Doing justice to corneal irregularities

Simple corrective procedures increase patient comfort, corneal clarity

EBMD
EBMD is characterized by reduplicated epithelial basement membrane that causes loose adherence of the corneal epithelium to the stroma leading to recurrent painful erosions and/or irregular astigmatism on slit-lamp examination that may or may not be apparent on corneal topography or K readings.

However, clinicians should be alert to irregular astigmatism, according to Christopher J. Rapuano, MD, because it affects vision. In addition, if a cataract or refractive surgery is being considered, it can result in inaccurate K readings and incorrect IOL power calculations, affect the postoperative quality of the vision, and worsen postoperatively, causing significantly decreased vision.

When diagnosed postoperatively, these issues become the surgeon’s problem, noted Dr. Rapuano, chief of the Cornea Service, Wills Eye Hospital, and professor, Sidney Kimmel Medical College at Thomas Jefferson University, Philadelphia.

Continues on page 24: Corneal

Brolucizumab: Practical use shows less frequent dosing, maintenance of visual gains in wet AMD

By Lynda Charters; Reviewed by Christopher J. Rapuano, MD

FOR MANY OPHTHALMOLOGISTS, epithelial basement membrane dystrophy (EBMD) or anterior BMD, Salzmann’s nodular degeneration, and band keratopathy are frequent offenders in clinical practices. Today, there are numerous techniques to identify these diseases, along with treatments that do not require complex surgeries.

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Continues on page 24: Corneal

BROLUCIZUMAB: Practical use shows less frequent dosing, maintenance of visual gains in wet AMD

By Lynda Charters; Reviewed by Arshad M. Khanani, MD, MA, and Joshua Mali, MD

RETINAL specialists are ushering in the year 2020 with the availability of a new anti-vascular endothelial growth factor (VEGF) therapy, since the FDA approval of brolucizumab (Beovu, Novartis) for the treatment of patients with wet age-related macular degeneration (AMD) in the last quarter of 2019.

“[Brolucizumab] is a welcome treatment for patients, and it is the first new treatment for wet AMD in about eight years,” according to Joshua Mali, MD, vitreoretinal surgeon, private practice in Sarasota, FL.

“There has been a meticulous process to create a drug that provides advantages over currently available therapies for wet AMD,” Dr. Mali added. “[Brolucizumab] maintains robust visual gains and provides superior retinal drying compared with aflibercept with the potential for 12-week dosing intervals.”

As background, the FDA approval was based on the results of the phase III HAWK and HARRIER 2-year clinical trials that placed brolucizumab head-to-head with aflibercept (Eylea, Regeneron Pharmaceuticals).

The key finding was that in both study arms at 48 weeks and two years brolucizumab achieved its primary endpoint and was found to be noninferior to aflibercept regarding the best-corrected visual acuity [BCVA].

“An important point to consider is that the dosing of the two drugs was quite different, with aflibercept dosed every four weeks for three loading doses with subse-
TED’S LONG-TERM DAMAGE IS SOMETHING SHE CAN’T COME BACK FROM.

Since there’s a limited window for treating active thyroid eye disease, every moment counts.1,2 To fight back against the impact of this disease, focus on early diagnosis, active monitoring, and prompt medical intervention.1,3-5

To learn more about what to look for, visit TEDimpact.com

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Research finds the highest doses had best responses with no retinal toxicity.
Complaining seems weak compared to others’ struggles

Later that morning, I went over to another part of the hospital to visit a friend who was recovering from surgery. As I walked toward the elevators, one set of doors stopped closing and reopened thanks to a nice man who saw me coming and pushed the “open” button in time. He looked to be about 30, had a cup of coffee in his hand, and looked somewhere between very tired and exhausted.

From his clothing and lack of an ID badge, I assumed he was a visitor and not a hospital employee.

As the door closed and we headed up, I thanked him for waiting for me and told him I hoped everything was going well. In very few words, he told me that his child had undergone surgery and that the problem was more complicated than initially thought.

What had originally been anticipated to be a one- or two-day hospital stay was now into the fourth day, and the doctors didn’t know when his son might be well enough to return home. I told him I wished his son a speedy recovery as the elevator door opened. He thanked me and headed back to his child’s hospital room.

MAKING A RESOLUTION
At that moment I made up my mind to have a resolution. In the year 2020, I have determined not to complain. About anything.

When there are people sleeping outside on cold nights, children struggling with major health issues, and their exhausted parents worried and feeling unable to help their children, whatever imperfections I might encounter during the course of this year in my daily existence are minor by comparison.

And so, in this new year I am not going to complain about politicians, declining physician reimbursement, my coffee being cold, the weather being inclement, or anything (at least that is the plan). If I forget and start to complain, I hope someone will punch me in the shoulder.

Lastly, I offer my best wishes to you and your family for a happy and healthy 2020!
2020: The year of the eye

Mike Hennessy Sr., Chairman and founder of Ophthalmology Times’ parent company, MJH Life Sciences

WE HAVE ushered in a new year, and 2020 promises to be the year of the eye. To kick the year off, Ophthalmology Times is offering content focusing on cutting-edge advancements that will provide the best care for your patients.

On the cover, we take a look at how corneal irregularities can be treated and resolved without complicated surgery in some cases. Ophthalmologists find that epithelial basement membrane dystrophy or anterior BMD, Salzmann’s nodular degeneration, and band keratopathy are frequent offenders in their practices. Christopher J. Rapuano, MD, points out that there are several techniques to identify these diseases, along with treatments that do not require complex surgeries.

Another key topic for clinical diagnosis, we examine treatment options for neurotrophic keratopathy, a challenging potentially blinding disease that is responding to recombinant human nerve growth factor, corneal neurotization, and matrix therapy agents to restore corneal sensation and visual acuity. Francisco Figueiredo, MD, PhD, tells us that new treatments, such as rhNGF, neurotization, have completely changed the current treatment protocol.

When it comes to surgery, observation may be key to learning new techniques for small-incision cataract procedures. We will show you how the complication rates associated with cataract surgeries performed by residents provide approximate information about the learning curve but not about the individual’s competency.

We provide some interesting details on the therapeutics front that may change how physicians treat inflammation. When battling inflammation, the ability of a drug to penetrate into the ocular tissues is key. Fluorometholone acetate may fill that role.

Device technology promises to be a hot topic in 2020, and we take a look at one cutting-edge advancement—a prosthetic system that may provide “sight” for blind patients. A visual cortical prosthesis system developed by Second Sight Medical Products provided some functional vision.

Gene therapy continues to provide a wealth of innovation for ophthalmology. Using gene therapy for Leber’s hereditary optic neuropathy appears highly promising for increasing the best-corrected visual acuity in this patient population. There currently is no treatment for LHON, so we will be watching this topic closely. Paulo E. Stanga, MD, details results of treatment of X-linked retinitis pigmentosa with AAV8-RPGR gene therapy that proved to be effective with durable improvements in vision occurring as early as one month following treatment.

We also are looking forward with advancements in imaging that could enhance the way physicians treat patients. Renowned ophthalmologist Carol L. Shields, MD, explains how ultrasound biomicroscope, and anterior-segment optical coherence tomography are better at some tasks than others, but both are valuable imaging technologies. Joel S. Schuman, MD, details the use OCT to trace subtle differences in structure, and glaucoma progression.

This issue also includes a special section that shines the spotlight on glaucoma. Danny A. Mammo, MD, discusses research that found the education of in-hospital care givers about anti-glaucoma medications required by inpatients significantly increases the adherence rate to the medication regimes. We also talk with C. Ellis Wisely, MD, MBA, who details a study that finds intraocular pressure-lowering drugs netarsudil ophthalmic solution 0.02% and latanoprost 0.005% administered separately and then compared with the fixed-combination formulation are similar regarding their effect on the corneal endothelium.

Rounding out our special section is a look at how different imaging devices can help detect the subtle differences in glaucoma progression. Joel S. Schuman, MD, details how optical coherence tomography can help physicians track disease progression. The various commercially available devices work in different ways and understanding those differences may matter during evaluations.

The new year promises to be an interesting year for ophthalmology, and we will continue to provide you with key information to help you provide the best care possible for your patients.
Enlightening patients about the ocular impact of not adhering to glaucoma medication regimens can be eye-opening for both patients and physicians.

