Managing Patients With Neurotrophic Keratitis:

Improve outcomes through recognition, applying updated staging, evidence-based treatment and team-based follow-up

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Overview

Definition

Preeya K. Gupta, MD: Today we're going to be talking about neurotrophic keratitis, and a good place to start is by defining the disease. Neurotrophic keratitis and neurotrophic keratopathy are often used interchangeably. It's a degenerative disease of the corneal epithelium that results from impairment of corneal innervation. The impairment or loss of corneal sensation innervation is the hallmark of this disease process and is responsible for this progressive process that initially starts with epithelial defects and then eventually leads to ulceration of the corneal stroma and, possibly, eventually perforation of the cornea. The dysfunction of the corneal innervation that results in dysregulation of the cornea as well as cellular functions of the cornea are characterized by loss of corneal sensation, as well as loss of neuronal homeostasis, and that leads to eventual breakdown and ultimately keratolysis of the cornea, if left untreated.

Epidemiology

Preeya K. Gupta, MD: When we look at the epidemiology of this disease process, it is classified as a rare or orphan disease. In the United States, the prevalence is about 21 per 100,000 in the population, and the average age of onset is about 68 years of age. Just over half are women, and there's several concomitant disease diagnoses with this condition. The most common being herpetic keratitis in about 34% of cases, diabetes in about 32% of cases and corneal transplantation in 14% of cases.

Natural History

Preeya K. Gupta, MD: The natural history of neurotrophic keratitis centers around the primary event of impairment of corneal sensitivity. When that process occurs, that initially leads to tear secretion reduction to the point where there's stress on the surface of the eye. It reduces epithelial cell turnover and then leads to kind of this irregularity of the epithelial cells within the cornea. They can often have this grayish and sort of abnormal appearance to them that's unique. That chronic epithelialopathy eventually leads to breakdown of the epithelium and 1 of the first signs can be an epithelial defect. That surface dryness, inflammation, and damage to the epithelium then exposes the underlying stroma to the inflammatory process, the keratolysis that occurs, and sometimes we can even see melting of the corneal stroma. In its end stage, there is the possibility of corneal perforation. There's so much loss of the stroma that the cornea perforates. This is definitely the end stage and 1 of the goals for us, as healthcare providers, is to try to prevent patients from getting to that stage.

Kenneth A. Beckman, MD: The natural history of neurotrophic keratitis is quite complex. There seem to be 2 different areas that we need to focus on. One is the corneal epithelium, and 1 is the tear film. And they are very much interrelated. In the early stages, when the condition is still mild, we see some changes in the corneal epithelium that would include things like reduced mitosis, reduced cell turnover, reduced vitality of the central corneal epithelial cells and there develops an increase in epithelium permeability. We eventually get thinning of the epithelium in the central cornea. We know that there's reduced tear production due to decreased nerve stimuli as well. This also contributes to having decreased epithelial turnover and increased amount of epithelial toxic agents. This perpetuates the cycle and leads to more of the reduced mitosis, etc.

Kenneth A. Beckman, MD: We then see some decreased tear film thickness with minimal protection against lid margin/wiping stress. The friction in the wiping stress leads to epithelial damage and then we start to see some punctate erosions on the cornea. That eventually will lead to epithelial defects which are very difficult to heal. We start to see damage in Bowman's membrane, eventually the stroma becomes exposed and that becomes vulnerable to enzymatic digestion as well. We start to see an instability of the tear film. There's more evaporate tear loss. The tear film becomes more hyperosmolar, and we see more proinflammatory cytokines which, again, is going to perpetuate this problem. We start to see the development of matrix metalloprotease or MMP-9 activation which also can lead to some destruction in the surface tissues. We get this imbalance of the MMP-9 activator inhibitor in the stroma and eventually this leads to stromal lysis. We get more inflammatory mediators joining in and that's where you get to the risk of thinning, and eventually perforation, and possibly even loss of the eye.

Patient Burden

Preeya K. Gupta, MD: When we look at the patient burden, our patients can have a broad variety of symptoms. They might initially come in with the complaint of dry eyes, redness, sensitivity to light, vision loss, certainly, as the disease stages progress. They can have difficulty with their daily activities, such as reading, driving, watching TV and then, of course, there's a frustration because this is often a difficult condition to turn around quickly. Patients can get frustrated with their vision loss. I think it's important to also remember, though, that these patients often have a clinical picture that's maybe different than their perception of pain because, remember, they're not feeling the cornea.

Screening and Diagnosis

Clinical Manifestations

Kenneth A. Beckman, MD: There are a number of ways that this condition can present. The tricky part is they don't have symptoms

because they've lost sensation. They may not perceive the dryness, per se. We know dryness, burning, are common, but with their blunted sensation, they may be more likely to report fluctuating vision without actually perceiving this because of the decreased corneal sensitivity. And so that's really the hallmark of the entire condition.

Preeya K. Gupta, MD: Sometimes, as a clinician, when we look in and say are you sure you're not having any pain, it's kind of a little bit of an ah-ha moment to look for something more like neurotrophic keratitis than your run-of-the mill dry eye, for example.

