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Neurotrophic Keratitis: Evolving Staging System and Emerging Agents

Announcer:
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CHAPTER 1

Dr. Hovanesian:
Hello everybody, I'm John Hovanesian, and welcome, good evening, across the country to this program, that is called "The Earlier, the Better." This is going to be an interesting look at neurotrophic keratitis with some people who I tremendously admire in ocular surface disease. We have a great faculty to help lead us through this hour-long program, and so let me just briefly introduce them. I'm John Hovanesian, and I'm in practice in southern California, where I do corneal external disease, a lot of cataract surgery, refractive surgery as well. I'm also on the faculty at the Stein Eye Institute at UCLA. Frank Bowden is a legend in ocular surface disease at his large practice, Bowden Eye in Jacksonville. Frank, nice to have you with us. Good to see you, my friend.

Dr. Bowden:
Thank you.

Dr. Hovanesian:
And we also have Jennifer Loh a great friend and a brilliant doctor and, you know, putting her genes together with those of Bill Trattler, their child, Danny, is like going to be the child prodigy. Does he already have his own clinic, Jenn?

Dr. Loh:
Yes, he actually does. He comes and sees patients.

Dr. Hovanesian:
I bet he's pretty popular with those – even though he's only 3, you know?

Dr. Loh:
Yeah, they like him.

Dr. Hovanesian:
He's about 3, right, now?

Dr. Loh:
Oh, yeah – actually 4, but yeah, pretty close. He has his own name badge.

Dr. Hovanesian:
Outstanding. So, at her practice, which is in the Miami area, she's really become an expert in ocular surface disease. And finally, we're honored to have the Dean of the University of Alabama School of Optometry, Kelly Nichols, who spends a lot of time thinking about ocular surface disease and educating the next generation of doctors. Kelly, it's great to see you.

Dr. Nichols:
Great to see you, too. Pleasure to be here.

Dr. Hovanesian:
Yeah, thanks for being part of this program. So, you know, there's really four things we want to get done tonight. One is to kind of, during this hour, and that is, talk about how we diagnose NK, especially the emphasis here is on early-stage disease. That's why the title is better, you know, the earlier the better. And then kind of talk about current, as well as evolving strategies for treating it, and kind of understand how we sort of personalize treatment for patients based on our findings. And then, talk about upcoming things – novel data on treatments for NK, and how they compare, as well as novel thinking, because that's a big part of what we're doing. So, let's get started.

You know, one background item that's important is to kind of think about how we think about NK. Recently, a group of us got together to talk about best practices, particularly with emphasis on diagnosis of NK, especially in the early phase of the disease, and this is the group that got together. Priya Gupta, formally at Duke, in private practice, Victor Perez who is at Duke, Karen Skvarna at Harvard Eye Associates, and Walt Whitley, who is in practice in the Midwest as well. So, great group of people, who – or sorry, he's not in the Midwest, Walt is at Virginia Eye, of course, and a great leader in ocular surface disease. Sorry to Walt for that.

So these are the, kind of the takeaways that we came up with. First, NK is – there's a lot more of it than we think, and we know that when we test corneal sensitivity, there's a lot more decreased sensitivity. And it's probably reasonable for us to do a lot of testing in patients who have 2+ staining and epitheliopathy and maybe suspected, you know, more signs than symptoms: dry eye patients with stain, no pain are the suspects for NK. Testing corneal sensitivity, Number 3, is really essential, and we probably need to do that in all 4 quadrants, as well as the center of the cornea. As we classify what we find, though, we're moving away from the traditional Mackie system that we're going to review, and toward a little bit different way of thinking about this. As we think about NK, our other consensus point was that we need to think about permanently improving the ocular surface, not just kind of treating the symptoms. That's particularly important for these stage 1 patients. And then, finally, maintenance therapy needs to think about the recurring nutrition of those corneal nerves – the continuing support of them, because whatever the underlying cause is, it's likely to continue and if the treatment is not aimed for that long-term outcome, we may miss the mark and not serve our patient as well as we can.

So, that's kind of the background point, and I'd like to, at this point, turn to Kelly to talk about that consensus point 1. We'll go through each of these with our faculty, and she'll explain some of the background, and how she thinks about and treats NK in her practice. So, Kelly, thanks.

Dr. Nichols:
Alright, so when we're talking about how prevalent something is, you know, I wish I had a crystal ball back, boy, 20 years ago, because I think so many dry eye trials that we were part of really would have benefited from doing corneal sensitivity testing on the patients that we were enrolling. Back in those days, the symptom requirements were less than they are now, for some dry eye trials, and so I really do think that there was some misdiagnosis made in some dry eye trials, which might have led to some early demises of some potential therapeutics.

So we're on the right track now, and I think we're thinking of things in the right way, so we'll be able to better diagnose when we really start looking a bit more closely.

There also – an important thing to remember is that ocular surface disease, a dry eye and whatnot, can occur concurrently with neurotrophic keratitis. They are not necessarily exclusive of one another, and ocular surface disease can lead to NK also. So there's some instances in which you would – might want to again, look more closely, and we'll talk about that in a second.

So, neurotrophic keratitis is thought to be rare, and what does that mean? I mean, this was approved under orphan disease sort of a scenario. And usually, orphan diseases are thought to be in less than 5% prevalence. But it's difficult to determine that sort of prevalence, because it's a rare condition, and we really haven't been looking for it all the time, and so it's hard to look at records, and ICD-9 codes, and ICD-10 codes, et cetera. Especially over time.

So there's a database that actually has been really valuable to eye care, I think, in terms of giving us some epidemiology that's, you know, really patient-centered. So this database is called IRIS – the Intelligent Research Insight Registry database. And cases are all submitted to this database, and then you can mine the data to ask a lot of different questions, not just about NK, but other things. So with this database, when they looked at 1,000 patients, I think consecutively, there were 21 cases found. So even if you make that into a prevalence, that's less than 1%. Now remember, it is underdiagnosed because we haven't' been measuring corneal sensitivity really, with any consistency over time. So it's been almost by ruling it out, and by having the worst cases that you're identifying, and being caught up into that particular statistic.