A recent study found that the overall topical glaucoma medication adherence rate for inpatients with a diagnosis of glaucoma was 75.3%. This rate increased to 85.1% among inpatients after providers were educated about the importance of continuous glaucoma treatment, according to Danny A. Mammo, MD, a senior resident at the Department of Ophthalmology and Visual Neurosciences, University of Minnesota, Minneapolis.

From the ophthalmologist’s perspective, strict adherence to glaucoma medication cannot be overemphasized. From the perspective of other medical specialists, the reasons for strict adherence are not always readily apparent given the nature of the disease. Sometimes, information about a prescribed glaucoma medication may not be available upon patient admission.

“Appropriate medication compliance has significant implications for ocular health,” Dr. Mammo stated and pointed out that by 2050, approximately 7.32 million people in the United States will have primary open-angle glaucoma.

Most previous research in anti-glaucoma medication regimen adherence has focused almost solely on outpatient adherence to these regimens. One study that addressed inpatient adherence took a look at hospitalizations from 2006 to 2009 (J Glaucoma 2011;20:573-6) and reported an adherence rate to topical anti-glaucoma medications of 51.6%.

Since that time, when less than 10% of hospitals used electronic medical records, many more hospitals (83.8%) have adopted electronic medical records-keeping. In light of this, Dr. Mammo and colleagues conducted a study in which they assessed adherence to topical anti-glaucoma medication regimens in an inpatient setting before and after an educational intervention of relevant health care providers took place.

**THE STUDY**

This nonrandomized comparative retrospective study included two groups of patients. The first included 142 inpatients with glaucoma who required topical anti-glaucoma medications between January 2014 and December 2018, the time period before the educational intervention of the care providers. The second included 36 inpatients with glaucoma who required topical anti-glaucoma medication from August 2018 to April 2019, the time period after an educational intervention was performed that targeted the inpatient care providers.

The patients’ medical charts were reviewed to identify all patients with a diagnosis of glaucoma admitted during two time periods at an 830-bed single center, academic hospital. The admission notes were examined to determine if the topical anti-glaucoma medication prescriptions were known on admission.

The authors defined adherence as administration of more than 75% of the doses of anti-glaucoma medications prescribed.

**INPATIENT CARE: STICKING TO GLAUCOMA THERAPY REGIMENS KEY**

Study finds medication rates increase when insurance providers are educated about importance

By Lynda Charters; Reviewed by Danny A. Mammo, MD

Patients must learn the importance of adhering to a medication regimen for the treatment of their glaucoma. Failing to adhere to the plan can impact their eyesight.

Enlightening patients about the ocular impact of not adhering to glaucoma medication regimens can be eye-opening for both patients and physicians.

A recent study found that the overall topical glaucoma medication adherence rate for inpatients with a diagnosis of glaucoma was 75.3%. This rate increased to 85.1% among inpatients after providers were educated about the importance of continuous glaucoma treatment, according to Danny A. Mammo, MD, a senior resident at the Department of Ophthalmology and Visual Neurosciences, University of Minnesota, Minneapolis.
Research finds fixed combination safe for corneal endothelium treatment

Netarsudil, latanoprost may provide physicians with another option to lower IOP in patients

By Lynda Charters; Reviewed by C. Ellis Wisely, MD, MBA

A STUDY HAS found a pair of IOP-lowering drugs in a fixed combination has been associated with a larger decline in central corneal thickness from baseline than that found with either drug alone.

A study of the IOP-lowering drugs netarsudil ophthalmic solution 0.02% (Rhopressa, Aerie Pharmaceuticals) and latanoprost 0.005% administered separately and in fixed-combination showed that the fixed combination was comparable to either netarsudil or latanoprost administered alone with regard to effects on endothelial cell health from baseline to month three of administration.

“After three months of administration, netarsudil 0.02%/latanoprost 0.005% fixed combination demonstrated no significant adverse effects on endothelial cells,” said C. Ellis Wisely, MD, MBA.

Dr. Wisely, a resident working under the direction of Terry Kim, MD, in the department of ophthalmology at the Duke University Eye Center, Durham, NC, worked with collaborators at Aerie Pharmaceuticals to evaluate a subset of patients with ocular hypertension or open-angle glaucoma in the Mercury-2 study, a phase III, prospective, randomly assigned, double-masked trial of the safety and efficacy of the combination of netarsudil 0.02%/latanoprost 0.005% administered once daily.

Dr. Wisely said the results of the fixed combination formulation were compared with the results obtained when the two drugs were administered separately.

The investigators evaluated the corneal endothelial cells using specular microscopy and ultrasound pachymetry to detect any changes in the cells. The main outcome measures were the endothelial cell density (ECD), coefficient of variation (CV), percentages of hexagonal cells (%HEX), and central corneal thickness (CCT). The outcomes were the changes in those parameters from baseline to three months.

A total of 415 patients were included in the study and randomly assigned as follows: 126 patients were treated with latanoprost, 143 with netarsudil, and 126 with the fixed combination.

Small changes were seen in the CCT ranging from 0.6% to 1.2% in all three groups.

“Mean CCT decreased more in the fixed combination group (6.4 µm, p=0.0001) than in either the netarsudil group (3.3 µm, p = 0.0248) or the latanoprost group (-1.2 µm, p<0.0001),” Dr. Wisely reported.

The investigators pointed out some temporary and minor adverse events associated with the drugs.

OBSERVATIONS

In commenting on these findings, the investigators pointed out that use of prostaglandin analogues, such as latanoprost, can result in reductions in the CCT with chronic use of more than 18 months (mean decreases, from 5 µm to 15 µm) during the first six to 12 months of treatment. These decreases are reversible with cessation of the drug. It is thought that up-regulated matrix metalloproteinases may promote likely negligible degradation of the ocular surface matrix.

Rho kinase inhibitors, such as netarsudil, can cause thinning of the CCT; however, the investigators noted that thinning has occurred only in eyes with pathology associated with corneal edema in which the thinning is an approach to normalization of CCT. The possible mechanisms include promotion of endothelial cell proliferation and migration, suppressed apoptosis, and faster corneal wound healing.

“The greater reduction in the CCT in our fixed-combination group may indicate that the effects of each drug on the CCT are additive. However, the magnitude of the effect seen for the combination group in this study (1.2%) is likely of negligible clinical significance,” Dr. Wisely concluded.
FEEL THE THRILL

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Alcon
Overcoming hurdles when branded drugs are what physicians ordered

While complexity of insurers, pharmacies is daunting, physicians can succeed

By Houman Vosoghi, MD; Special to Ophthalmology Times

As physicians, we usually want to prescribe what’s best for our patients. Sometimes that means specifying a branded glaucoma drop rather than a generic.

Perhaps a patient needs the predictability of branded latanoprost (Xalatan, Pfizer) because the molecule is sensitive, and differences in manufacturing process, quality of bottling material, or the vehicle can affect its efficacy. Or maybe a patient who has been using a generic drop has ocular surface irritation, and I want to prescribe a preservative-free brand-name formulation.

It used to be that physicians could prescribe any medication they felt was necessary for patients and the patient would be able to get the same medication with little hassle. Those days are in the past. In prescribing a brand-name medication over a generic in the current insurance market, my staff and I often must scale three or four obstacles, but I think it is still worth it to do what is best for my patients. Here are some tips for facing those obstacles, based on my experience.

Succeeding with insurers

When I prescribe a branded glaucoma drop, insurance companies frequently tell us it is a non-preferred or non-formulary medication, and they do not cover it, trying to prompt a switch. With so many different plans and sub-plans, it is hard for us to know what will be covered for a specific patient in advance. When a medication is not covered, one strategy is to seek prior authorization. My staff goes through that process, which entails an approval period and sometimes even an appeals process if prior authorization is not granted. To bridge the gap, we usually give patients a sample. Delays in approval or appeals usually do not outlast the sample.

Pick a pharmacy

Pharmacies represent another complex challenge. Some pharmacists feel, even if the prescription states “dispense as written,” that they are free to substitute a generic. Occasionally, pharmacists also speak directly to patients about accepting a cheaper generic option, implying that the medication works just as well for facing those obstacles, based on my experience.

Delivering the best care

Fighting for a brand-name glaucoma drug when appropriate is the ethical thing to do for our patients. There are logistical difficulties and a financial burden to the clinic, but do not give up and prescribe generics that you do not believe are in your patient’s best interest. There are programs and rebates for patients with insurance, but do not give up and prescribe generics that you do not believe are in your patient’s best interest.