Possible Candidates for Screening

Preeya K. Gupta, MD: When I think about patients that I might want to screen for this rare disease process, it is associated with a number of conditions that are both rare or quite common. There's several genetic conditions, such as Riley-Day syndrome, Goldenhar-Gorlin syndrome, Mobius, familial corneal hypoesthesia, that I would put in very rare categories of patients. There are systemic diseases, such as diabetes, which we see in droves in this modern age. And certainly, patients that have poorly controlled diabetes are more at risk for something like this. Other systemic conditions, such as vitamin A deficiency, amyloidosis, multiple sclerosis, and then the use of certain systemic medications can lead to this. And then, finally, there is the category of central nervous conditions. Whether there was a neoplasm, cancerous lesion, aneurysm, stroke or iatrogenic or neurosurgical procedures that affect the nerve branch that innervates the cornea.

Preeya K. Gupta, MD: There's also a large category that, as ophthalmologists, we're often seeing more commonly as opposed to our primary care colleagues and that's ocular contributors to neurotrophic keratitis. We mentioned earlier that herpetic disease is very common in this patient population, but there are other infectious etiologies, such as acanthamoeba and damage related to acanthamoeba, chemical burns, or anesthetic abuse that can contribute to NK. Some emergency rooms give patients topical anesthetic drops for corneal abrasions that can lead to neurotrophic keratitis from overuse. And then, probably the most fascinating one to me is chronic use of our topical medications that contain BAK (benzalkonium chloride) and other preservatives. As ophthalmologists, we often treat many conditions like glaucoma with topical eye drops and patients are on these drops for decades at a time. Decades of exposure to preservatives can lead to corneal nerve sensation issues.
The list for other diseases that can contribute to NK is quite extensive and I think it's important to keep these conditions in the back of your mind as a clinician when you're seeing someone that has some of those clinical manifestations that we mentioned.

Tools to Test Corneal Sensitivity

Kenneth A. Beckman, MD: There's several ways to test for corneal sensitivity, but the most important thing is to remember to test. You really need this to confirm the diagnosis. Decreased corneal sensation is the key component of the diagnosis. We have seen in many of the clinical trials where 4 quadrant testing of the cornea may be needed. I think that's more of a clinical trial type thing. I rarely do that in my practice. In general, I typically will check just 1 location in the center of the cornea. If I'm suspicious for decreased sensation and they get a normal test, I may then start checking other areas because oftentimes the decreased sensation can be segmental.

Kenneth A. Beckman, MD: The way we do it, typically in clinical practice, is some sort of subjective test, such as with a cotton wisp application. Then there's more of a quantitative type, using an esthesiometer, whether it's the Cochet-Bonnet which uses a thread vs the Belmonte noncontact gas esthesiometer. Both of these, while they are much more precise and give us actual quantitative data, their clinical utility is pretty limited. They're typically used in clinical trials. Most people don't have access to these in their office. That's why the tool itself is not so important. What is important is testing for it and testing early so we know what we're treating.

Subjective Corneal Sensitivity Testing

Kenneth A. Beckman, MD: Subjective corneal sensitivity testing can be done several ways. Probably the most common, in my experience, is to roll up the tip of a cotton tip applicator and create a wisp. I personally prefer to use a tissue, a corner of a tissue paper, rolled up. I feel like that gives me the most control. Dental floss is also commonly used, specifically unwaxed because the wax becomes very firm and may be more likely to cause an abrasion, but you can use any of them. We use a reference scale. Normal, decreased or hypoesthetic and anesthetic corneas. When I test the patient, I have them looking straight ahead and I come from the side. It's important to come from the side so they don't see you coming because there's a blink reflex, they're going to have just from seeing the object coming. You really don't want them to do that. That's why I start inferiorly.

Kenneth A. Beckman, MD: A normal response would be a quick blink and a sense of sensation. The hypoesthetic response, while it may be no blink, but they still feel it, it may also just be a delayed blink or a limited feel. In my experience, you sometimes can touch these corneas a little more aggressively before they withdraw. And the anesthetic cornea will have no sensation and possibly no blink. I'm less concerned about the blink part because, like I said, they sort of sense it and they see things coming, particularly in the peripheral vision they see your hand, so sometimes they'll blink because of what they see, not what they feel. I look a lot of times at the withdrawal as well.

Quantitative Corneal Sensitivity Testing

Kenneth A. Beckman, MD: The quantitative corneal sensitivity testing is something that's typically used in laboratory or clinical trials. The Cochet-Bonnet is probably the most well-known type, and it quantifies based on a filament. There's a thin thread or filament that's extended from the device and the further that the filament is extended, just like a thread, it's going to become more floppy and easier to move. It doesn't put as much pressure on what it's touching. Therefore, if the patient can detect the sensation of the filament when it's fully extended, they actually have greater sensation. And as we progress through patients that have less and less sensation, you withdraw the filament so it's sticking out less and it becomes more rigid. Therefore, if somebody needs a shorter filament to detect it, they have less sensitivity. The Belmonte noncontact gas esthesiometer is similar, except it uses a gas puff and it's usually something that's mounted on a slit lamp. I have never had the opportunity to use this device and I think it's one that would be more for laboratory or clinical studies.