Then also, 31,915 cases were identified over this period from 2013-2018. And so, if you look at how many years that is, and divide the number of years into basically 32,000, that's about 5,300 patients a year. So stop and think about that, because there's about 40,000 opthalmol – or, so 20,000 ophthalmologists and 40,000 optometrists out there that could be identifying these patients, and yet only 5,000 of them are being found, which means we all could look a bit closer, but it still probably is a rare disease.

So, this database, as I was mentioning, again, is a – has given us a lot of data, and looking at those patients who were hearing the diagnostic code for neurotrophic keratitis, found that those were generally older adults, women, white, and really essentially not Hispanic or Latino. Again, most of these patients had unilateral disease – 58%, which I think is notable because the most common concomitant ocular condition is herpetic keratitis, at 33.7%. But you can't forget about diabetes, at 31.6% of the patients with neurotrophic keratitis have diabetes. That's at least in the bilateral involvement, and again, that number is, you know, reasonably high as well, at 16%. So, the findings of this study, though, showed that if that both a – well, all of these – age, male sex, black race, Hispanic or Latino ethnicity – those that are things that are more rare in patients with neurotrophic keratitis, usually presented with significantly worse visual acuity at diagnosis.

So, if you have an African American aging male, for instance, who has bad visual acuity at presentation, it would be worth doing gram sensitivity testing to see if they might be a candidate for neurotrophic keratitis.

More that they found was – well, let's get into a bit of definition here. So, as was mentioned just a couple of minutes ago, neurotrophic keratitis is lots of corneal sensation – so sometimes we'll see that it's stained without the pain. That is different from neurotrophic pain, which is the opposite – pain without stain. So, that's when you don't see anything and yet they have – the pain that they have far outweighs what you're looking at. So that's a bit different from the kinds of patients with neurotrophic keratitis. And there are a number of diseases that do have overlapping features. Some of these can reduce corneal sensitivity, like dry eye disease can, on its own, reduce corneal sensitivity. Ultimately, that could lead to NK, but again at the same time and due to some other concomitant disease, they could have dry eye, for example, a history of herpes keratitis, and then end up with NK.

Certain contact lens-related disorders, or even the length of time of wearing contact lenses. For example, a patient that might have worn rigid, gas-permeable contact lenses for a disease like keratoconus, for years and years and years could eventually end up with a loss of corneal sensitivity. Chronic blepharitis, that has caused chronic inflammation on the ocular surface, or cases like stem cell deficiency or topical drug toxicity, like with glaucoma medications with patients that basically elderly and have been using these medications for a long time, can get that neurotrophic cornea. And again, it's important to keep mentioning and reminding people about herpes simplex keratitis, which tends to occur over and over time. You can have the stromal component of it which can lead to corneal thinning, and ultimately, neurotrophic keratitis that perhaps won't heal, and could be treated with more modern approaches.

And this is sort of a busy slide of all of the types of etiologies, some of which I just mentioned. The ones in red are the ones that perhaps you should consider, or you'll see more commonly in practice, so herpes simplex and zoster, corneal incisions due to things like surgery or Lasix. Again, diabetes, diabetes, diabetes. Again, that's how – a common cause of bilateral decreased sensation of cornea, and we do have patients that occasionally have chemical burns. Even if they've recovered from those chemical burns, they can have some effects down the line. Corneal dystrophies might be one that you don't typically consider, but if you think about those corneas that are not being regular integrity of the cornea, that certainly things can happen with the nerves and the nerve patterns in those corneas.

And then there's lots of medications – hopefully, you don't have patients that have managed to do anesthetic abuse, but we have patients on chronic medications for glaucoma, or maybe who are using some other types of medications on a more long-term basis. Increasing age, of course everything seems to happen with increasing age, but again, that's been associated, at least in the epidemiology studies with increased risk for having neurotrophic keratitis, as well as long-term contact lens wear, and then there's probably reason, you know, so there's types of cancers that have led to all kinds of things that are more rare, but do occur, that should be on your list of differentials.

CHAPTER 2

Dr. Nichols:
Alright, moving on to consensus point number 2 – and 2 and 3 are rather similar to one another, so – but you'll find that number 2 and number 3 blend. Diagnosing corneal sensitivity is reasonable for patients with 2+ staining, epitheliopathy and suspected NK symptoms, which means they have more signs and symptoms. One of the most common questions that I get is when should I measure corneal sensitivity? Clearly, I shouldn't measure it all the time – or should I? And so, that kind of depends on your mode of practice. Of course, it takes time, and if you've put anything in the eyes, like anesthetic, you know, of course that then makes doing corneal sensitivity testing like defunct after that.

So, the recommendation of the group – the panel – was that sensitivity should be tested at some point, in a workup for dry eye, and

certainly if you're in a clinic, where you're dry eye primarily, or ocular surface primarily. It may be that you do do every patient that comes into you, because perhaps you are getting the referrals from the community – the patients that might be more advanced or more severe. Certainly, if you have a patient that isn't responsive to your dry eye therapies, and you've been good with them – like you've put them on therapies, the patients have been taking them, hopefully consistently, and are not achieving the result that you would hope, that's a time to consider measuring corneal sensitivity.

Again, taking a good clinical history, doing corneal sensitivity testing, a complete slit lamp exam, and then if you have a diabetic patient, of course, looking for diabetic retinopathy with dilation. Corneal staining, hopefully with fluorescein, and even lissamine green, if you can, if you can find it. And that's, you know, of course, prior to anesthetic. The Schirmer test, usually that's done non-anesthetized, but that can also be reduced when you have a reduction in corneal sensitivity, so is that aqueous-deficient dry eye, or is that related to the cornea, sort of neural patterns being disrupted? In the end, it kind of doesn't matter. You need to sort of look at the corneal sensitivity and decide whether or not it looks reduced, and all the whole picture of what you're looking at. Certainly, if you think it's an ulcer or you have really bad lid margins that you think could use culture, because it's maybe not responding to your treatment, that's something to rule out.