Partnering with patients

In every aspect of this process, my patients and I need to be on the same page. That simply means educating them about why I want them using certain medications. When I want a patient to use a brand-name medication, I explain the reasons.

Keeping costs down

When we get approval for a branded medication, some insurance companies add the caveat that it is a “higher tier” medication, which will cost patients more out of pocket. However, most drug companies offer discount programs and rebates for patients with commercial insurance. It is important for physicians to know about these programs and to have staff educate commercial insurance patients to use these programs to minimize their costs. Patients are a lot more likely to be compliant when they can afford to buy their medications.
One issue faced by many patients is inflammation, and ophthalmologists may have an new weapon in their arsenal to combat the issue.

The ability of a drug to penetrate into the ocular tissues is key to controlling inflammation, and fluorometholone acetate may fill that role for physicians. “All fluorometholones are not the same,” noted Beeran Meghpara, MD, and with good reason. Fluorometholone is the active steroid in formulations used to treat ocular inflammation; however, it is what doesn’t meet the eye that makes the difference, i.e., the vehicle.

If the vehicle prevents the drug from optimally penetrating through the ocular surface into the underlying tissue, the drug will not be as effective as if the penetration was at its potential peak.

According to Dr. Meghpara, fluorometholone acetate ophthalmic suspension (Flarex, Eyevance Pharmaceuticals) is proving to be a key option in his practice. He is co-director of Refractive Surgery at Wills Eye Hospital, and clinical assistant professor of ophthalmology, Sidney Kimmel Medical College at Thomas Jefferson University, Philadelphia.

“The acetate in the formulation makes the drug more lipophilic, which facilitates better penetration into the ocular surface,” he noted. It results in a more potent treatment effect compared with a regular fluorometholone, i.e., without acetate, with the same side effect profile.

The side effects of the steroids used to treat ocular diseases have historically been the greatest concerns. These include elevated IOP leading to glaucoma, a higher incidence of cataract formation, worsening of concurrent infections, and delayed healing.

“Generally speaking, the higher the potency of the steroid, the more likely it is that side effects will develop and that they will be worse,” Dr. Meghpara explained. Fluorometholone acetate, however, is considered one of the safer steroids. When side effects do occur, it is with a lower frequency and they are less severe.

**CALMING OCULAR SURFACE DISEASE**

Probably the most common ocular surface disease of patients presenting to a cornea practice is dry eye syn-

**Continues on page 13:** Fluorometholone
Stent offers IOP stability more than three years after surgery

Registry data finds microstent lowers pressure in patients with primary open-angle glaucoma

By Lynda Charters; Reviewed by Prof. Gus Gazzard, FRCOphthMA, MBBChIR, MD

THE INTERNATIONAL SPECTRUM Registry recently completed enrollment of patients for the Hydrus Microstent (Ivantis Inc.), a microinvasive glaucoma surgery device used to treat patients with mild to moderate primary open-angle glaucoma. In the United States, the device is indicated for placement in combination with cataract surgery or as a stand-alone procedure.

The Spectrum Registry currently includes almost 3,000 eyes enrolled; of these, 700 surgeries in which the Hydrus Microstent was implanted were stand-alone glaucoma procedures. Seventy percent of the patients have completed the three-year follow-up examination.

At the three-year time point, probably the most important findings are not only the marked stability of the intraocular pressure (IOP) over the long-term following placement in the eye but also the improvement following the wearing off of the effect of phacomulsification in the patients who underwent the combination procedure, said Prof. Gus Gazzard, FRCOphth MA, MBBChir, MD.

Prof. Gazzard, professor of ophthalmology University College and consultant ophthalmic surgeon, Moorfields Eye Hospital, London, said patients seem to have stable pressures out that far and beyond that point.

“I have been implanting the microstent for several years and, thus far, have implanted between 250 and 300 of the devices,” he said. “The device provides great pressure control and it may even be greater than we are seeing with alternative devices.”

He emphasized that the microinvasive glaucoma surgery (MIGS) effect in patients implanted with the microstent in combination with cataract surgery seems to be increasing with time as the phaco effect wears off.

“The data are both reassuring and powerful because they show that the Hydrus effects are increasing, which is both surprising and gratifying,” he explained.

The key to this control may be the manner in which the implantation process modifies Schlemm’s canal. This microstent, which lives up to its name in that it is the size of an eyelash, focuses on the natural outflow system of the eye with a trimodal mechanism of action. A large opening is created in the trabecular meshwork, the canal is dilated and scaffolded, which increases the cross-sectional area of the outflow system, and about 90 degrees of the outflow system is covered.

“What is exciting for me is that the microstent keeps the canal open, it does not simply obtain access to the physiologic Schlemm’s canal,” Prof. Gazzard said. “The fact that there is a scaffolding dilatation of the drainage duct provides more robust long-term pressure lowering.”

Practically speaking, he continued, surgeons can be absolutely certain that they have achieved access to the canal and that there is viable communication between the anterior chamber and the natural outflow channels. Other mechanisms and devices may not access the natural drainage channels and there is no real certainty of the correct placement of the devices.

In the Horizon Trial, which compared pure phacoemulsification with phacoemulsification and Hydrus Microstent placement and cataract extraction, found that at three years, which is the longest outcome reported with a MIGS device, the microstent enhanced the IOP lowering achieved by cataract surgery alone.

“There was persistent, maintained, greater pressure lowering with the Hydrus device compared with only cataract extraction,” Prof. Gazzard said. “Fewer drops were used and the procedure was seen to be very safe.”

Another noteworthy finding was that the rate of trabeculectomy decreased with the use of the microstent. In the control arm of the trial, 3.9% of patients went on to trabeculectomy because of glaucoma progression compared with 0.6% in the treatment arm, which Prof. Gazzard described as a robust clinical outcome. The endothelial cell count showed a positive result in patients who had completed four years of follow-up.

The full results of the Horizon Trial will be released in the spring of 2020 with more to follow in 2021.

OTHER CONSIDERATIONS

Placing the Hydrus is a safe procedure with low risk of adverse events. Prof. Gazzard reported no problems with chronic inflammation, allergy, obstruction, and uveitis in his patients.

Outside of the U.S., the microstent can be placed in patients with angle closure glaucoma, uveitis, trauma, congenital anomalies, and neovascular glaucoma. In the U.S., the stent is limited to patients with mild to moderate primary open-angle glaucoma in conjunction with cataract surgery.

“The results provide a glimpse into what the future of MIGS in the U.S. might look like once the indications are expanded. It also speaks to how important following patients is over the long term,” said Dave Van Meter, president and chief executive officer of Ivantis.
**BROLUCIZUMAB**  
*Continued from page 1*

quent extension to every eight weeks,” according to Mali, who is also founder and chief executive officer of Mali Enterprises. “In contrast, brolucizumab was dosed every four weeks for three loading doses and then extension to every eight or potentially 12 weeks based on the assessment of the disease activity.”

Other relevant findings, Dr. Mali pointed out, were that the visual gains achieved with brolucizumab were noninferior to those achieved with aflibercept at the two time points with longer treatment intervals in most patients; about 56% of patients in the HAWK trial and 51% in the HARRIER being treated with brolucizumab were maintained on three-month dosing during the first year. In addition, the central retinal thickness in patients receiving brolucizumab in both study arms decreased more compared with aflibercept at both week 16 and years one and two, he noted.

“Retinal fluid is a critical indicator of disease activity in patients with wet AMD and how they are responding to treatment,” he said. “The presence of fluid is also an extremely important factor in the determination of BCVA.”

Safety profiles of the two drugs were similar. A difference was seen in inflammation between brolucizumab and aflibercept, 4% and 1%, respectively.

**IMPACT IN CLINICAL PRACTICE**

Brolucizumab is a single-chain antibody fragment and is a smaller molecule compared with other anti-vascular endothelial growth factor (VEGF) formulations that are currently available, according to Arshad M. Khanani, MD, MA, clinical associate professor, University of Nevada, Reno School of Medicine.

“The small size of the molecule and the 6-mg injection results in a relative molar dosing of about 12 times compared with aflibercept,” Dr. Khanani said. “This is what accounted for the greater drying of the retina compared with aflibercept in the HAWK and HARRIER phase III studies.”