Other Clinical Testing

Kenneth A. Beckman, MD: Some of the other clinical testing that can be involved is actually often neglected, but really important. It's not enough to merely say the patient has decreased sensation. We really need to figure out why. You want to do a careful cranial nerve examination because you're looking for several things—tumors, for example, stroke, things that you may pick up on the cranial nerve exam. Looking at a detailed eye exam, obviously looking at the orbit, the adnexa, the eyelid, etc. Evaluating tear film, a good slit lamp exam. Confocal microscopy is very useful in looking at the appearance of the corneal nerves, but much like the esthesiometer, very few practices have this accessible. And then there's blood work. Depending on what you are looking for and what you're suspicious for, blood work can be important. As we know, things like diabetes and thyroid disease may be contributors to having decreased sensation. And finally, imaging should not be forgotten about. You're looking for tumors and other things. You're going to need imaging to identify these issues.

Diagnostic Algorithm

Preeya K. Gupta, MD: I would say that neurotrophic keratitis can be a little overwhelming for clinicians, but the first, easiest place to start is actually to have a suspicion for it. I would say whatever tool you want to use, whether it's a wisp of cotton, a piece of dental floss, something to check the presence or absence of corneal sensation which should be your first step, because if the patient has normal corneal sensation, then they do not have neurotrophic keratitis. That is a very easy first step, something that every clinician is capable of doing, and from there, you can start to kind of piece all of the different complexities together. If the patient has normal corneal sensation, you'd want to look for other etiologies, but if they have abnormal corneal sensation, then you should put neurotrophic keratitis in the differential and, to me, it's important to go back to our list of potential contributors to neurotrophic keratitis. You can go back to the patient's medical list, look at their medication list, look at their past history and sometimes I even ask the patients about some of these other conditions or whether they've had maybe a surgery that we didn't know about or other things from in their past. It's your chance to really kind of shine as a clinician and dive a little deeper into their clinical history.

Conventional Staging

Kenneth A. Beckman, MD: Mackie classification, which has been around for a long time, I think is a good, basic, fundamental way to separate the stages, especially if somebody is not doing clinical research or not seeing a lot of these. It gives you a basic framework. Stage 1, which is the mildest level, typically starts with 2 important components. There's decreased sensation, which is involved in all 3 of these classifications, but number 2 is punctate corneal staining. That's really the definition. But in stage 1, you are going to see some other things. We may see some con staining. We may see findings such as a decreased tear break-up time or an increased viscosity of the tear mucus. We may start to see Dellen formation or small facets of drying epithelium. The cornea may become scarred or vascularized. We often see hyperplasia and irregularity of the epithelial surface and a hyperplastic precorneal membrane. But, ultimately, it's the staining and the presence of decreased sensation that defines stage 1.

Kenneth A. Beckman, MD: Stage 2 is a moderate NK case, and these are patients without, or with decreased corneal sensation, but, by definition, they have an epithelial defect. The epithelial defect though has a particular pattern or appearance. It's usually a circular- or an oval-appearing defect with a surrounding rim of loose epithelium and, over time, sometimes those edges become sort of smooth and rolled. And once you see these, you really become familiar with them, and you can almost identify the NK even before you test for sensation. You also may find some stromal edema, particularly in the area where the defect is, and there may even be a mild anterior chamber inflammatory reaction. It's important to remember that a patient can have an epithelial defect in the presence of decreased corneal sensation, but that is not necessarily the same as neurotrophic keratitis stage 2. Somebody with diabetes and decreased corneal sensation can get poked in the eye and just may have a traditional epithelial defect that may heal. The type of defect that you see here is really classic.

Kenneth A. Beckman, MD: Stage 3 is severe. These are patients that have a defect, but we are seeing corneal ulceration or thinning. The stroma begins to melt and, over time, it gets thinner and thinner and may perforate. And these are the patients that are at high risk to get severe infections and even lose the eye.

Neurotrophic Keratopathy Study Group Classification

Preeya K. Gupta, MD: In the Mackie classification that was just reviewed, there's really the 3 stages of the clinical picture of neurotrophic keratitis and, as clinicians, we see many more presentations than just those 3 stages. The intent behind the NK Study Group classification was really to help clinicians match a picture to a disease stage and help them pair what treatment might be beneficial in the various stages. Instead of it being those 3 or 4 stages, there are 6 stages. End-stage is, of course, corneal perforation, but stage 1, I think, is really an interesting one. Patients with altered sensation without keratopathy. Patients all start from somewhere. We don't often do an amazing job at checking corneal sensation until we see more severe disease, but if we check corneal sensation in patients, we will find them at that very early stage 1. And then, from there, stage 2 is the start of that breakdown of the epithelium, but without haze of the stroma. And that's very critical because that is a very different picture in terms of visual recovery and severity of disease. And stage 3 is persistent and recurrent epithelial defect. There's breakdown of the cornea. These patients, stage 3 and below, still have a very good

prognosis because there isn't a visual compromise. There might be as part of the initial process, but if you can resolve it, the patients don't have haze or loss of the stromal tissue. They do need help in repairing their epithelium and getting their epithelium intact and healthy, but if you can do that and prevent the patient from progressing to stage 4 and higher here, they generally have a very good visual prognosis. It's important to make an early diagnosis, but also to intervene early, in these patients.

