NK management is dependent upon disease severity. For patients with early-stage NK, the therapeutic goal is to improve the quality and transparency of the corneal epithelium and restore corneal nerves. First line therapies generally include preservative free artificial tears, gels or ointments, punctal occlusion, and bandage contact lens.[13] While these treatments help replenish the tear film and protect the corneal epithelium from further desiccation, these treatments do not directly treat the damaged underlying nerves. For patients who fail to respond to conservative treatment, recombinant human nerve growth factor (rhNGF) or cryopreserved amniotic membrane (CAM) are often recommended. CAM is particularly beneficial for NK due to its anti-inflammatory and anti-scarring properties, which help to modulate wound healing and restore damaged tissue to its original state.[14] In a review article of 15 studies by Mead et al, transplantation of CAM resulted in complete epithelialization in nearly 90% of eyes with corneal epithelial defects and ulcers secondary to NK.[15] While historically used for more severe forms of NK, CAM has been increasingly used in the management of early-stage NK due to its ability to promote corneal nerve regeneration and improve corneal epithelial integrity compared to maximum conventional therapy alone.[16] This is further supported by a recent retrospective study, in which treatment with self-retained CAM significantly improved corneal staining scores and visual acuity in patients with stage 1 NK.[17] Ultimately, cryopreserved AM (which has been shown to contain neurotrophic factor) plays a valuable role in stage 1 NK due to its ability to restore the corneal epithelium, reduce inflammation, and increase corneal nerve density.[16,18]

A fully hydrated, shelf-stable CAM has been recently developed to optimize treatment in patients with relatively more mild forms of ocular surface disease. This CAM configuration is novel in being a hydrated and sterile AM that is shelf-stable and can be stored at room temperature. In contrast to Prokera®, which retains CAM on the ocular surface with a polycarbonate ring and is regulated as a class II medical device, CAM360 is a CAM sheet that can be placed over the cornea and retained with a carrier such as a bandage contact lens or collagen shield. While CAM360 has been shown to retain the key structural and biological properties of AM,[19] no studies have assessed whether it can improve corneal sensitivity and epithelial integrity in patients with NK. Thus, the purpose of this study was to assess the short- and long-term clinical outcomes following treatment with shelf-stable CAM in patients with early-stage NK.

Materials and Methods

Following Institutional Review Board (IRB) exemption and waiver of authorization by Sterling IRB (IRB ID: 4722-ABauza), a multi-center, retrospective chart review was conducted on patients with a diagnosis of NK who were treated with shelf-stable, cryopreserved AM in conjunction with a 24-hour collagen shield by the author at Freehold Ophthalmology (Freehold, NJ) and Santamaria Eye Center (Perth Amboy, NJ). The IRB granted exemption status with a waiver of authorization for this retrospective study, as it involved analysis of existing medical records, could not be practically conducted without the waiver, was recorded in a de-identified manner, and posed minimal risk to subjects. NK was defined as the presence of superficial punctate keratopathy in conjunction with reduced corneal sensitivity in the central corneal zone, which is consistent with the Mackie grading scale.[5] All study procedures were performed in accordance with the tenets of the Declaration of Helsinki, and proper measures were undertaken to maintain and safeguard the confidentiality of study subjects. Patients were included for analysis if they met the following inclusion criteria: at least 18 years of age, had a documented diagnosis of NK, failed prior conservative therapies (eg. artificial tears, punctal plugs, lifitegrast, cyclosporine, etc.), and were treated with shelf-stable, cryopreserved AM (CAM360 AmnioGraft; BioTissue Holdings Inc., Miami, FL) in conjunction with a 24-hour dissolvable collagen shield (Oasis Medical, Glendale, CA). Patients were excluded if they were lost to follow-up or missing data related to the outcome measures at baseline. Data collection was limited to information existing in the electronic medical records between January 2024 and September 2025 and included the following measures: patient demographics (age, gender, race, ethnicity), comorbidities, relevant ocular history including surgical procedures, prior treatments, concomitant procedures and treatments, duration of treatment, length of follow-up, corneal staining score, tear break up time, symptoms, tear film regularity, visual acuity, corneal sensitivity, and complications.