And if you have the good fortune of being able to do in vivo confocal microscopy, you can look directly at the nerve base which is really valuable, and some of the research that's come out recently about that, and regeneration of it, is really, really quite interesting. And then you also want to check for systemic immune disorders. So they can have concurrent Sjögren's, and that aqueous-deficient dry eye, or other things at the same time.

So, the panel really came up with a list here of Strongly Recommended and Could Be Considered, in terms of when to do corneal sensitivity testing. So if you have a persistent epithelial defect, which doesn't improve within 14 days, that's worth testing. Painless, my – the key word here is painless – and newly observed epithelial defects of unknown etiology. Now this is unusual too – pain in the affected eye but multiple concomitant risk factors, like they have poorly controlled diabetes, reduced blink, history of corneal procedures, et cetera. A history of procedures for conditions that may have affected the trigeminal nerve, and a history of herpetic eye disease would be strongly recommended. And it can be considered, a limbal stem cell deficiency, or new epithelial staining, but very uncontrolled diabetes. So again, you'll see sort of the diabetes all over here. If you have patients, you should – and that have corneal disorders, again you should be looking at those patients. If you have persistent, poorly-controlled diabetes and vision changes, even in the absence of annual corneal findings, you should consider testing for corneal sensitivity.

Okay. We're going to do a polling question. The question is, Do you currently perform corneal sensitivity testing in your practice? There is no wrong answer here. You're all here to learn, so if you don't, that's okay, just let us know. And has it – if you do or don't, has it led to a change in your rate of diagnosis? Some of you might have, you know, been reading about this and have been making some changes to your practice. So your choices are: No, I don't perform corneal sensitivity testing; Yes, I do but it hasn't really changed the rate of NK diagnosis; Yes, I do, but – and it has increased it by about 5-20%; Yes, I do, and it's increased it 20-40%; or Yes, I do, and it hasn't – it has decreased the rate of NK diagnosis – and I hope that isn't your choice.

Dr. Hovanesian:
So, Kelly, you know, in your own practice –it's a 2-part question. How long does it take you to do corneal sensitivity testing in a patient – typically, what would you guess? And how often does it redirect your way of thinking about treating whatever underlying disease they have?

Dr. Nichols:
Well, always. Part B is that it always does, because maybe you found something that you thought, or you didn't find something that you thought. So I would say it always changes your ideas, because you're getting more information.

How long – you know, sometimes it takes a bit to, in my place, to find the Q-tip, you know. So I use a cotton wisp usually, and so if I can find that quickly, or if there's one sitting out or close by, it's just half a minute. I mean, it's really not that long at all. That's a – I never have thought about timing it. What about you?

Dr. Hovanesian:
Yeah, no, I think that's about right. And I agree with both parts of your answer. It – the problem is not that it takes so long, it's just that we don't think of it. It needs to become top of mind, because I think there's a bifurcation in our treatment of disease, and we're going to – I don't want to steal the thunder from Frank and Jennifer, but – I think they're going to get into that a little bit.

Dr. Nichols:
70% of you say that you don't normally do it, so hopefully after listening to us tonight, you'll be encouraged to try a little bit more, hopefully on a few patients. And some of you have been and have been seeing some improvement, so that's really great. Now

remember, it is rare, and if you are seeing primarily, you know, regular patients, so you're not in the dry eye or highly specialized corneal practice, if – you might not find as many, but that's okay. I think getting it into your mind that you're going to be looking is really, really important.

Alright, moving on. Okay, consensus point number 3. Diagnosis of NK should hinge on testing for corneal sensation, ideally across the center, and all four quadrants. So again, like I told you, number 2 and number 3 are similar. If testing for corneal sensitivity, anesthetic should not be part of the protocol, so that's your, sort of, red-flag warning. And again, sometimes you may have a situation in which a tech has put something in the patient's eye before, and you want to do it. So have them back. You know, I guess that's the – or make a note to the – on their next visit to do it, because that would be, you know, this stuff happens, and so as your staff get into the right sort of training too about when you would want it done, that will be important. As with all ocular surface disease, staff are critically important to actually being able to do a wonderful job for your patients.

So, how do you do it, again is asked a lot. And, so I have talked to some doctors who use a very I don't want to call it labor intensive, but they use dental floss, and they tape it to forceps, and then they have those ready in the exam room. Or, cotton wisps, which again you do have to be able to find the Q-tip. But you can also use like an edge of a tissue, you know, something small that you can get up close to their eye, without them, you know, blinking right over it. And you should test all the 4 quadrants as well as the central, and an easy way to evaluate it, rather than getting all difficult, is sensitivity present, absent or reduced, and those are words that are easy to remember.

If you remember back to anatomy, the central cornea is the most sensitive of all the places in the cornea, but also decreases with age, and is not affected by iris color, and I don't know if you caught it earlier, that having dark irises might be one of the factors associated with NK. I would say the jury is still completely out, because that doesn't really make sense that if it's more commonly found in, you know, white elderly women – not exclusively, because there's lots of other systemic conditions that can impact all different kinds of people – that iris color would not be dark, it might be lighter. Having said that the data about the more rare patients being the ones that actually have the worst visual acuity on presentation, could lead to having a data point like that. So, I would say that iris color is to be determined, probably not that important in terms of trying to figure out who might have NK in the long run.