For Dr. Khanani, perhaps the greatest impact brolucizumab will have for both patients and physicians is a substantially reduced treatment burden. “Patients with neovascular AMD require treatment more immediate relief for his patients. In contrast, brolucizumab during the first year.

**TAKE-HOME**

➤ Brolucizumab is a single-chain antibody fragment and is a smaller molecule compared with other available anti-VEGF therapies.

**FLUOROMETHOLONE**  
*Continued from page 11*

drome, which results from inflammation of the ocular surface, tears, and lacrimal glands.

“The goal is to break the cycle of inflammation,” Dr. Meghpara said.

When treating these patients over the long term, among some “go-to” drugs he notes as safe for chronic use are cyclosporine ophthalmic emulsion 0.05% (Restasis, Allergan), lifitegrast ophthalmic solution 5% (Xiidra, Novartis), and cyclosporine A ophthalmic solution 0.09% (Cequa, Sun Pharmaceuticals).

“These are great drugs for treating dry eye,” Dr. Meghpara said. “However, the beneficial effects of these drugs require time to build up.”

Until those beneficial effects become apparent, he uses fluorometholone acetate for the short term in combination with one of the long-term therapies to obtain more immediate relief for his patients.

“This approach calms the inflammation, and the patients feel better and often see better,” he said.

For dry eye, Dr. Meghpara prescribes fluorometholone acetate twice daily for about four to six weeks. By that time, the benefits of the chronic-use medication are beginning to kick in. Allergic conjunctivitis is the second most common chronic offender seen in cornea practices, especially in the spring and fall when symptoms tend to become more severe.

In these patients, a short controlled course of fluorometholone acetate can calm the ocular surface and provide relief from the characteristic symptoms of tear, itching, and discomfort. Giant papillary conjunctivitis, or contact lens-induced papillary conjunctivitis, tends to appear less often in clinical practice, but it is a common complication associated with wearing of contact lenses.

Despite the lower incidence, these patients seek treatment and can benefit from short-term treatment with fluorometholone acetate, which allows them to resume wearing their lenses more quickly.

Steroids generally are not intended for use while wearing contact lenses. Other less common ocular surface disorders include episcleritis, generally a self-resolving condition that responds rapidly to treatment with fluorometholone acetate, and marginal ulcers. The latter, while not technically an infection, is an inflammatory response to staphylococcal antigens on the eyelid surface.

Dr. Meghpara noted that a steroid in addition to an antibiotic is helpful in this scenario. In blepharitis, a related condition, the inflammation can spill over onto the ocular surface and cause blepharocconjunctivitis or blepharonkeratoconjunctivitis, also responsive to a topical steroid.

“Fluorometholone acetate provides the potency of a strong steroid, but the drug has the side effect profile of a milder steroid,” he concluded. “The drug provides the best of both worlds. I am confident starting treatment with the drug and confident it is going to work. I am concerned about side effects, but not greatly.”

**TAKE-HOME**

➤ When battling inflammation, the ability of a drug to penetrate into the ocular tissues is key. Fluorometholone acetate may fill that role for ophthalmologists.
AMD

(Continued from page 13)

ment anywhere from four to eight weeks,” he said. “When considering the real-world outcomes, the gains in vision are minimal, about eight to 12 letters, compared with the results in the clinical trials. This speaks to the unmet need for durable agents that last longer to decrease the treatment burden.”

Another factor, he noted, is many patients still have active disease despite monthly injections. These patients have persistent fluid and a high need for anti-VEGF therapy. Two weeks after an injection the retina is dry, but by four weeks, the fluid returns.

“Having a more potent drug to control the disease in a patient with a higher VEGF load is a big advantage,” he said. Dr. Khanani is in his clinical practice, brolucizumab fulfills two needs for patients, Dr. Khanani noted. He starts treatment-naive patients with the more durable brolucizumab to control the disease for a longer period. For his previously treated patients who have persistent fluid on monthly injections, their regimen can be switched to brolucizumab to dry the retina and better control the disease.

Patients receive three loading doses of the drug followed by two doses at 8 or 12 weeks based on the HAWK and HARRIER trials.

“Even if patients had been previously treated for AMD, they can be treated according to this schedule, but they may not need the loading doses if the retina is dry after one injection,” Dr. Khanani said.

Dr. Khanani has not observed any significant adverse events in patients he has treated so far in brolucizumab clinical trials or in his clinic after approval. He is, however, aware of higher rates of inflammation in brolucizumab-treated patients in the HAWK and HARRIER studies.

“As with any new drug, we need to watch for any adverse events that can develop in patients who are receiving treatment,” he said.

Patients are encouraged about the increased time between treatments, thus lessening the burden on them and their families, he noted.

“We have not had a new drug for these patients since 2011 when aflibercept was approved. It is exciting for our patients and for physicians to have this new drug that is more durable than the available drugs and achieves better drying of the central retina and better control,” Dr. Khanani concluded.

Beovu was granted a Permanent J code that began Jan. 1, 2020.

Novartis assistance program offers support for patients, caregivers

THROUGH ITS “BEOVU YOUR WAY” program (https://www.yourway.beovu.com/), Novartis provides personalized, one-on-one support for patients undergoing treatment with brolucizumab for age-related macular degeneration (AMD) and their caregivers.

“This is a program that was built by patients and caregivers for patients and caregivers,” said Patrick Mooney, vice president and franchise head of U.S. Ophthalmics at Novartis. “As a responsible company developing a treatment, we believe it is important to understand the holistic needs of the patients and caregivers.”

Novartis developed the treatment support program by conducting in-depth focus groups and interviews in an attempt to understand the areas of the greatest struggles, that is, beyond the physical injections, the areas for which the most support is needed.

“Understanding those factors, not just their journey, but the accompanying emotions and the challenges they face, facilitated the ways in which we can help and support patients in appropriate ways,” Mooney said.

Support offered by the program includes educational materials that are designed to empower patients with wet AMD to facilitate their living safety and independently.

The materials introduce brolucizumab to facilitate patient understanding of their treatment.

Patients receive a personalized welcome kit that provides more detailed information about the program, wet AMD, care specialist support services, and ways to enroll in the program.

Mooney also explained that the program is anchored in several key areas that were dictated by patients and caregivers: assistance with understanding their financial support for eligible patients; reminders and coordination for upcoming appointments; resources to answer questions regarding wet AMD and brolucizumab therapy for patients and family/caregivers; and patient advocacy groups beyond the typical material available or from healthcare providers.

For eligible patients, the Novartis Patient Assistance Foundation assists in seeking financial support, such as co-payment support for commercial patients.

Perhaps the most important component of the program is the access patients have to a unique care specialist committed to understanding the patients’ specific needs and preferences, he noted.

Mooney pointed out that all “care champions” are nurses who have been trained specifically regarding brolucizumab and following specific protocols and safety and efficacy.

“This program has been a highlight and a ‘wow’ factor for patients based on the feedback we are receiving as early as a couple of months after the launch of the program, which coincided with the approval of [brolucizumab] in early October,” Mooney said.

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The number of surgeries performed during residency training varies from institution to institute, and this can raise the question: How many surgeries are adequate to ensure patient safety and good outcomes after cataract surgery?

The complication rates associated with cataract surgeries performed by residents provide approximate information about the learning curve but not about the individual’s competency. The International Council of Ophthalmology’s Ophthalmology Surgical Competency Assessment Rubric (ICO-OSCAR) facilitates an objective assessment of the surgical skills of a novice surgeon for performing a particular surgical task.

Rajesh Vedachalam, MBBS, highlighted the results obtained using the ICO-OSCAR in an analysis of the learning curve. Dr. Vedachalam, from the Department of Cornea, Aravind Eye Care, Puducherry, India, presented the study findings on behalf of Aravind Haripriya, MBBS.

OBSERVATION IS KEY
Dr. Vedachalam pointed out that more manual small-incision cataract surgeries (MSICS) are performed in India during residency training compared with phacoemulsification, and are associated with lower complications rates (1.75% versus 8.2%) among novice surgeons.

Dr. Haripriya and colleagues conducted a prospective cohort study in which they sought to predict the average number of surgeries required for a resident to gain competency in MSICS using ICO-OSCAR. All residents who started residency training at the Aravind Eye Hospital were included. The first 15 procedures and every tenth case thereafter were assessed using ICO-OSCAR, Dr. Vedachalam explained.