Preeya K. Gupta, MD: Stage 4 is our traditional stage 2 or 3. There's actually haze in the stroma plus the epitheliopathy that's present, and the stromal haze is why these patients maybe have a slightly worse prognosis. And then stage 5 and 6 are really patients that tend to have a poor prognosis because they have these persistent epithelial defects, corneal ulceration, they'll have those classic onion skin or onion peel type appearance, those rolled edges to the ulcer base. Ultimately, something we try to avoid in all patients is corneal perforation, just because it's a devastating complication of this disease process.

Preeya K. Gupta, MD: A picture is worth a thousand words and the NK Study Group did attach some clinical presentation examples to the various stages. And you can see here that at stage 1, 2 and 3, these patients do have still a relatively clear stroma. They do have dysfunction of their epithelium, but really in, stage 5 and above is when patients really start to potentially lose vision because they have these nonhealing defects and ulceration which, once there's loss of that stromal tissue, that is very difficult to recover from visually, and even if you are able to heal the ulcer bed and the epithelium, these patients often have severe irregular astigmatism and vision loss related to an abnormal shape to their cornea.

Considerations for Referral

Preeya K. Gupta, MD: For the clinicians both in primary care and within ophthalmology, I think really the key is to get this patient treated as soon as possible to avoid complications and progression. And, as cornea specialists, we all wish we were getting patients that were in stage 1 through 3 of the NK Study Group classification because those are patients where we can aggressively treat them to rehabilitate the ocular surface and then hopefully preserve their vision potential. For our non-ophthalmologists, I think if patients have some of those systemic diseases that we mentioned, that would be a good screening tool. I know that a lot of times it's difficult to have access to a slit lamp and other eye exam tools, and so screening by way of their clinical history can be a huge help to the specialists out there in ophthalmology because often we're seeing the patients on a referral basis. They aren't always our primary patients.

Preeya K. Gupta, MD: And really, any ophthalmologist, this doesn't have to be a corneal specialist, but any ophthalmologist can diagnose or start treatment that is relevant to healing the epithelium and/or the stromal defects, if present. Eventually, if it's a general ophthalmologist, there are corneal specialists and other providers that have more advanced training in treating this disease process. I always tell my referring colleagues that it's better for you to start something and then send them as opposed to just waiting, because this disease process—and every patient's very different—this disease process can progress very rapidly, or it can just be slow and smoldering. It is great to get these patients on treatment just as very soon as possible.

Treatment

Team Responsibilities

Kenneth A. Beckman, MD: Clearly, as complex as NK is, it requires a team to treat it. It's very difficult, even as corneal specialists, to manage every aspect of it on my own and so I think you really rely on several different characters here. The primary care physician, while they may not necessarily be involved in the active treatment, they're useful for so many factors. Number 1, they may pick up these things first. They may have a patient who had nerve palsy or something and they pick it up and they know to send them to their eye doctor to get checked. Or they may look at the eye and it looks funny. I think they just, in general, should be looking at eyes when they do their exams and sending them on.

Kenneth A. Beckman, MD: In addition, there are several systemic diseases that contribute. These are the docs who are going to be managing them. They make sure that their diabetes is under control. They make sure that their MS is under control. Not only do they have to manage it when we identify the problem, they also, when they're treating these patients, know that they should be under the care of an eye care physician anyway. The optometrist is usually the first person to really see this because they're doing a slit lamp examination, so what they need to do is recognize signs and symptoms. Probably not a lot of them are going to manage true NK, but in the early stages they might and that's fine. These are usually associated with dry eye and many optometrists are very comfortable with managing dry eye. At least initiating that process is important, but they really need to refer if it gets out of their ballpark.

Kenneth A. Beckman, MD: The general ophthalmologist is probably the 1 who sees most of these, at least once they're identified, and, again, they need to recognize signs and symptoms. They're more likely to start treatment early on, whether it's things like a bandage contact lens or other medications, and if it gets beyond to the point where they're comfortable, then obviously they're going to send to a corneal specialist. The corneal specialist is going to confirm the diagnosis if it's not already made. Many times, they are the ones that are making it because the referring doc just sends them over because it's a refractory dry eye and they don't know why it's a refractory red eye or whatever and they don't know why. The corneal specialist is going to determine the optimal treatment, but this is where it gets hard. The optimal treatment is very complex and oftentimes involves multiple medications. It's important to educate the patient. Oftentimes, there's family members involved because a lot of times these are elderly patients who may have a spouse or a child who's taking care of them. And then coordinating the follow-up. These are long, involved processes with multiple visits. And finally, this leads to the allied health professionals who are critical to manage this.