Also, there have been papers that have reported diabetes type 1 and 2 and dry eye both have decreased corneal sensitivity. So how do you do it? You see in this video here, a – it's a very short video. It's not testing all the quadrants, just inferior, and you're looking for the blink in a patient and so, and you would kind of test not only the center, but the temporal, which is more sensitive than the inferior but less sensitive than the central. The Cochet-Bonnet esthesiometer – you hear about that. It's used in studies, so you'll find data on that in the studies, but you generally don't use it in clinical practice. The instrument hasn't changed in, like, decades, but you can still purchase them if you want to try and get one, and use it in your practice, but you will read literature about it. And ho – what is it? Well, it is a handheld instrument. Not too big – you know, about that big. And it has a filament that you actually can kind of roll out and roll in, so to do it and start out, you roll it all the way out, and you touch the eye and the patient doesn't flinch or make any movement, then you start rolling it in, and you keep going until you – until they flinch. And the shortest length is what you record. And in this instance, the shorter the length indicates decreased sensation, so if you touch it with it really long and they feel it, then they are normal. And you repeat that in each of the quadrants as well as centrally.

Alright. Pass it over to Jennifer.

Dr. Loh:
Yeah, thanks for starting the path for us, Kelly. Great job. So now I'll be diving into consensus point number 4, and that classification of NK is moving away from the Mackie system, which as John alluded to earlier has sort of been the traditional system we all learned about in school. And there was a neurotropic keratitis study group that created a new definition, or a new way to grade NK. And again, highlighting the need that a new classification system is needed because there are actual subtle variations and it may not be as simple as a 1, 2, 3 type system. And again, having a better classification system could help give us confidence as clinicians in recommending earlier treatment for earlier stages of NK.

Alright, so to review, the Mackie classification was a 3-stage classification. Stage 1 included punctate epitheliopathy, which is like our traditional SPK that we may see on fluorescein staining, decreased to break up time and even stromal haze. Stage 2 is when the patient begins to have a persistent epithelial defect, with the smooth rolled edges and the stromal opacity, whereas stage 3, the worst stage, you actually end up having stromal thinning and ulceration, as well as corneal perforation.

So, what the NK study group proposed was a new, 7-step clinical staging system, to help better classify the signs and symptoms associated with NK, and to be more precise, and they've actually submitted a white paper, for publication on this. The classification is designed to allow for earlier diagnosis, and allow us to accurately monitor progression, evolution and recurrence of NK, and to assess and evaluate the response to treatment. And these are all big questions that we have, and like Kelly was saying, NK is rare, so it's not

something we're necessarily used to seeing every day in clinical practice unless we're, you know, in a tertiary advanced academic center. So again, it's really nice to have these guidelines for us.

So the proposed staging system, again, has this 6 stages, so zero – it's technically 7, because it goes from 0-6, so 7 stages. At stage 0, is altered sensation without keratopathy. So, their clinical exam is going to look normal, and they're obviously not going to have any complaints. So this is probably the hardest one to detect, unless you're routinely just checking every patient that walks in the door. However, stage 1, you're going to start to see the epitheliopathy, or the staining on the cornea, but you won't see stromal haze. So this can also be very easily confused with typical dry eye, or ocular surface disease. Stage 2 will start to show stromal haze, along with epitheliopathy, so you may start to get more of an indication. And then, stage 3, of course, you're starting to get these persistent or recurrent epi defects. Stage 4 includes persistent and recurrent epithelial defects with stromal scarring, however without corneal ulceration – so, very important to distinguish. Stage 5, you get the persistent or recurrent epithelial defects, with the corneal ulceration. And stage 6, unfortunately, is corneal perforation, so obviously very end-stage, and where we do not want to get.

So again, going into stage 0, your patients aren't going to have any sensation. They're not going to have any corneal findings, so again, they're probably going to be very easily missed in routine clinical practice. Stage 1, though, can start to give us a clue. A patient may come in, we're probably going to diagnose them first with dry eye and start treatment. Because again, they don't have any other indicators, and they're the patients that, you know, stain without pain. But the fact that they don't have pain, and you see a cornea like this could, and probably should, you know, that's some indication that something's going on.

Because we know that, you know, when you have SPK, or you have staining on the cornea, oftentimes patients are symptomatic. So that could be the first clue – that they're not complaining, but we are, as the doctors. Stage 2, again, you're going to start to get the epitheliopathy with the stromal haze. Stage 3, you're going to start to get persistent or recurrent epithelial defects, and you can see that, of course, with the fluorescein staining. Stage 4, now you're having the epithelial defect that's persistent and the stromal scarring, but no ulceration. Stage 5 is leading to the corneal ulceration in the cornea, with the persistent epithelial defect. And stage 6 is corneal perforation, again. Definitely what we're trying to avoid for all patients.

So here's a polling question. Do you currently stage NK in your practice? A would be No, I don't see many patients with NK; B – No, I don't see the relevance of staging NK; C – No, none of the classification systems are appropriate; D – No, but I will consider adopting the NKSG system; E – Yes, I use the Mackie classification system; and F – I use the Mackie classification system but may switch to using the NKSG system; and G – Yes, I use other classification system.

Dr. Hovanesian:
You know, my biggest takeaway from the NK study group changes that it's really qualifying NK at a much earlier stage, right? We're not necessarily required to see stromal changes or stromal haze, which to me is a whole lot more relevant, because – and right up the alley of what we're talking about today, isn't it, Jenn?

Dr. Loh:
Exactly. In fact, I think getting the word out there, letting us recognize it, because if we're not thinking about it, we're not going to be diagnosing it. Cool, interesting results. Okay, so 57% of people responding don't see many patients with NK. And we do have 1% that doesn't see the relevance of staging NK. 33% are considering using the updated NKSJ system, and 1% using the Mackie system, and then 7% considering switching to the NKSG. Okay, so interesting variety of results.

Okay, so consensus point number 5. Stage 1 NK should be treated with the intent of permanently improving or long-term improvement on – of the ocular surface. So again, this is stage 1. Very early stage. We want to actually get to the patients early on. We don't want to let them get to stage 3, 4 or 5, and definitely not 6. We have time now. We have treatments, so we need to treat them earlier. It's a progressive disease, and earlier treatment may help prevent progression.