The ICO-OSCAR scoring tool contains 20 objectives, and scores each surgical step. The total score is then evaluated. In this study, all surgical complications were documented during the step at which it occurred. A form was completed regarding various factors that may have affected the surgical outcome to determine their effect on the learning curve. The investigators compared the preoperative and postoperative visual acuities for significant differences, Dr. Vedachalam explained.

Twenty residents (mean age, 27.8 years) were included in the study, and two were excluded for excessive absences. Of the 18 remaining (11 women, 7 men), 15 had previous surgical experience with other surgeries.

A total of 2,021 surgeries were performed between September 2016 and May 2018. Surgical complications developed in 62 (3.06%) procedures, with posterior chamber opacification and zonulysis the most common complications.

“This complication rate is much lower than in other studies,” Dr. Vedachalam pointed out.

Twenty-eight (1.38%) patients underwent second surgeries. The mean best-corrected visual acuity at follow-up was 20/20.

POSITIVE FACTORS IN THE SURGICAL OUTCOME
Two factors were found to have a positive impact on the surgical outcome: watching videos of MSICS or observing surgeons perform before operating and the confidence level or mood of the surgeon.

Other influential factors included wet lab practice performed on a simulator and the laterality of the patient’s operated eye.

When the relationship between the ICO-OSCAR score and potential predictive factors was analysis, the number of surgeries performed and simulator practice both had significantly higher scores (p < 0.001 for both comparisons). Other positive factors were previous general surgical experience (p = 0.002) and female gender (p = 0.04). Eye laterality had no role in improving the OSCAR score, a finding that was in contrast to other studies.

“We also found that surgeons who performed micro hand movement activities, such as those during piano playing or eating with chop sticks, did not perform better during surgery,” Dr. Vedachalam said.

The research indicated 119 surgeries were needed to reach competency to achieve a competency score of 80. For a score of 90, 172 surgeries were required.

Other such studies have assessed the numbers of surgeries required as indicators of experience and the complication rates, and the reoperation rate, but did not assess surgical competency of the surgeons or the learning curve, Dr. Vedachalam noted.

“We believe that the measure of competency as measured by the objective ICO-OSCAR in each surgical step and the surgeons’ ability to perform surgeries independently are important and that assessment of competency and learning curve is a strength of our study,” he said.

Dr. Vedachalam pointed out that using the ICO-OSCAR tool, a minimum of 119 MSICS surgeries is recommended to achieve competency with a score of 80 and above.

CONCLUSION
“The positive factors predictive of higher ICO-OSCAR scores are female gender and previous general surgical experience,” he concluded. “Simulator practice before surgical training is correlated with better scores. Residents find that observing surgeries and being in the right frame of mind are useful for better surgical performance.”

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This article is based on Dr. Vedachalam’s presentation at the American Academy of Ophthalmology 2019 annual meeting. Dr. Vedachalam has no financial interest in any aspect of this report.
A RELATIONSHIP EXISTS between the posterior and anterior surfaces of the cornea, such that the posterior surface diminishes the power of the total cornea.

A ratio is believed to exist between the anterior and posterior powers of the cornea that varies from 0.8 to 0.9 in normal eyes. In keratoconus, a progressive eye disease, the normally round cornea thins and begins to bulge into a cone-like shape. The cone shape of the cornea deflects light as it enters the eye on its way to the retina, causing distorted vision in patients.

Wallace Chamon, MD, explained that the ratio is used to estimate an artificial refractive index for the cornea that compensates for the posterior surface of the cornea with its real refractive index of 1.376. Smaller indices are used to compensate for the negative power of the posterior that ranges from 5 to 7 D.

However, in order to calculate the ratio in the refractive indices, some presumptions must come into play, namely, that the factor between the two surfaces is a constant factor in all kinds of eyes, regardless of whether they are normal or not and the cornea has a constant thickness, said Dr. Chamon, adjunct professor of ophthalmology, Department of Ophthalmology and Visual Sciences, Paulista School of Medicine, Federal University of São Paulo, São Paulo, Brazil, and volunteer clinical faculty, Department of Ophthalmology and Visual Sciences, University of Illinois at Chicago.

“That with these assumptions, there is good accuracy in determining the total corneal power by measuring only the anterior surface of the cornea,” he said.

While that last statement has been a consis-
tently held belief, Dr. Chamon and his colleagues challenged both presumptions. He was joined in his research by Rafael Kobayashi, MD, Felipe M. C. Taguchi, MD, and Ibraim V. Vieira, MD.

Regarding keratoconic eyes, Dr. Chamon pointed out that the progression of thinning of the cornea differs from that in normal eyes and that progression is more aggressive toward the apex or the thinnest part of the cone.

According to Dr. Chamon, when comparing maps of thinning progression, ophthalmologists can see clearly that a keratoconic eye does not follow the progression of thinning in normal eyes.

“In a normal cornea, the ratio between the anterior and posterior surfaces can be very predictable,” he explained. “However, if we assume that the keratoconus begins with the thinning of the cornea and leads to progression to a steeper cornea, we have to assume that the ratio has changed because with corneal thinning, the posterior curvature will increase.”

**POINTING TO EXAMPLES**

As an example, Dr. Chamon demonstrated that in a normal eye based on Gullstrand’s theory, the anterior surface has 7.7 mm of curvature, leading to 43.05 D using the refractive index of 1.3315. The posterior cornea would have 6.8 mm of curvature. In contrast, in a keratoconic eye with an anterior surface curvature of 7.7 mm, the posterior curvature would be even steeper at 6.00 mm. In the normal eye, the ratio would be 0.883 compared with 0.857 in the keratoconic eye.

“This means that in keratoconus, the posterior corneal surface theoretically has a much higher effect than it does in normal eyes,” Dr. Chamon said.

To determine if their theory was correct, Dr. Chamon and colleagues analyzed every patient who underwent a Scheimpflug examination using the Pentacam in three Brazilian institutions from October 2012 through January 2019.

After duplicate examinations of the same eyes were excluded, ultimately 33,638 examinations were unique. Of those, the examinations that were considered unreliable, abnormal, or performed after a corneal surgery were removed. The final number of unique examinations was 24,060. Of these, 16,192 were normal, and 7,868 were keratoconic. The Pentacam provided nine classifications of the keratoconic eyes from normal to grade 4.

Dr. Chamon showed that in normal eyes the average anterior-posterior ratio was 0.82. In those with possible keratoconus, no difference was detected between normal eyes and possible keratoconus. As the keratoconic grades increased, the ratios ranged from 0.82 down to 0.79 in grades 3 to 4 as expected, and 0.80 in grade 4 likely because of the small number of patients, he noted.

**CONCLUSION**

Dr. Chamon concluded that the anterior:posterior ratio has been well determined for normal corneas.

“Keratoconic corneas present a different anterior:posterior ratio with a greater effect of the posterior interface,” he said. “The more advanced the keratoconus, the greater the influence is. Formulas that estimate the total corneal power and, therefore, astigmatism, should not be used in eyes with keratoconus.”

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The early results of a feasibility study of a visual cortical prosthesis system (Orion, Second Sight Medical Products) indicate that the product has significant potential to provide some functional vision to previously sighted patients with no light perception with a good safety profile.

“The goal of this study was to develop a visual cortical prosthetic device that stimulates the visual cortex directly by bypassing the eyes and the optic apparatus in blind patients,” said Nader Pouratian, MD, PhD. “This approach was designed to leverage the available and approved retinal prosthetic technology.”

Dr. Pouratian is professor and vice chairman of Academic Affairs, Department of Neurosurgery, David Geffen School of Medicine, University of California Los Angeles.

The device uses glasses, a camera implanted into the glasses, and an adapted video processing unit that converts the video input into a stimulation pattern. An electrode array is implanted over the medial occipital lobe over the V1 and V2 areas, and facilitates communication through wireless radio-frequency communication and power.

This phase I interim feasibility study, which is the first test performed in humans to evaluate this device, evaluated the safety of placing and activating an electrode array on the medial surface of the occipital lobe in blind patients, the functionality of the device in providing some artificial vision, its utility in these patients, as well as the nature of the vision provided. The investigators also wanted to obtain user input in order to iterate the design of the device and software and proceed with the next study phase, according to Dr. Pouratian.