Kenneth A. Beckman, MD: If I have a patient who comes in with NK that's advanced and I'm starting multiple medications, I really need these people, in my office -I think of our technicians. They help with

education, they help with compliance with their instructions and, most importantly, the insurance coverage. There's a lot of work involved to get the necessary drugs approved because a lot of times we're dealing with specialty pharmacies. In my particular office, I have a couple of technicians who are assigned to this role, and they get to know the reps of the companies that produce the products that we want to use and they get the system in place. They become familiar with the specialty pharmacies that are going to help us and they're the ones who are going to handle the phone calls. A lot of times these patients are going to call back in a day or 2, or a week or 2, with issues and they really need to know how to handle it. The corneal specialist doesn't have the availability to do all of this, so the allied health professionals are critical in making sure that the treatment is successful.

Treatment Considerations

Kenneth A. Beckman, MD: There are several considerations that we look at with treatment. In the beginning, everybody gets some sort of preventive and symptomatic care. They all start with dry eye. It's easy to use lubricants. But as things start to develop, you want to get a more targeted or an advanced treatment. The NK Study Group referred to stage 2, which is where you start to get some epitheliopathy, but you don't have any haze yet. But that's an appropriate time to really do intervention. Stage 1 just means they have decreased sensation, but a normal-appearing cornea, so you're not even going to detect it because you're not going to think of testing for it. These are the patients that I think of where I have a patient who clearly has dry eyes, they're not showing any damage yet, but I'm surprised by their lack of symptoms. Maybe they have a very high osmolarity and a rapid tear break-up, but they're not complaining that much, and I ask them, are you using tears and they say, no, I feel fine. Those are the patients that are probably to stage 0, or stage 1 where they have no surface changes.

Kenneth A. Beckman, MD: Then you must think about the type of treatment. Patient adherence and compliance is really 1 of the main factors. Some of our main treatments involve intensive therapy. Obviously, cost is critical, and the risk of adverse events from the treatment. All this must be weighed in. At the end of the day, our goal is to stop progression and reverse the NK changes, if we can, and to keep the eye as comfortable as possible and to keep them seeing.

Prevention

Preeya K. Gupta, MD: I always like to have patients discontinue any preserved eye drops or switch them to preservative-free drops. Anything that's sort of caustic or toxic to the surface, sometimes our anti-inflammatory drops can have negative consequences with the epithelial health. And then avoiding irritating cosmetics or considering some nutritional add-ons, like omega-3 fatty acids, or something that they can take orally to help nutritionally support the ocular surface. The 1 that I think is the most important off this list is actually to treat and work with your colleagues. As ophthalmologists, treating underlying systemic or nervous system conditions isn't something that is in our wheelhouse and so I have a very low threshold to involve their primary care doctor. I think this is a great example here where patients may have very uncontrolled hemoglobin A1C and daily blood sugar level, and so sending them to their primary care doctor for optimization of their blood sugar is critical in this condition because it's part of what is driving the underlying disease process.

Symptomatic Care

Preeya K. Gupta, MD: Other treatments that we might quickly put patients on are topical immunomodulators, such as cyclosporine or lifitegrast, perfluorohexyloctane eye drops, and those are there to support that sort of anti-inflammatory effect that we're looking for in these patients that have a lot of inflammation. You want to treat any coexisting infections. Remember, in later stages, patients will have epithelial defects, and even exposure of the stroma, and so those patients can get secondary, for example, bacterial infections, even though they have a primary corneal nerve sensation problem.

Preeya K. Gupta, MD: Other things to not ignore would be ocular surface disease related to blepharitis or inflammation along the eyelids. Putting patients on autologous serum eye drops can be helpful as it has lots of anti-inflammatory as well as nerve growth factor support properties. Platelet-rich plasma and similar therapies and then amniotic membrane—I use this a lot in my clinic—I think it's an excellent treatment, and I have a very low threshold to use amniotic membrane, especially in somebody that's maybe failed some of these conservative, more topical eye drop-based therapies.

FDA-Approved Medication

Kenneth A. Beckman, MD: The FDA-approved medication is a topical human recombinant nerve growth factor, cenegermin. The trade name is Oxervate. It is approved for treating NK. It was evaluated and studied in all 3 Mackie stages which would be the equivalent here in the NK Study Group of stage 2 and above.

Cenegermin Phase 3 Trial

Kenneth A. Beckman, MD: The pivotal trial that led to the approval of cenegermin had 48 patients involved and they were all in stage 2 or 3 NK. They were randomized to either cenegermin or a vehicle 6 times a day for 8 weeks. There were 2 primary outcome measures that looked at corneal healing of the lesion. It was either the conventional treatment of having the defect get down to less than 0.5 mm of staining or the more conservative, or you could say more aggressive treatment, where the staining was completely resolved. There were some secondary endpoints, including complete healing at week 4, changes in best corrected distance visual acuity, change in corneal sensitivity, and the percentage of patients experiencing deterioration.