Patients with stage 1 NK should receive treatment for the epithelial and the nerve components. They should not be ignored. Now that we have a treatment, the – you know, it's very exciting. We can – we have a lot to offer our patients, so cenegermin, which many of you know about already, is effective for stage 1 NK, and should be considered in those who do not respond to conventional therapies, and for whom the cost of the drug justifies the likely benefits.

So, again, going back to the Mackie stages, there is articles that discuss different treatments for the different Mackie stages. Mackie stage 1 classically has been treated with tears, ointment, taping, punctal plugs. Mackie stage 2 is where we get into a little more aggressive treatment, such as serum drops, tarsorrhaphy, Botox injections, NSAIDS and steroids, although I would actually argue that stage 1, we could now start treating more aggressively, and probably should be introducing some of the stage 2, and even stage 3 treatments in the stage 1, including amniotic membranes, serum tears, and even cenegermin. In Mackie stage 3, of course, you know, that's dealing with the ulcers and the perforations, so that's when we're dealing with transplantations, amniotic membrane, conj flaps,

cenegermin, and neurotization, which we'll discuss in a second. But again, I think there's the – a lot of room for more aggressive treatments earlier on, that would be more updated and modern than what this chart would be suggesting.

So serum and plasma therapy has been reported efficacious as a primary adjunct therapy. The success has ranged from 71 to 100%, within 90 days. Umbilical cord serum may be more effective. Epi defects healed in 97.4% of stage 2-3 NK, after 11 weeks of plasma-rich growth factor, so it's pretty impressive. And it's interesting, you can use serum safely with silicon hydrogel contact lenses, and so that's obviously really interesting and important for our patients.

I think another really interesting topic is amniotic membranes, and how important they are in treating ocular surface disease, and NK. And there was a randomized, clinical trial that reported healing of neurotrophic ulcers with conventional therapy, or amniotic membrane tissue, and those healing rates were similar although the AMT group was better. And AMT was also found to be equivalent to autologous serum. And so, patients that don't have access to autologous serum or aren't able to get it, you know, we have a great option now in amniotic membrane. And you can use multi-layer AMT, recommended for the deep ulcers and descemetoceles, when we take our patients to surgery.

So corneal neurotization – so try and say that three times – I think is a really interesting surgery that I just recently learned about, a couple of years ago. But basically, you're able to restore corneal sensitivity after performing a sural nerve graft, and for those of us who don't remember what a sural nerve is, it actually comes from the lateral outer part of the leg, and the sural nerve is a sensory nerve that controls the lower outer third of the leg, the ankle and the foot. And they actually take the graft and, you know, integrate it with the supratrochlear nerve and the distal portions of the nerve are extended to the corneal limbus, and that allows better sensitivity of the nerve. So, very, very fascinating concept in surgery and something that has been shown to improve corneal sensitivity.

Alright, so nerve growth factor. So this is something, of course, exciting that was approved – cenegermin BKBJ was approved by the FDA in 2018 for the treatment of all stages of NK, so it's really, really important. It actually was approved for all stages. And it's an ophthalmic solution containing 20 micrograms per milliliter of recombinant form of human nerve growth factor. It's a neurotrophin that promotes corneal reinnervation and healing, promotes tear production, and induces epithelial self-proliferation and differentiation, and helps maintain those important corneal epithelial stem cells. It's a novel, recombinant, human nerve growth factor, and it's structurally identical to the native NGF protein. Again, some really interesting science behind it. And with that, I'd like to pass it on to Frank.

CHAPTER 3

Dr. Hovanesian:
Frank, bring us home with the consensus points 6 and more information that you've got for our audience, and I'll advance the slides for you.

Dr. Bowden:
Okay, thank you. Well, first of all, the homeostasis of the ocular surface certainly depends on healthy corneal nerves, and maintenance therapy to support these nerve functions is currently an unmet need. Newer therapies are the focus of several clinical trials that we'll kind of discuss, and reference later. And these are in progress at this time. It's hoped that the new NK study group classification along with novel endpoints beyond epithelial defect closure will facilitate the development of some newer treatments that can allow earlier intervention, particularly in stage 1 disease. Next slide.

So, we understand that endogenous nerve growth factor maintains corneal integrity by supporting sensory nerve trophic functions, i.e., nerves so in supporting nerve survival and regeneration when those nerves are injured. It also stimulates corneal epithelial cell proliferation, differentiation, and survival, and further also it binds to receptors in the lacrimal glands to promote centrally mediated reflex secretions as well. Next slide.

Now, there are 2 pivotal, multicentered trials, which have established the safety and efficacy of cenegermin for Mackie stage 2 and 3 neurotrophic disease, NK disease. Both the REPARO, European trial, and the NGF0214, United States trials, were randomized, double masked vehicle controlled, 8-week studies that utilized the cenegermin 0.002%, 1 drop, 6 times per day. Both trials demonstrated cenegermin advantage over vehicle in the percentage of patients who achieved complete corneal healing at weeks 4 and 8. And this was with statistical significance. Now, pooled – next slide.

Pooled safety data for both trials showed no serious adverse effects, and the adverse reactions that did occur were mild and transient ocular reactions that required no interruption in the study, and certainly no corrective treatments were required. 16% of the patients experienced eye pain following installation – and this has certainly been our experience in utilizing the cenegermin product in clinical fact. And in 1-10% of patients with experienced, or they saw corneal deposits, foreign body sensation, irritation, inflammation, and tearing. Next slide.

The two studies basically were conducted over 50 sites across the United States and Europe, and involved about 152 patients with moderate to severe disease – NK disease. They were all treated in the fashion previously, you know, referred to – 0.002%, 6 times per day, one drop, and this was extended over an 8-week period. In the U.S. trial, 65, 0.2% of the patients had complete corneal healing at the 8-week point, with a vehicle response rate at 16%. In the European trial, 72% of patients were healed at 8 weeks, and of those, 80% of those patients remained healed at a year. Next slide.