SAFETY

The primary concern with an experiment such as this, Dr. Pouratian explained, was induction of seizures as a result of direct cortical stimulation,” he explained, and also pointed out, that the investigators were unclear about what results to anticipate from the blind patients using the device.

The study included patients who had been previously sighted and who became blind (no light perception vision or bare light perception) as the result of any cause other than damage to the visual cortex, which included optic neuropathy, head trauma from various causes, endophthalmitis, and congenital glaucoma. Patients with brain injuries were excluded. Five men and one woman were included in the study. The average duration of blindness was 15 years, Dr. Pouratian recounted.

Six adverse events related to the implant procedure or the device occurred in two of the six patients. These included a seizure in one patient, which occurred in a clinical setting where the initial three months of testing took place; the patient recovered and returned home the same day. Nonserious events in two patients were bilateral hand twitching, headache, visual aura, and visual phenomen-
UCLA Health neuroscientists use EEG to observe brain activity in Jason Esterhuizen. He is only the second recipient of an experimental brain implant that helps blind people detect motion and distinguish light from dark. (Image courtesy of UCLA Health)

The other four patients had no events related to the device or procedure, Dr. Pouratian reported.

**FUNCTIONALITY**

Another study end point was the determination of the reliability of the device in eliciting phosphenes. Among the six patients, the average threshold at which phosphenes were perceived was about 2,000 microamps to obtain visual perception of a flash or circle of light.

"Importantly, of the 60 contacts that were implanted over the primary and secondary visual cortices, the vast majority of the contacts resulted in a perceived phosphene," he commented.

During testing, the implanted patients were evaluated with a square localization task. Dr. Pouratian demonstrated that with the device turned on, the patients were able to locate the square; this was in contrast to testing without the device during which the investigators found a great deal of variability in the patients’ ability to locate the square. All but one patient showed improvement in their ability to complete this task after using the device for 12 months.

Another test evaluated the identification of the direction of motion, in which lines moved across the screen viewed by the patients. With the device off, they were unable to detect the direction of motion and with the device on they were able to do so. After 12 months, all patients showed improvements in detecting the direction of motion.

The final test was that of grating visual acuity, a much more difficult task in which gratings were presented for 5 seconds.

At the six-month time point, no patients scored on the scale either with the device on or off. At 12 months, two patients scored on the scale with the device on (2.8 and 2.2 logarithm of the minimum angle of resolution visual acuity).

An important consideration, Dr. Pouratian explained, is that the previously described tasks are artificial, not real, vision.

"A quality-of-life assessment by all five patients with 12-month follow-up reported mild or positive improvement with use of the device," he said.

Generally, the patients have reported success with use of the Orion in practical everyday tasks, such as the ability to find cars parked on the side of the street, find a cue ball on a pool table with no problem, determine if they were walking from left to right or right to left along a wall, and sort laundry.

A comparison with the Argus II, a retinal prosthesis also from Second Sight Medical Products, at 12 months showed that patients had relatively similar outcomes in functional improvement with both devices.

"The early results with the Orion are promising and the device has a favorable safety profile," Dr. Pouratian concluded. "A seizure occurred in one patient in a controlled setting when stimulation paradigms were being explored. No system failures occurred. All subjects with 12 month follow-up perceived phosphenes and reported functional improvements. Although this study included only a small number of patients, the results are encouraging. Visual rehabilitation is important; we are providing artificial vision and not restoring vision, which is an important consideration."

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The recommended dosage is one drop in the affected eye(s) once daily in the evening.

**IMPORTANT SAFETY INFORMATION**

**WARNINGS AND PRECAUTIONS**

**Bacterial Keratitis:** There have been reports of bacterial keratitis associated with the use of multiple-dose containers of topical ophthalmic products. These containers had been inadvertently contaminated by patients who, in most cases, had a concurrent corneal disease or a disruption of the ocular epithelial surface.

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The most common ocular adverse reaction observed in controlled clinical studies with Rhopressa® dosed once daily was conjunctival hyperemia, reported in 53% of patients. Other common (approximately 20%) adverse reactions were: corneal verticillata, instillation site pain, and conjunctival hemorrhage. Instillation site erythema, corneal staining, blurred vision, increased lacrimation, erythema of eyelid, and reduced visual acuity were reported in 5-10% of patients. The corneal verticillata seen in Rhopressa®-treated patients were first noted at 4 weeks of daily dosing. This reaction did not result in any apparent visual functional changes. Most corneal verticillata resolved upon discontinuation of treatment.

Please see brief summary of full Prescribing Information on the adjacent page.


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RHOPRESSA® (netarsudil ophthalmic solution) 0.02%
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BRIEF SUMMARY
Consult the Full Prescribing Information for complete product information.

INDICATIONS AND USAGE
RHOPRESSA® (netarsudil ophthalmic solution) 0.02% is indicated for the reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension.

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WARNINGS AND PRECAUTIONS

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ADVERSE REACTIONS

Clinical Trials Experience
Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.

The most common ocular adverse reaction observed in controlled clinical studies with RHOPRESSA dosed once daily was conjunctival hyperemia which was reported in 53% of patients. Other common (approximately 20%) ocular adverse reactions reported were: corneal verticillata, instillation site pain, and conjunctival hemorrhage. Instillation site erythema, corneal staining, blurred vision, increased lacrimation, erythema of eyelid, and reduced visual acuity were reported in 5-10% of patients.

Corneal Verticillata
Corneal verticillata occurred in approximately 20% of the patients in controlled clinical studies. The corneal verticillata seen in RHOPRESSA-treated patients were first noted at 4 weeks of daily dosing. This reaction did not result in any apparent visual functional changes in patients. Most corneal verticillata resolved upon discontinuation of treatment.

USE IN SPECIFIC POPULATIONS

Pregnancy
There are no available data on RHOPRESSA use in pregnant women to inform any drug associated risk; however, systemic exposure to netarsudil from ocular administration is low. Intravenous administration of netarsudil to pregnant rats and rabbits during organogenesis did not produce adverse embryofetal effects at clinically relevant systemic exposures.

Animal Data
Netarsudil administered daily by intravenous injection to rats during organogenesis caused abortions and embryofetal lethality at doses ≥0.3 mg/kg/day (126-fold the plasma exposure at the recommended human ophthalmic dose [RHOD], based on Cmax). The no-observed-adverse-effect-level (NOAEL) for embryofetal development toxicity was 0.1 mg/kg/day (40-fold the plasma exposure at the RHOD, based on Cmax).

Netarsudil administered daily by intravenous injection to rabbits during organogenesis caused embryofetal lethality and decreased fetal weight at 5 mg/kg/day (1480-fold the plasma exposure at the RHOD, based on Cmax). Malformations were observed at ≥3 mg/kg/day (1330-fold the plasma exposure at the RHOD, based on Cmax), including thoracogastroschisis, umbilical hernia and absent intermediate lung lobe. The NOAEL for embryofetal development toxicity was 0.5 mg/kg/day (214-fold the plasma exposure at the RHOD, based on Cmax).

Lactation
There are no data on the presence of RHOPRESSA in human milk, the effects on the breastfed infant, or the effects on milk production. However, systemic exposure to netarsudil following topical ocular administration is low, and it is not known whether measurable levels of netarsudil would be present in maternal milk following topical ocular administration. The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for RHOPRESSA and any potential adverse effects on the breastfed child from RHOPRESSA.

Pediatric Use
Safety and effectiveness in pediatric patients below the age of 18 years have not been established.

Geriatric Use
No overall differences in safety or effectiveness have been observed between elderly and other adult patients.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility
Long-term studies in animals have not been performed to evaluate the carcinogenic potential of netarsudil. Netarsudil was not mutagenic in the Ames test, in the mouse lymphoma test, or in the in vivo rat micronucleus test. Studies to evaluate the effects of netarsudil on male or female fertility in animals have not been performed.

Manufactured for: Aerie Pharmaceuticals, Inc., Irvine, CA 92614, U.S.A.
For more information, go to www.RHOPRESSA.com or call 1-855-AerieRx (1-855-237-4379).