Kenneth A. Beckman, MD: The results of the trial were quite impressive. The 2 primary endpoints were a decrease in staining to less than 0.5 mm or complete resolution of the defect. First, to get

down to 0.5 mm, there was almost 70% of patients who reached that in the cenegermin group whereas less than 30% reached that in the vehicle group which was statistically significant. When you look at complete healing, almost all of those that got less than 0.5 mm got complete healing, 65%, but only 16% of the vehicle group which was highly significant. And finally, we see how rapidly this medication worked. 58% of the patients in the cenegermin group achieved complete healing at 4 weeks, whereas only 12% achieved complete healing with the vehicle. What we found is this worked really pretty quickly, and the majority of patients did resolve completely or almost completely and, of the ones that almost completely resolved, almost all of those did completely resolve. In the other categories, there was no statistical significance, whether it was looking at best corrected visual change, corneal sensitivity change, or patients that experienced deterioration.

Kenneth A. Beckman, MD: In summary, the cenegermin was well-tolerated during the blinded and follow-up period. We found eye pain was really the most common adverse event and that was only in 3 treated patients as opposed to 1 vehicle patient. Seven of the patients had serious adverse events, but these were not considered related to the study treatment itself. Fortunately, no deaths and analysis of vital signs, ophthalmic parameters, etc. did not show any specific significant patterns related to the treatment.

Cenegermin – Place in Therapy

Preeya K. Gupta, MD: I think this is such a foundational therapy. It is something that has really impacted patients in such a positive direction. I think we used to dread treating neurotrophic keratitis patients and so, in all of my patients, I start those basic therapies that we talked about. We'll often start the approval process for cenegermin in anybody with Mackie stage 2 or 3. Even patients that are kind of in that stage 1 to 2, I will also use this therapy if they've failed some of those primary interventions.

Preeya K. Gupta, MD: In terms of the results that were presented, cenegermin has been shown to have positive results in anyone with stage 2 or higher, but I think we're just starting to learn about cenegermin in early stages of the disease process. What I think was great about that classification is the differentiation of that stromal haze or absence of stromal haze. And so if we can get these patients started on a therapy that we know is efficacious earlier in the disease process, I do believe that they will probably have a better chance at maintaining their vision or regaining their vision.

Cenegermin – Cost of Therapy

Stephanie L. Conway-Allen, PharmD, RPh: The retail cost of cenegermin can be expensive. Fortunately, there is a connect care program that Dompe has put into place which allows for information for patients to get enrolled into a program, prior authorization information, verifying benefits, assisting with some of the finances, but again, of course, the general cost is pretty expensive. The medication is also only available through the Accredo Health Group, located in Massachusetts.

Cenegermin – Storage and Administration

Stephanie L. Conway-Allen, PharmD, RPh: Within 5 hours of receiving the medication, patients should place them in their refrigerator as these vials are only good for 14 days. When it is time to begin administration, patients should wash their hands, remove their contact lenses. Essentially what the patients should do is pull the plastic cap from the vial, and then attach an adapter. Once the adapter is attached, this vial is now good for only 12 hours. One vial will be appropriate to use for the 6 times daily dosing over the course of those 12 hours.

Stephanie L. Conway-Allen, PharmD, RPh: Once the multidose vial is prepared, the patient is going to remove a pipette from its protective packaging, screw it onto the multidose vial, invert the vial and pull the plunger back until it stops. At this time, the patient should make sure that the vial does not contain air bubbles and contains the liquid. They will then unscrew the pipette from the vial and prepare for the dose. Either sitting or lying back, the patient should then tilt their head back. With their other hand, pull down the lower eyelid and gently push the plunger down until the drop drops into their eye. The pipette should not touch the eye at any point. Once the drop enters the eye, the patient should blink. The pipette can be thrown away. Any contact lenses or additional eye drops, ointments, gels, etc. can be utilized 15 minutes later. Two hours from this dose is when the next dose would need to be administered -keeping in mind that after the 6 doses are administered or 12 hours have passed, the multidose vial will need to be discarded. If a dose is missed, the patient should not do 2 drops or 2 doses at 1 time. Instead, they would just skip that dose and move onto the next scheduled dose.

Corneal Neurotization

Preeya K. Gupta, MD: We know that medical therapy is not sufficient for all patients, and in extreme, more advanced cases, patients can undergo corneal neurotization. This is a complex surgery that has the primary goal of trying to reinnervate the cornea by rerouting or relocating a healthy sensory nerve. The sensation can take several months, often 3 to 6 months, to recover and to have nerve regeneration. It can take even up to 6 to 12 months. This is a very complex procedure; however, a meta-analysis was done of 54 eyes that underwent corneal neurotization and showed that there was an improvement in visual acuity and corneal sensation after this procedure, and corneal scarring was a great limiting factor and presented in about a third of the patients.

Other Therapies

Preeya K. Gupta, MD: Other therapies that are more interventional or surgical can include tarsorrhaphy, which is sewing the eyelids together to reduce the amount of exposure. Punctal occlusion is something that's a little less invasive. I will often do it in these patients as part of our initial therapy. It's certainly not an advanced surgical technique. Therapeutic contact lenses can be of benefit for some of these patients that will have breakdown or recurring breakdown of the epithelium. The scleral therapeutic contact lens can maintain a reservoir of fluid to support those corneal epithelial cells to help them to not break down. And then, finally, conjunctival flap techniques in which the conjunctiva can be advanced to function as a barrier against that corneal epithelium breaking down.