Treatment Intervention

Shelf-stable CAM (CAM360 Amniograft, BioTissue Holdings Inc., Miami, FL) was removed from its packaging using forceps and placed onto the concave surface of a hydrated 24-hour dissolvable collagen shield (Oasis Medical, Glendale, CA) with the gridded backing paper face down. Using forceps and a sterile, polyester-tipped applicator swab, the backing paper was removed, and a moist swab was used to smooth out the CAM in the collagen shield. One drop of topical anesthetic and prophylactic antibiotic (Ofloxacin) was applied to the ocular surface prior to insertion. Using a gloved index finger, the prepared collagen shield and CAM were placed onto the ocular surface using the same technique for inserting a contact lens. Following insertion, the ocular surface was assessed to ensure proper centration and fit of the collagen shield with CAM over the cornea. A tarsus eyelid patch (Nictavi, Los Angeles, CA) was applied to the closed upper eyelid, and patients were instructed to administer preservative free artificial tears at least three times daily during treatment. The tarsus eyelid patch was removed from the eye after two days, and the status of the collagen shield and CAM was noted (dissolved or present). Patients resumed prior ocular medications as necessary during the post-treatment follow-up period.

Clinical Assessments

Assessments were conducted by the author at baseline as well as 1 week, 1 month, and 3 months post-CAM treatment and included corneal staining score, tear break up time (TBUT), symptoms, tear film regularity, visual acuity, and corneal sensitivity. Corneal staining was assessed using sodium fluorescein dye under a cobalt blue light and graded on a scale of 0 to 3 as follows: no superficial punctate keratopathy (SPK) present (0), trace punctate staining (0.5), minimal punctate staining (1), moderate punctate staining (2), and severe punctate staining (3). Following corneal staining, TBUT was assessed under the cobalt blue light using a stopwatch and defined as the time interval between the last blink and the first appearance of dry spots, which was recorded in seconds. Tear film height was assessed under a slit lamp by inspecting the tear meniscus and measuring its height along the lower eyelid. Less than 0.3 mm was recorded as reduced, 0.3–0.5 mm was defined as normal, and greater than 0.5 mm was increased. Patients were also assessed for presence of symptoms at each visit including dryness, ocular discomfort, foreign body sensation, pain, burning/stinging, photophobia, visual disturbances, and itching. Corneal sensitivity was assessed using the cotton wisp test. Patients were instructed to maintain a fixed gaze forward, and the cotton wisp was advanced toward the ocular surface until it made direct contact with the central cornea. The patient's reaction, including blinking and withdrawal, was assessed and recorded as normal, reduced, or increased. Best corrected visual acuity (BCVA) was assessed using a Snellen chart and was transformed into logMAR units for statistical analysis. Patients were also assessed for complications or adverse events following insertion as well as at all subsequent follow-up visits.

Statistical Analysis

All statistical analyses were conducted using IBM SPSS Statistics version 30.0 (IBM; Armonk, NY, USA). All continuous variables are described using mean ± standard deviation (median, maximum/minimum) and categorical data are reported as frequencies and percentages. A paired *t*-test for repeated measures was used to assess continuous outcomes across timepoints, and a Wilcoxon Signed Rank Test was used to assess changes in non-parametric data at follow-up visits compared to baseline. McNemar's chi-squared for within-subjects designs was used to assess binary dependent variables, such as proportions of eyes with reduced corneal sensitivity before and after treatment. A p value less than .05 was considered statistically significant.

Results

A total of 18 eyes (10 OS and 8 OD) of 13 patients met the eligibility criteria and were included for analysis. Patients were predominantly female (84.6%, n = 11), White Caucasian (100%, n = 18), and non-Hispanic (69.2%, n = 9), and the mean age at the time of treatment was 69.4 ± 14.6 years. Comorbidities included cataract (n = 6), blepharitis (n = 6), autoimmune disease (n = 4), meibomian gland dysfunction (n = 4), anterior corneal dystrophy (n = 3), diabetes (n = 3) Sjogren's syndrome (n = 2), dry age-related macular degeneration (n = 2), glaucoma (n = 1), multiple sclerosis (n = 1),

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Bell's palsy (n = 1), band keratopathy (n = 1), retinal vein occlusion (n = 1), proliferative diabetic retinopathy (n = 1), and pterygium (n = 1). Surgical history included cataract surgery in 11 eyes (61.1%) as well as panretinal photocoagulation (n = 1) and blepharoplasty (n = 1). No patients were current or previous contact lens wearers. All patients had failed prior therapies including preservative free artificial tears (100.0%), punctal plugs (66.6%), cyclosporine (55.5%), lifitegrast (50.0%), steroid drops (5.6%), and perfluorohexyloctane (11.1%).