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U.S. Patent Nos.: 8,450,344; 8,394,826; 9,096,569; 9,415,043.
Neurotrophic keratopathy: Finding different treatments

New breakthroughs restore corneal sensation, vision in patients

By Lynda Charters; Reviewed by Francisco C. Figueiredo, MD, PhD, FRCOphth

Neurotrophic keratopathy: an uncommon degenerative disease. Depending on the severity of the disease, the clinical manifestations can range from punctate epitheliopathy, persistent epithelial defects, to corneal perforation. A specific therapeutic approach is required to address the disease presentation, which is described by Mackie’s classification of three stages of severity. The clinical presentation is always the same regardless of the etiology, according to Francisco C. Figueiredo, MD, PhD, FRCOphth. Stage I is characterized by epithelial hyperplasia and irregularity, haze, punctate keratopathy, superficial vascularization, and stromal scarring; stage II by a superior epithelial defect usually in the superior quadrant, with smooth and rolled edges of the defect, and stromal edema; and stage III corneal ulceration, stromal melting, and even perforation. The causes of the disease are highly variable and range from genetic, ocular, neurological, and systemic, with herpes virus, post-surgical trigeminal nerve damage, chemical burns, and diabetes causing the preponderance of the cases; according to Dr. Figueiredo, professor of ophthalmology, Department of Ophthalmology, Newcastle University, Newcastle-upon-Tyne, United Kingdom.

DIAGNOSIS AND MANAGEMENT

Patients present with nonspecific complaints such as dryness, discomfort, photophobia, decreased vision, and worse symptoms upon awakening that are aggravated by environmental factors such as air conditioning and personal computers. Slit-lamp examinations show findings similar to dry eye disease, i.e., decreased tear film breakup time, superficial punctate keratitis, and decreased blinking. Dr. Figueiredo noted that the clinical picture may progress to show healing of the epithelial defect with smooth and rolled edges with or without stromal involvement. A diagnosis can be established by testing the corneal sensation using cornealesthesiometry in the central and peripheral parts of the cornea. Touching the cornea with a cotton swab is a qualitative test of sensation. The most widely used test is the Cochet-Bonnet direct contact test. This noninvasive test measures corneal sensitivity. In vivo confocal microscopy can provide quantitative and qualitative assessment of the corneal nerves and can show mild to total damage of the corneal nerves. A neurologic examination can provide a full assessment of the cranial nerves.

MANAGING DISEASE

Management requires grading of the disease stage and an array of medical and surgical interventions. Dr. Figueiredo noted that with stage I disease, it is imperative to review the use of all the topical treatments, and discontinue most of them, particularly the ones with preservatives because of potential toxicities that can worsen the corneal surface. This may be combined with “unpreserved lubricants, i.e., artificial tears and ointments, and punctal plugs,” he said. In stage II disease, he recommends the same approach as in stage I with the addition of prophylactic topical antibiotics; eyelid closure that includes tarsorrhaphy, taping, pads, or botulinum toxin; bandage contact lens; serum eye drops, including autologous/allogeneic; and amniotic membrane transplantation in some cases. Stage III requires all the factors in stages I and II plus topical matrix metalloproteinase inhibitors to prevent collagen layer breakdown, tissue adhesives plus amniotic membrane plus bandage contact lens for small perforations, and surgery such as corneal gluing, tectonic lamellar or penetrating keratoplasty for larger perforations.

NEWER TREATMENTS

The newest treatments include the use of ReGenestTing Agent, which facilitates reconstruction of the extracellular matrix that will help tissue repair and regeneration. Cacicol (Thea Labs), a new matrix therapy to promote corneal healing, is currently in a clinical trial. However, the results are as of yet unpublished. Recombinant human nerve growth factor (rhNGF), a topical therapy applied six times daily for eight weeks, also is being used rather successfully in moderate to severe neurotrophic keratopathy that has been refractory to surgical treatment; the product was approved recently in the United States, and is available under the name Oxervate (cenegermin, Dompe).

Direct corneal neurotization involves transplanting contralateral supraorbital and supratrochlear branches of the ophthalmic division of the trigeminal nerve. Indirect neurotization involves using sural nerve transplantation that connects the contralateral branches of the ophthalmic division of the trigeminal nerve, Dr. Figueiredo explained. Dr. Figueiredo described the case of a 24-year-old man who sustained severe ocular chemical burns bilaterally and underwent a series of repeated treatments that provided partial healing in the left eye and not in the right eye. According to Dr. Figueiredo, he began instilling Oxervate in the right eye of the patient and after only eight weeks was completely healed.

CONCLUSION

According to Dr. Figueiredo, rhNGF is promising and has shown extremely good results. “Neurotrophic keratopathy is a chronic, serious potentially blinding and refractory corneal degenerative disease that often poses significant treatment challenges, especially when complicated by other concurrent ocular comorbidities, such as exposure keratopathy, dry eyes, and limbal stem cell deficiency,” he concluded. “New treatments, such as rhNGF, neurotization, and matrix therapy are helpful and has completely changed our current treatment protocol.”

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This article is based on Dr. Figueiredo’s presentation at the American Academy of Ophthalmology 2019 annual meeting. Dr. Figueiredo has no financial interest in the subject matter of this report.
AI screening: Allowing physicians to see eyes more clearly from afar

System for diabetic retinopathy offers reduced cost, faster treatment for patients

By Lynda Charters; Reviewed by Srinivas R. Sadda, MD

THE NUMBER OF people affected by diabetes is expected to exceed 640 million by 2040. That fact fosters an environment in which the barriers of the current telescreening programs, i.e., cost and delays in image grading, can be surmounted and diabetic retinopathy (DR) detected earlier followed by rapid treatment.

According to Srinivas R. Sadda, MD, the availability of artificial intelligence (AI) systems should reduce the cost, improve the performance, and increase the efficiency of point-of-care DR screening programs.

“Automated screening for DR would be of value and this may be the right time for it, considering that the implementation of AI is on the upswing,” said Dr. Sadda, the Stephen J. Ryan Endowed Chairman, professor of ophthalmology, Doheny Eye Institute, and University of California Los Angeles.

A number of automated systems for DR screening are available and are CE marked, namely, Ret-Marker (Critical Health), iGradingM (DigitalHealthcare), IDx-DR (IDx), and EyeArt (Eyenuk). Several of these systems were assessed for the National Health Service in a study,1 in which Dr. Sadda and colleagues participated as the adjudicating reading center.

THE UTILITY OF DR SCREENING

Of the listed programs, the IDx-DR system screening solution was cleared in 2018 by the FDA. The system demonstrated a sensitivity of 87%, specificity of 90%, and imageability of 96%, according to Dr. Sadda. A possible limitation of this system is that it was approved for use with only one camera, the Topcon non-mydriatic camera, which may not be applicable in communities in which different cameras are used, Dr. Sadda pointed out.

In contrast, the EyeArt system can work with many camera systems. In a study in which Dr. Sadda and colleagues evaluated this system,2 they evaluated 850,908 images obtained from 101,710 patients from an EyePACS telescreening database. The investigators reported that the EyeArt system had a sensitivity of 91.3% and specificity of 91.1% (area under the receiver operating curve, 0.965) for detecting DR that required referral.

The Diabetic Retinopathy Clinical Research Protocol AA study is currently in the pipeline, and the hope is that this study will shed light on whether the peripheral retinal DR lesions should be considered in patients being assessed for disease severity and prognosis, according to Dr. Sadda.

“We are excited at the prospect of using the DR screening systems to study and quantify lesions throughout the retina,” he said.

The outputs of these systems are based on the International Clinical Diabetic Retinopathy severity scale, with referable DR defined as moderate or greater nonproliferative diabetic retinopathy (NPDR) or the presence of macular edema and vision-threatening DR defined as severe or greater NPDR or the presence of macular edema.

The purpose of this study was to determine the ability of the system to detect referable and vision-threatening DR on two-field nonmydriatic fundus photographs and determine the sensitivity and specificity.

This ability was compared with the clinical reference standard, which is standardized, adjudicated Early Treatment of Diabetic Retinopathy Study (ETDRS) grading of four-wide field stereoscopic mydriatic fundus photographs, Dr. Sadda recounted.

In this study, two-field nonmydriatic photographs were obtained and submitted for the automated AI-based analysis. The eyes then were dilated and four-wide field stereoscopic mydriatic fundus photography was carried out, he explained.

The study population included 1,830 that met the inclusion criteria and ultimately 1,674 were evaluated by the EyeArt system. The cohort was comprised of 50.3% men (mean age, 53.9 years; 73.3% Caucasian; 76.9% type 2 diabetes).