Therapies Under Investigation

Preeya K. Gupta, MD: There are several therapies that are under investigation. The RGTA or ReGeneraTing Agents are large polymers that replace broken heparin-sulfate molecules and create a cellular environment that is more favorable for healing. These are still in very early, preliminary stages. Topical insulin and topical thymosin beta-4 have been studied for epithelial healing. As well as oral nicergoline and substance P-derived peptides with insulin-like growth factor 1. Again, these are all investigational therapies that are in the pipeline and, to this point, are not FDA-approved.

Patient Education Discussion and Cases

Patient Education

Preeya K. Gupta, MD: Ken, let's talk about a few of these just key educational principles. You know, for our patients that are suffering from NK, what do they really need to understand about this disease and maybe some of the treatments that we might select?

Kenneth A. Beckman, MD: Well, I think the problem is most of these patients have never heard of this condition, so they really don't understand it. And because they are neurotrophic, they are often asymptomatic. A lot of times, they're coming in and they don't really feel bad, and we have to somehow educate them and tell them, your eyes are in bad shape, you're at risk to lose your eye and they say, well, I feel fine or maybe they just have bad vision. I think we need to spend a lot of time going over what the process is and how the nerve endings are damaged. I often relate it to patients with diabetes. They seem to understand—a lot of times patients with diabetes will get ulcers on their feet and they don't feel them. I like to give them a reference like that and then they get it. I say the same thing's happening in your eye. You're not feeling your eye, but your eye is breaking down.

Preeya K. Gupta, MD: I love the relatability of that. Our patients aren't going to understand the complex information about the disease state and so I'm going to use that 1 in my own clinic. One of the other things that I think is so valuable is the importance of our staff in the office. These are complex patients and 1 thing I like to underscore is that this is a chronic condition and you're going to have times when it's okay and times when it's not okay and you are going to come to our office and we're going to check you. We're going to get to know each other very well, but our patients often spend a lot of time with our staff. With some of the newer treatments and the intensity of the treatments, it can be something that's overwhelming for a patient to even think about how they get all these drops in and all these treatments in. What are you doing in your office to help patients get over that complex barrier?

Kenneth A. Beckman, MD: I really utilize my ancillary staff. I have a couple of technicians that are the leads on this entire process. I have somebody who, in the beginning, will get the prescription filled. There are forms that they must fill out. My technicians are familiar with the paperwork, and they show the patients what they need to participate in and what I need to do. Then they explain the process, what to expect, when the drops will come, that they're going to get phone calls from the pharmacy that they need to respond so that they can actually get the order to go through because they have some responsibility themselves and we have to train them that they understand that. That they have to be invested in being responsible for their own care. It's not going to just fall in their lap. It is a complex thing.

Kenneth A. Beckman, MD: Then we give them the hot line, who to call when you're in trouble, meaning if your symptoms are getting worse or if you're having trouble with the prescription and basically an A—Z. And after you do several of these, you come up with a cookbook and, at this point, it's seamless. I just tell my technician, let's get them started and they take care of the whole thing.

Preeya K. Gupta, MD: I think that's amazing. Dr. Conway-Allen, what do you think the role is for our allied health professionals? In the pharmacy world, etc, what are ways in which they can be involved in the care of these patients?

Stephanie L. Conway-Allen, PharmD, RPh: We really are on the front lines in different ways. As pharmacists, especially in our community pharmacies, we have patients that will come up with new issues or new questions and maybe they've never had any issues with their eyes before. I think just being aware of not only the fact that referrals are necessary and that we should always encourage our patients to go and see their eye care provider, but acknowledging that, just trying to encourage patients about how to avoid dry eye, is maybe not quite enough. Maybe there's a few more questions we want to ask. Maybe we want to ask about nerve conditions, did they recently have any type of herpes infection, does this person have diabetes, do they have MS, do they have something underlying that maybe this is something more than a seasonal dry eye or a medication-induced dry eye situation. As pharmacists, being aware that there are so many complicated ocular illnesses and conditions and just making sure that we're asking the questions, referring the patients, and encouraging them to be active in their prevention when it comes to their eye care.

Preeya K. Gupta, MD: I love that, and I find that we are often intimately involved with the pharmacist helping us to coordinate access to cenegermin, in particular, and so there is a big collaborative role there for sure. Similarly, I love to involve the primary care doctors if there's systemic disease that can be optimized because this is a condition that requires treatment from all aspects, and so I do like to pick up the telephone and call or send them a note or give the patient a note to take to their doctor so that they can really work on some of those aspects that will help heal the eye and ultimately help the patient see better.

Managing Patients With Neurotrophic Keratitis:

Improve outcomes through recognition, applying updated staging, evidence-based treatment and team-based follow-up

Case: Patient with Vision Loss and Diabetes

Preeya K. Gupta, MD: Ken, walk us through this. We've got a case for everybody here with a patient that has diabetes.