At baseline, all eyes had reduced corneal sensitivity (n = 18, 100.0%), and the tear film was diminished in 15 eyes (83.3%). Mean corneal staining score was 1.69 ± 0.79 (median: 2), and mean TBUT was 3.1 ± 1.8 seconds (median: 3). All patients reported symptoms prior to treatment including dryness (66.6%), discomfort (88.8%), burning/stinging (44.4%), itching (33.3%), foreign body sensation (66.6%), photophobia (22.2%), pain (33.3%), and visual disturbances (100%). BCVA logMAR was 0.32 ± 0.19 (median: 0.30, range: 0–0.70).

All patients were treated with CAM for two days without any concomitant medications, aside from one patient who received treatment for only one day and continued use of perfluorohexyloctane (MIEBO) and lifitegrast ophthalmic solution (Xiidra). Following removal of the tarsus eyelid patch, the collagen shield and CAM were noted to be dissolved in all cases. One patient reported the collagen shield falling out prematurely.

At a mean of 10.5 ± 4.9 days (median: 11.5) post-CAM treatment, corneal sensitivity returned to normal in 1 eye (9.1%) and remained reduced in all 10 (90.9%) remaining eyes (p = 1.0). Slit lamp examination revealed a normal tear film in 3 eyes (23.1%), an increased tear film in 1 eye (7.7%), and reduced tear film in 9 eyes (69.2%, p = 0.25). TBUT, BCVA logMAR, and corneal staining significantly improved from baseline (Figures 1–3). TBUT improved to 6.9 ± 3.0 seconds (p = 0.007), BCVA improved to logMAR 0.25 ± 0.23 (median: 0.18, range: 0–0.70) (p = 0.008), and corneal staining improved to 0.46 ± 0.85 (p = 0.002). A total of 61.5% of eyes (8/13) had no epitheliopathy as demonstrated by complete resolution of corneal staining. BCVA improved in 64.3% (9/14) of eyes and remained unchanged in 35.7% (5/14) of eyes. Improvement or complete resolution of all pre-existing symptoms was noted in 92.8% (13/14) of eyes. One patient with lupus and common variable immune deficiency received a second CAM at this visit due to unresolved corneal staining (ie. grade 3 severe punctate staining).

At 31.2 ± 10.8 days (median: 29) post-CAM placement, corneal sensitivity was normal in 73.3% (11/15) of eyes and reduced in 26.7% (4/15) of eyes (p < 0.001). Tear film was normal in 36.4% (4/11) of eyes, increased in 9.1% (1/11) of eyes, and reduced in 54.5% (6/11) of eyes (p = 0.50). TBUT significantly improved to 7.43 ± 1.7 s (p = 0.003), corneal staining significantly improved to 0.13 ± 0.23 (p < 0.001), and BCVA logMAR significantly improved to 0.17 ± 0.19 (median: 0.10, p = 0.003). A total of 11 eyes (73.3%) had no epitheliopathy as demonstrated by complete resolution of