The safety and efficacy of cenegermin in patients with stage 1 NK disease has been specifically studied in the DEFENDO trial. Patients received 1 drop of cenegermin, 0.002%, 6 times per day, 8 weeks, and they were monitored for 4, 8 and 32 weeks. The novel efficacy endpoints in this study included mean change in best corrected distance visual acuity 15-letter gain in best corrected distance visual acuity from baseline to week 8, and improved corneal sensitivity, measured at weeks 8 and 32. Next slide.

The results of the study were impressive, with 82% of patients reporting an improvement in corneal sensitivity through week 32. And moreover, 91% of patients actually reported improvement at week 8.

All of the patients that improved, best corrected distance visual acuity, and from baseline to week 8, and 15% of the patients had a 15-letter gain of best corrected distance visual acuity from baseline to week 8. Eye pain was the most common adverse event, and long-term study follow-up study with stage 1 NK patients who completed the DEFENDO trial is currently in progress. And these patients will be followed for 24 to 30 months following treatment. Next slide.

Long-term studies following cenegermin treatment in stages 2 and 3 NK disease have been performed, and are referenced here in this slide. A retrospective review of 18 patients who completed cenegermin therapy at 8 weeks demonstrated a very low, recurrent NK disease recurrence. There were 3 recurrences at year 1, 0 at year 2 and at year 3, 1 of 10 remaining patients had a recurrence, and at year 4 none of the 9 remaining patients studied had a recurrence. Visual acuity, corneal sensitivity, and tear production were improved at the 1-, 2- and 3-year time frames. A prospective study, small as well, involved – was performed and 14 of 18 patients with complete corneal healing after 8 weeks of cenegermin therapy stayed clear at 4 months and at 8 months following treatment. Significant peripheral corneal nerve growth and branching were seen in – with in vivo confocal microscopy at 2 months, and with central advancement of the nerves at 8 months so corneal sensitivity was also improved. I think the major takeaway from this study that intrigued me is that 6 – that this study suggested that corneal nerve regeneration, stimulated by cenegermin therapy, was sustained beyond the 8-week treatment. Next slide.

Now, cenegermin has also been compared with autologous serum, as well as cryopreserved amniotic membrane. With regard to the comparison with autologous serum tears the – both treatments were deemed to be effective. However, cenegermin – it had an advantage, with approximately 2 weeks shorter time period for complete corneal healing. This is likely related to the more robust peripheral corneal nerve regeneration. The comparison with cryopreserved amniotic membrane transplantation, with 12-months follow-up similarly showed near equivalent efficacy with epithelial defect closure. However, the edge I think went to cenegermin, largely on the basis of patient satisfaction, as the patients had a better patient experience, avoiding a surgical experience or trip to the O.R. with the transplantation. Next slide.

So this brings us to discussion points that should kind of come to mind, and that includes the – that cenegermin is approved for all stages of neurotrophic keratitis, but is commonly cited as a treatment for stages 2 and 3 disease.

And the likely explanation that I can – that comes to mind is that, well it was essentially, in the pivotal trials, studied in stage 2 and 3 Mackie disease. And so, in terms of the barriers to use in earlier stages for – as has been alluded to earlier, cost in many situations, or access to, the medication, and in some situations, it may be poor disease state awareness among some eye care professionals in terms of the nature of NK disease and the opportunity that we have in treating early stage disease to avoid structural damage, scarring that would impair vision. There's a certain – we've alluded to some of the concerns regarding, which patient should be offered cenegermin therapy in stage 1 settings, and certainly, I think as we've talked about, patients who have significant risk factors for NK disease patients with epitheliopathy, ocular surface disease that is poorly responsive to conservative measures that have been outlined earlier certainly raise the awareness that this corneal sensitivity should be tested, and cenegermin therapy should be considered as well. Next slide.

So, there are several pipeline investigational studies that we talked about earlier that should be discussed, and certainly intranasal varenicline therapy, which involves increased tear production by nerve stimulation, has recently completed a phase 2 clinical trial in stage 1 NK disease patients, and results are pending. The human recombinant, 5 acid deleted hepatocyte growth factor has some observed benefit in reducing inflammation from the – on the ocular surface and promoting epithelial cell repair and this is a promising agent which may benefit epithelial surface healing, and is currently being studied in stage 2 and 3 NK disease. And these are phase 1 and 2 clinical trials. The results have been, or are pending next year. The udonitrectag is a unique, low molecular weight, synthetic peptide, which mimics nerve growth factor. And that particular product is in phase 2 ongoing studies for stage 2 and 3 NK disease. It

may represent a lower cost option to patients achieving the benefits of nerve growth factor. Thymosin beta 4 is another promising product that has demonstrated reduction of inflammation and proliferation of epithelial cells in the ocular surface, and it is also in phase 2 and 3 studies and may provide, again, a lower cost option for patients as well. The insulin – topical insulin is another product that actually is, likely readily available at a lower cost option for patients, and it represents a mitogenic agent that actually can stimulate epithelial cell proliferation, and migration on the ocular surface. Again, it's in phase 2, 3 clinical trials, and results should be, early results should be anticipated in January 2024.

CHAPTER 4

Dr. Hovanesian:
Frank, that's terrific. I appreciate that. The you have such a great eye on what's coming in the future, and that was a great review of some of the technology that we should keep our eyes on.

Before we start the case studies, I want to address just one question that came in through the panel, which was about an esthesiometer called the Brill esthesiometer, that is, you know, a quantitative instrument for measuring corneal sensitivity. And although none of our panelists have extensive experience with it, we understand it's a non-contact device, and that may be appealing for some. I think most of us feel that, you know, what's most important is that you measure corneal sensitivity, and there are different ways to do it, and that you have spectrum of knowing, you know, in your hands what is, you know, what is normal, what is reduced, what is absent, and perhaps some other breakdowns in between there, so you can stage a patient over time. That's what's valuable, so, you know, find what tools work well for you.