Kenneth A. Beckman, MD: This is a 67-year-old female with a history of uncontrolled type 2 diabetes, and she presents with complaints of decreased vision. So again, we think about this for a second. Patients who are going to have NK, in fact even severe NK, may have no sensation of any irritation or anything other than the vision. Right away, this has to be on your mind if you see any findings on the cornea. What can the clinician do to screen for NK? As an ophthalmologist, I am going to do an exam. I mean, you start with the slit lamp exam because just blurred vision is not narrowing this down at all. It could be they need glasses, or they have cataracts. We need to do a good slit lamp exam. What you're looking for is ocular surface disease. Do they have staining? Do they have dry eyes? Do they have a defect? Now, once you've established that they do have keratitis and you've ruled out all those other possible causes of decreased vision, what can you do to screen? Good history and corneal sensation.

Kenneth A. Beckman, MD: The history. Did they have a stroke? Do they have diabetes? Do they have MS? Did they have Lasix surgery or anything that could lead to this type of condition? And obviously, checking the corneal sensation that we did before. As far as the treatments or prevention, what can we do, what can a general ophthalmologist do while they're waiting? Well, I think this is the good part. Most general ophthalmologists are comfortable in treating ocular surface disease, at least initially. Any of them can initiate whatever dry eye therapy they need. It's initially like a corneal abrasion. You see a patient who comes in, even with a neurotrophic defect in the beginning, you can start doing some work-up. You still want to treat the abrasion. You want to keep them lubricated, give them antibiotics, etc. and usually this is the kind of condition that the corneal specialist should be able to get in the office reasonably quickly.

Kenneth A. Beckman, MD: And then, the use of the primary care physician. Do they have uncontrolled diabetes? Do they have some other issues that we have to manage or are we going to use them to initiate the work-up if we have no diagnosis? Maybe they're going to need to order imaging or something else. So again, it's a team approach. We need communication from all 3 arms, the primary care physician, the corneal specialist, and then either optometrist or general ophthalmologist who initially saw the patient.

Case: "I Feel Worse With Treatment"

Preeya K. Gupta, MD: We have another case of a patient with postherpetic neuralgia who lives in a rural setting and started cenegermin 4 weeks prior, but comes to the pharmacy complaining of eye pain. Dr. Conway-Allen, what would you say to the pharmacist that's there? What education can the pharmacist provide to this patient?

Stephanie L. Conway-Allen, PharmD, RPh: That's a great question, especially being that this medication does come from a specialty pharmacy. The most important piece of information I would provide to your community pharmacists not familiar with cenegermin would be that the pain associated with the cenegermin use is normal. Expect it. It indicates that it is likely working because the cornea is healing. Counseling the patient and encouraging them to continue the medication. If they truly have any concerns, contacting their provider, their corneal specialist and asking those questions to the technicians that are very familiar with the side effects and things to expect would certainly be important. A very strong counseling point would also be encouraging patients to not go on their own and start using other medications and old products or antibiotics in your cabinet because you think maybe there's something else going on. I would really encourage the pharmacists to be available, let patients know that they're available for any types of questions, to not try to self-diagnose any sort of side effects or pain associated with this treatment, especially because it is such a specific and complicated treatment. They really should be reaching out to their corneal specialist or whoever has implemented the medication if they really do have concerns as to whether or not it is appropriate for them at that time.

Stephanie L. Conway-Allen, PharmD, RPh: Dr. Beckman, would you have any additional comments regarding other healthcare professionals, other allied professionals that might participate in education and assisting with this patient when they're complaining of this worsening pain upon 4 weeks of use?

Kenneth A. Beckman, MD: It starts with communication. When I start these patients, I like to let the team know. They may be under the care of a rheumatologist or a primary care physician or a neurologist because they probably have some other conditions that are already established. I like to let them know that they're going to be starting on these meds and hopefully we can educate those other physicians to be aware of what's going on. I typically tell the patient that I would expect pain to start because it's kind of like when you fall asleep on your arm and it goes numb and, as it wakes up, you get the pins and needles. I feel like what's happening in the cornea is the nerves are waking up. If these physicians are aware, then they're going to get the call too and they can explain the same thing. It also goes through the pharmacist, as you said, they need to be familiar with it. And I think they are starting to be more familiar with it, but most importantly really, to me, the gatekeeper is my staff. The technicians are the ones that are going to get the calls. The patients are not going to understand, and the call could be the pain, but it could also be the delivery of the product in the mail or just something about the pharmacy itself. You need a point person who really can manage the entire process and I just defer to them for all of this.

Key Points

Preeya K. Gupta, MD: I think that today we've really covered such a broad area of neurotrophic keratitis and our cases really highlighted the critical points which are that early diagnosis is key and coordination among a variety of specialists provides the highest level of care for our patients with this rare disease that is maybe even not as rare as we thought, as we get better at testing corneal sensitization. The key to the diagnosis is just that, testing the sensation of the cornea and then having the tools for early intervention and then more advanced intervention as well as a referral to specialists that can help to coordinate care amongst the variety of team members amongst the care team.

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