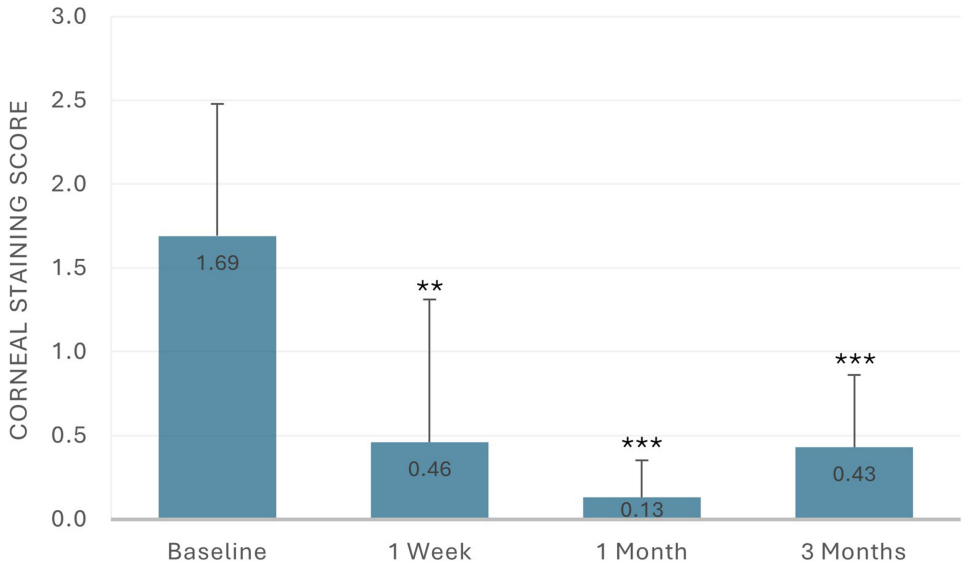

Figure 1 Corneal Staining Scores Pre- and Post-CAM Placement. *P < 0.05, **P ≤ 0.01, ***P ≤ 0.001.

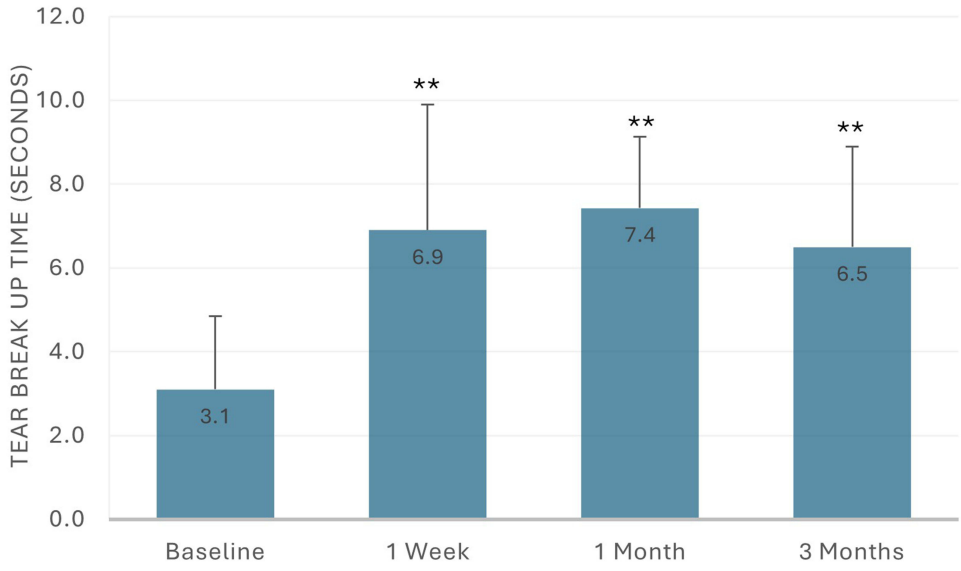

Figure 2 Tear Break Up Time Pre- and Post-CAM Placement. *P < 0.05, **P ≤ 0.01, ***P ≤ 0.001.