So, I'd like to use our remaining time to talk about some case studies, starting with one that Jennifer submitted. A patient, I think, that is really kind of instructive in this way. So Jenn, I'm going to give back control to you for the slides, and why don't you take us through this case?

Dr. Loh:
Sounds great. Thanks so much, John. Alright, so this is my case of unilateral keratitis. So recently I had a 69-year-old woman, who was sent over as an emergency visit from her local eye doctor, and there was a concern for HZV keratitis on her right eye based on her exam findings. The referring doctor did start her on oral valacyclovir. What was interesting was she did report that, a couple weeks before, she had also been diagnosed with a corneal abrasion by a different eye doctor at the time. Her main complaint was actually blurred vision, and she didn't have any pain or any eye irritation at all, to speak of. So, on exam, her vision on the right eye was reduced, 20/70 without improvement with pinhole. Left eye was normal, 20/20. And interestingly enough, her pressure was 29 on the right and 32 on the left, and I wanted to highlight that I did – luckily in our practice we typically have techs use the eye care for the exam, which I really love because it prevents them from putting any drops in advance of the doctor, you know, seeing the patient, because of course, as we just discussed, having any drops prior to the doctor seeing them could affect the corneal sensation. So in this case, it was lucky. Her past ocular history included using latanoprost previously. She had been prescribed that, but she stopped it due to the recent wave of eye issues that she was having, which resulted in her pressure getting high. What was the most interesting was that she also reported that she just had surgery a couple months ago on her trigeminal nerve, in order to reduce her pain from trigeminal neuralgia. And she even said this, quote, I quote: "Since the surgery, I haven't been able to feel the right side of my face." So, that was obviously concerning to her, as well as to me.

So, of course, this was a pretty big red flag, and I immediately tested with the cotton wisp prior, you know, to a – you know, just make a note, I – we had not installed fluorescein or proparacaine in advance, so that was, you know, very fortunate. And she did not have any corneal sensation whatsoever on her right eye, but her corneal sensation was normal and intact in the left.

So here's an exam of her actual eye – a photo of her eye with fluoresceine staining. You can see there's just diffuse epitheliopathy or FPK. No thinning, no stromal haze, right? So she would be considered, in the new staging system, like a stage 1 Lids exam were normal. No abrasion, no dendrite. So I wasn't concerned really about HCV, although it's something, of course, certainly to keep in the diagnosis and the differential diagnosis, of course. I – on another note, she did have enlarged nerves. There was some thinning on her RNFL layers, so I also had to address this whole issue of, you know, possible glaucoma with her. So of course, I advised her to restart the latanoprost, or – although I knew it may not really help ocular surface, but I felt like I had no other choice, given her other findings. And I did diagnose her with stage 1 NK secondary to the trigeminal nerve surgery she had. I placed upper and lower lid punctal plugs in the office. I started preservative-free artificial tears. I advised her to stay out of her contact lenses, and I also started a process to get her on cenegermin. So the question, sort of in my mind, was, is cenegermin helpful in patients following trigeminal surgery? I know we don't have a lot of, you know, time to really discuss this, with the time allotted, but, you know, I decided I didn't really have the answer to that, but I figured it was worth a try, and as we saw in earlier slides, you know, even if corneal sensation is not reinstated, it could help the epithelial, you know, process of the cornea. And so, we decided to get started. We were lucky – we got it approved, and she was

approved and started on cenegermin 6 times a day, and she completed the full 8-week course.

So, 10 weeks after the initial visit, she completed her course. She was still on her latanoprost and artificial tears, and her vision was back to 20/20. And this is a picture of her actual cornea. Really no epitheliopathy whatsoever. Of course, she didn't have any pain or discomfort, still. And she did not have any corneal nerve sensation. I will say that. But her cornea looked a lot better, and I had not put her on any other drops besides artificial tears and latanoprost, so she wasn't on any of the other, typical ocular surface drops that we've done. So I do really attribute a lot of her, you know, improvement to the cenegermin.

And just as an example, this was her pretreatment. So again, I'm really happy with this case because I see – I believe that we saved her from, you know, further worsening, and then corneal thinning, and then corneal perforation, so getting early treatment in the game, I think, was a game changer for her.

Obviously, there's some questions to consider. I don't really have time for this, but the question is how long will the improvement last? Should I consider doing another course of cenegermin? And then also, you know, should I do any other glaucoma treatment to get her off of latanoprost? But, thank you for allowing me to share my case.

Dr. Hovanesian:
Great case, and it's, you know, it's illustrative of how potent the effect of desensitizing the cornea is on the ocular surface, and how potent our treatments are even here, in a case where you'd really wonder if the mechanism of action would work.

Before we move into Frank's case, for the last couple minutes, there was a question from the audience about, would we expect to see increased vascularization in the cornea, and, Kelly, do you mind, answering that? Do we expect to see in cenegermin-treated patients increased vascularity?

Dr. Nichols:
I don't think so, but I would throw that back out to all of you to answer. It's not common in what I've seen.

Dr. Loh:
Yeah, well, I can say in the few cases that I've done, I have not seen any increased corneal vascularization.

Dr. Bowden:
I would agree. I would agree with that as well.

Dr. Hovanesian:
Yeah, you know, it's – the mechanism for this is neurotrophic growth factor. It's, you know, it drives nerve growth. It may have a minor impact on vascular growth, but not one that's clinically evident in most of the patients we treat.

Obviously, that would be very contrary to our aims in these patients, where we're trying to clear the cornea and not vascularize it. So, Frank, just a couple minutes left here, but if you can kind of delve a little bit into your case, and we'd appreciate it, and I'll advance the slides for you. Go ahead.

Dr. Bowden:
Okay, thanks. This is a complex patient that was referred to me by another cornea specialist, which certainly raises red flags, in the private practice. This is a patient who had NK disease in the left eye, that was unresponsive to conservative measurable therapy, and even had a gold weight, upper lid implant to address her seventh nerve palsy. They had previously had a resection of a squamous cell CA of the – with partial nerve sacrifice in the left temporal area, and this was followed by extensive facial reconstructive surgery and radiation therapy. And he likely had a radiation optic neuropathy worse in the right than the left eye, without significant discomfort. Next slide.