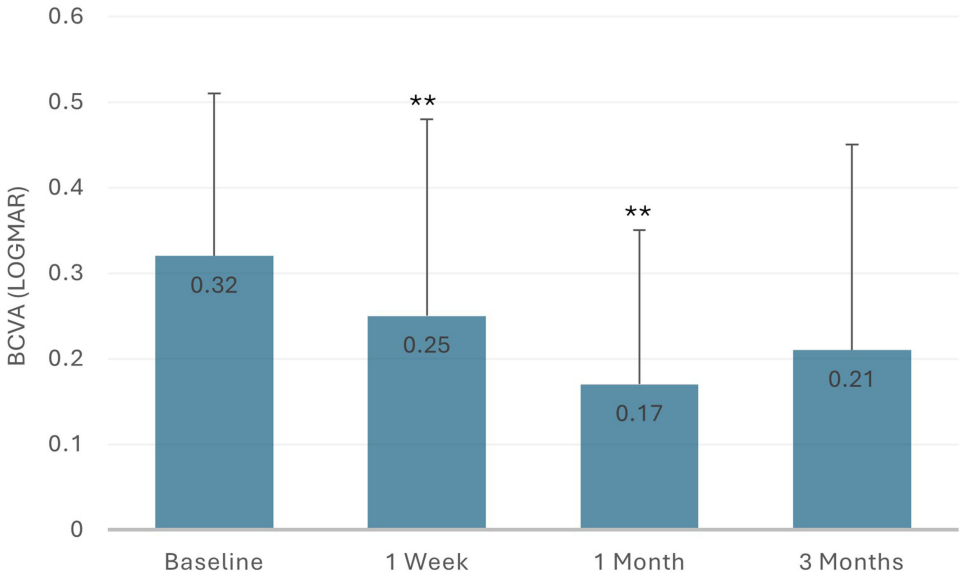

Figure 3 BCVA logMAR Pre- and Post-CAM Placement. *P < 0.05, **P ≤ 0.01, ***P ≤ 0.001.

corneal staining, and 4 eyes had trace staining (26.7%). BCVA improved in 73.3% (11/15) of eyes and remained unchanged in 26.7% (4/15) of eyes. All symptoms were improved or absent in 93.3% (14/15) of eyes. One eye received additional treatment with CAM.

At 14.7 ± 3.7 weeks (median: 13.9) post-CAM placement, corneal sensitivity was normal in 61.5% (8/13) of eyes and reduced in 38.5% (5/13) of eyes (p = 0.008). Tear film was reduced in all eyes (p = 1.0). TBUT significantly improved to 6.5 ± 2.4 s (p = 0.005; Figure 2), corneal staining remained significantly improved to 0.43 ± 0.43 (p < 0.001; Figure 1), and BCVA logMAR was 0.21 ± 0.24 (p = 0.13; Figure 3). BCVA improved in 57.1% (8/14) of eyes, remained unchanged in 28.6% (4/14) of eyes, and slightly worsened in 14.3% (2/14) of eyes. A total of 5/14 eyes (35.7%) had no corneal staining, and 7/14 eyes (50.0%) had trace corneal staining. All symptoms were improved or absent in 50.0% (7/14) of eyes, with the remaining patients reporting at least one or more ocular symptoms. There were no complications throughout the study period.

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Discussion

The corneal nerves plays a fundamental role in the blinking and tearing reflexes as well as maintaining homeostasis of the corneal epithelium.[20–23] As a result, corneal nerve damage diminishes corneal sensitivity and impairs epithelial wound healing.[3, 4] Self-retained CAM in the form of Prokera has been previously shown to promote epithelialization as well as improve both corneal nerve density and corneal sensitivity in patients with moderate to severe dry eye disease.[16] However, the clinical effectiveness of a newer shelf-stable CAM in managing early stage NK has not yet been assessed.

This study found that two-day treatment with shelf-stable CAM in conjunction with a 24-hour collagen shield resulted in complete corneal healing in 62% of eyes at one week and 73% of eyes at four weeks. At three months, corneal staining scores remained significantly improved, with 86% of eyes having trace or absence of corneal staining. This is comparable to a recently published study, which found that CAM treatment resulted in complete corneal healing in 70% of eyes at one week and 73% of eyes at one month in 34 eyes with recalcitrant keratopathy.[24] The ability of CAM to promote corneal epithelial healing is further supported by previous studies, which have shown a significant improvement in corneal staining scores up to three months post-treatment with self-retained CAM.[16,18,25,26] The improvement in corneal epithelial integrity in this study was accompanied with a significant improvement in BCVA at one week and one month post-treatment, with 57% of eyes demonstrating visual improvement at the last follow-up. The enhancement in BCVA and corneal staining within a week of treatment is noteworthy, as visual deterioration is common in patients with stage 1 NK and is more difficult to reverse as the disease state progresses.[27] Additionally, many existing therapies for early stage NK require four to eight weeks of treatment to observe a clinical benefit.[28,29] Thus, CAM may be a beneficial treatment for cases where expedited corneal healing is imperative, such as in patients with visually significant ocular surface disease who are planning to undergo cataract surgery. This is of particular relevance, given 58% of patients with DED who present for cataract surgery consultation have reduced corneal sensitivity.[10]

CAM may be particularly beneficial for patients with corneal nerve damage due to its ability to promote corneal nerve regeneration and improve corneal sensitivity.[16] In this study, we found that corneal sensitivity, which was reduced in all patients at baseline, returned to normal in 73.3% of eyes at four weeks post-CAM placement. This is supported by previous studies, which have shown that CAM can improve corneal sensation at one and three months post-treatment.[16,24] Corneal sensitivity is an important indicator of corneal health, with increased corneal sensitivity correlated with corneal nerve density.[30,31] While corneal nerve density was not assessed in the present study, other studies have found a significant increase in corneal nerve density following treatment with self-retained CAM.[16,32] Additionally, we found that the improvement in corneal sensitivity was accompanied with a significant increase in TBUT at 1 week, 1 month, and 3 months post-CAM. Corneal sensitivity has been shown to be correlated with tear break up time,[33,34] with reduced corneal sensation associated with a more rapid tear break up time. Thus, it is possible that restoration of corneal sensitivity in these patients may result in improved tearing and blinking reflexes, as demonstrated by a more stable tear film.

Lastly, all patients tolerated CAM treatment, and no adverse events or complications were reported throughout the study period. In a Phase IV prospective study, 38% of patients who were treated with cenegermin for stage 1 NK reported ocular pain.[29] Other studies that have assessed the use of dehydrated AM with a bandage contact lens for ocular surface disease have reported infectious or sterile infiltrates in 9.7% of eyes[35] as well as lens-related discomfort in 63% of patients including dryness/grittiness (56%), blurred vision (50%), irritation (18%), redness/swelling (13%), pain (4%), and photophobia (3%).[36] The lack of treatment emergent complications in this study may be attributed to the use of a collagen shield as a carrier in lieu of a bandage contact lens. Collagen shields have a high oxygen permeability and degrade over time, reducing the risk of inflammation and complications associated with hypoxia.[37] Ultimately, this study suggests that CAM treatment with a collagen shield is safe and tolerable.

While this preliminary data suggests that shelf-stable CAM may improve both signs and symptoms associated with stage 1 NK, this study has several limitations of note. As with any retrospective study, there is potential bias due to reliance on retrospective data present in medical records. The lack of a prospective design with an established treatment protocol and follow-up visits may also undermine the validity of the data. The study also includes data from patients who were treated with CAM in both eyes, which ultimately increases statistical power and ensures all viable data is assessed

but may also introduce statistical bias. Nevertheless, because the sample size was small, statistical methods to account for inter-eye correlations were not employed. Additionally, corneal sensitivity was assessed using a cotton wisp, which provides a more qualitative versus quantitative assessment of corneal sensitivity. Additionally, corneal nerve density was not assessed using methods such an in vivo confocal microscopy. Nevertheless, a recent study has shown that the cotton wisp test demonstrated high sensitivity (98.2%, CI 93.8–99.8%) when defining hyposensitivity as a level 4 or higher with a non-contact esthesiometer, suggesting a cotton wisp is effective at detecting patients with severe hyposensitivity.[38] Prospective studies that utilize more quantitative methods to assess corneal sensitivity are warranted to confirm our findings, as well as determine if various NK etiology is associated with treatment success.

Conclusions

This exploratory, retrospective study suggests that treatment with shelf-stable CAM may improve corneal epithelial integrity and visual acuity, restore corneal sensitivity, and alleviate ocular symptoms in patients with early-stage NK. Prospective studies are warranted to confirm our findings.

Disclosure

Alain Bauza is a consultant for BioTissue Holdings, Inc (manufacturer of CAM), which had no role in the design or conduct of the study; collection, management, analysis, or interpretation of the data. BioTissue provided an unrestricted grant for the pass-through charges related to IRB review.

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