His clinical findings were as noted. He had best corrected acuity. He had motion in the right, 20/200 in the left. He had normal intraocular pressures. External findings of ridge vascularization of lid margins, with scarring of the lid margin, and there was a lower lid entropion as well, and thalamus in both lower lids. His slit lamp findings showed a 2x1 millimeter inferior corneal erosion, with stromal haze and surrounding edema, and the anterior chamber showed minimal AC reaction, and both eyes showed punctate erosions. Optic neuropathy was seen on the fundus exam. Diagnostics were as noted. He – the patient had diminished corneal sensitivity by a cotton-tip applicator wisp. He had the low speed score. He had hyperosmolar tears, with positive MMP-9 levels, and a low lipid layer thickness in the tear film – only 8 meibomian glands were expressible in each lower lid. And meibography imaging showed that severe gland atrophy was present. Corneal scrapings of the ulcer showed no growth, and my impressions are listed on the left. Medical therapy was initiated, with topical antibiotic, moxifloxacin and doxycycline, to address the potential collagenase activity. Lid hygiene measures – warm compresses, glove – copious preservative-free tears, ointments, and cyclosporin and GOA were included in the initial therapy.

Additional therapeutic measures included the use of cryopreserved amniotic membrane tissue, modified with a central aperture to permit retention of functional vision. Autologous serum tears were used, serial bandage lenses, and NGT treatments listed were also performed. So, despite the diligent and closely monitored care over the next 5 months, attempt was made to remove his bandaged lens and he, shortly thereafter, had a recurrent ulceration of the inferior peripheral cornea. At that point, I performed a periph – a partial Gunderson flap that was performed to, again, spare his visual axis, maintain functional vision in his only eye, and his central punctate erosions limited his vision at the 20/100 level, with fluctuation. Next slide.

After 6 months of observation, serial bandage lens placements every 7-10 days, he consented to lateral tarsorrhaphy to further address his ocular exposure component. And he has experienced significant visual improvement, and improved comfort, and his caregivers were given some respite as well. He required less frequent lubrication, and maintained bandaged contact lens wear. He required blepharoexfoliation treatment periodically, to address keratinization of the lid margins, that was causing a mechanical irritation. Next slide.

With the diligent ocular surface management in our practice, he essentially achieved best corrected or actually, unaided vision at the 20/50 level. And he remained under close observation, very pleased with his outcome, and was grateful for the functional vision until he passed. And this was a patient that I saw several years ago, and this was prior to the availability of cenegermin, which would ver – certainly have been a wonderful therapeutic adjunctive measure in his case. I just wanted to bring this case to your attention. It illustrated a lot of the conservative, the advanced corneal interventions that have been, I think, reduced with the availability of cenegermin, as we implement it in earlier stages of disease.

Dr. Hovanesian:
Yeah, very well said. All I can say is wow. Only the great Frank Bowden could have that complex case in 4 minutes. And like, effortlessly. Just – that's impressive. You are such a great teacher, Frank. Frank has probably taught more doctors about ocular surface disease and its management than a – certainly anybody I know, and who does this? So, I thank you.

So, we had a couple questions before we sign off here, and some of them we've answered online, some live. The question that arose about how do you specifically get cenegermin? We'd refer you to the reps for that. This is not a promotional program. Really, our goal today is to get you to think about corneal sensitivity and measure it in your patients. I'm going to ask our panelists each for any last words, you know, for our audience, before we sign off, and thank Evolve Medical Education for this program. Who wants to start?

Dr. Loh:
I'm happy to start. Again, thank you again, for having me as part of this great program and panel. It's an honor, and again, I think that the key takeaway is just to be aware of the diagnosis, and prepare to test for it in any suspected cases, because treating early is essential to help our patients.

Dr. Hovanesian:
Okay, great. Kelly?

Dr. Nichols:
I'll go next.

Dr. Hovanesian:
I'm always…Frank last. Sorry, Frank.

Dr. Bowden:
No, that's okay.

Dr. Nichols:
Save the best for last. But, thank you all for allowing me to be here with you today. It's been a pleasure, and audience, thank you for sticking with us, a little bit over time. I hope this will encourage you to do some corneal sensitivity testing, and don't forget that you don't have to wait until your patient is at stage 2 and 3, in order to make a difference.

Dr. Hovanesian:
Yeah, great point. And Frank?

Dr. Bowden:
Yeah. The thing I would mention is I always have had an adage in cases like this, and that is, as providers we don't recognize, we don't diagnose things that we're not looking for. And, I think, with increased awareness of disease state awareness, and the availability of newer modalities, technologies that can allow us to intervene early in chronic diseases, allow us to mitigate the morbidity and vision loss that may result accordingly.

Dr. Hovanesian:
Yeah, I'm – I guess my last comment would be that, you know, these are your toughest, toughest patients – the patients you kind of almost dread seeing, even if they're the nicest people, because you feel like – you feel powerless to solve their complicated problems. There are very few things we have to offer these people that have the kind of results that some of our newer treatments have, and whether their disease is severe like the cases – the case Frank showed you, or very mild, we have treatments like recombinant human neurotrophic growth factor or cenegermin, that they work really well, you know, much more effectively than anything else in their category. So we encourage you to think about diagnosing early, use advanced therapy when it's justified by the situation, justified for its cost. And we hope this leaves you, you know, our goal is always to maybe help you practice a little bit better for your patients, and I hope this program today leaves you doing that just a little bit better than you were an hour ago.

So I'd like to thank Frank Bowden, Jennifer Loh, and Kelly Nichols. What a terrific program, I really enjoyed participating in. I want to thank the great folks at Evolve Medical Education, who put this together. So, thank you. Thanks to everyone.