The study found that of the 1,194 EyeArt referable DR-negative eyes, 1,180 were found by the Wisconsin Fundus Photograph Reading Center to be referable DR-negative and 14 to be referable DR-positive.

“In all of the 14 cases deemed to be DR-negative by the EyeArt system, the level of the DR was low,” Dr. Sadda pointed out.

Discussing the false-positive cases, those for which the reading center saw no evidence of referral-warranted DR, Dr. Sadda explained that most cases had either some DR or other non-DR ocular diseases.

“Overall, the sensitivity and specificity of the system were 95.5% and 86.5%, respectively, if the ungradable cases (12.5%) were diluted,” he said.

The sensitivity and specificity values with no dilation were 95.5% and 86.0%, respectively.

CONCLUSION

According to Dr. Sadda, the EyeArt AI eye screening system for DR has high sensitivity and specificity for referable versus nonreferable DR compared with the standardized, adjudicated ETDRS grading of four-wide field stereo images.

“The system meets the pre-determined eye level sensitivity and specificity endpoints,” he concluded.

“The hope is that these systems will be useful tools to help our patients in telescreening programs.”

REFERENCES


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This article is adapted from Dr. Sadda’s presentation at the American Academy of Ophthalmology 2019 annual meeting. Dr. Sadda has received National Eye Institute Small Business Innovation Research and Small Business Technology Transfer grants in collaboration with Eyenuk.
Detecting EBMD can be tricky in some cases, but Dr. Rapuano explained that fluorescein staining will often make it readily apparent. When deciding whether to treat, he shared some pearls.

“If there was no negative staining or irregularity on topography or K readings centrally, then the problem probably does not require treatment,” he explained. “Consider treating if the patient is symptomatic or awaiting cataract or refractive surgery and wait about six weeks before re-checking the biometry twice to ensure the stability.”

Treatment can consist of epithelial debridement alone, or debridement in conjunction with diamond burr polishing or excimer laser phototherapeutic keratectomy (PTK). The process of debridement includes removal of all loose or irregular epithelium and basement membrane with a cellulose sponge or blade. Dr. Rapuano said he likes to perform diamond burr polishing, which begins with epithelial debridement. He then uses a 5-mm diameter diamond-dusted burr to polish Bowman’s layer uniformly over the entire cornea for about five to six seconds to ensure that all reduplicated basement membrane has been removed.

According to Dr. Rapuano, some patients who undergo this procedure may have transient haze postoperatively that can be alleviated with steroids. The key when performing excimer laser PTK, after debridement, he advised, is treating the entire epithelial defect with a uniform ablation of only about 5 μm.

This pathology presents a creamy white mild to moderately elevated lesion often in the peripheral cornea, but occasionally is seen centrally. It can be associated with EBMD and can cause dry eye symptoms and irregular astigmatism despite a peripheral location.

Dr. Rapuano advised treating in the presence of any centrally located irregular astigmatism. If the patient is awaiting a cataract or refractive surgery, he also suggested waiting about six weeks after treatment before re-checking the biometry before any surgery.

The treatment options include lamellar keratectomy using a blade with or without diamond burr polishing. In some cases, he noted, the nodules will easily peel off of Bowman’s layer and leave a smooth surface. In cases in which the underlying stroma remains unsmooth, he performs excimer laser PTK with or without mitomycin C (MMC).

If PTK is performed, he usually uses MMC. During this procedure, he advises using a blade to remove the nodules and subepithelial fibrosis and then smooth the surface with PTK. MMC 0.02% should be applied on an 8-mm sponge for 60 seconds and then irrigated with 30 cc of saline.

This pathology, which appears as a white calcium deposit, is frequently related to chronic inflammation but may be idiopathic.

If located centrally, the vision can be affected. However, if elevated and in the periphery vision also can be affected. In cases when it is elevated or irregular, it can cause patient discomfort.

Dr. Rapuano advised performing a workup to determine the etiology.

The treatment is ethylenediaminetetraacetic acid (EDTA) chelation. The key point in this procedure is removal of the epithelium over all of the calcium using a number 15 blade or Tooke knife.

The presence of any epithelium will prevent absorption of the EDTA. Diluted EDTA 3% to 4% should be applied to the calcium on a cellulose sponge or cotton-tipped applicator for 10 to 45 minutes until the calcium has dissolved.

“Corneal irregularities and opacities are common and they can affect comfort, clarity, and corneal curvature, making it especially important to diagnose before cataract and refractive surgeries,” Dr. Rapuano concluded. “There are numerous techniques to identify them, and there are excellent treatment options for clinically relevant pathology.”
UBM, AS-OCT viable for use with anterior segment lesions

Physicians find that technologies complement each other, excel in different scenarios

By Lynda Charters; Reviewed by Carol L. Shields, MD

When considering ultrasound biomicroscopy (UBM) or anterior-segment optical coherence tomography (AS-OCT), ophthalmologists are finding that they both are excellent in different scenarios because they complement each other.

UBM makes use of sound waves to obtain images of the anterior segment of the eye. In contrast, AS-OCT uses light waves for the same task, according to Carol L. Shields, MD, chief of the Ocular Oncology Service, Wills Eye Hospital, Philadelphia.

In her practice, she prefers UBM to get the best look at the iris stroma, iris pigment epithelium, and the ciliary body, in which the lesions are “deep and dark.” In contrast, AS-OCT, she noted, is better for lesions that are very “superficial and light.”

The technology also may be better for use in very young patients, those unable to cooperate, and in the presence of a thin cornea or infection. Some cysts in the iris stroma and lesions in the conjunctiva can be visualized by AS-OCT.

Dr. Shields described a comparative study that looked at the use of both of the technologies in 200 consecutive cases of anterior-segment tumors (Ophthalmology 2011;118:1297-1302).

“We found the UBM allowed better visualization of all margins and overall better images for the entire tumor configuration,” she said.

Dr. Shields demonstrated cases supporting these views. “AS-OCT provides nice details in these cases,” she said. “Often, the posterior margin of the lesion is not visible. For solid iris lesions, UBM is better than AS-OCT. For iris/ciliary body lesions, UBM better displays all margins compared with AS-OCT. For iris tumors that extend into the ciliary body, we strongly prefer UBM.”

NOTABLE CASES

Case I was that of a 45-year-old white woman referred with a ciliary body melanoma. Upon dilation, the lesion looked similar to an iris pigment epithelial cyst. UBM showed the cyst “beautifully,” according to Dr. Shields, as did AS-OCT.

In this case, both provided good images, but UBM was more reliable. This turned out to be a case of an iris pigment epithelial cyst and not melanoma.

Case II was an 84-year-old white woman with an iris stromal lesion that had previously been aspirated but recurred. UBM showed that the cyst did not extend into the ciliary body; AS-OCT showed fluid and septations within the cyst that were not visible on the UBM images.

Case III was a 6-year-old boy with an iris lesion in the inferonasal iris of the left eye. UBM in such a case can be performed in the office or the operating room. The image showed a multicystic ciliary body mass that suggested a medulloepithelioma confirmed by fine-needle aspiration biopsy of the anterior portion. The patient underwent plaque radiotherapy.

Case IV, a 6-year-old boy, presented with a red eye with some conjunctivitis and a small mass in the angle at 4 o’clock. UBM demonstrated a solid tumor that was confirmed by a needle biopsy to be ciliochoroidal Langhans histiocytosis. The patient was treated with low-dose plaque radiotherapy to which the tumor was highly responsive.

Case V was that of a 16-year-old girl with an iris abnormality that could have been a melanoma requiringenucleation. UBM of the affected eye showed a thickened iris compared with the healthy fellow eye. Dr. Shields considered a diffuse iris melanoma. AS-OCT showed a pathognomonic finding. Treatment included topical steroids that saved her from enucleation.

A new generation of swept-source AS-OCT (Anterior) is being developed by Heidelberg Engineering. This instrument is not yet approved by the FDA and remains under study.

“UBM and AS-OCT are critical for assessment of anterior segment tumors. I believe that the two techniques are complementary,” Dr. Schields concluded. “UBM is preferred if the tumor is ‘deep and dark’ in the ciliary body or angle and AS-OCT if the tumor is ‘superficial’ on the anterior surface of the iris or cornea.”

TAKE-HOME

- Ultrasound biomicroscopy and anterior-segment optical coherence tomography are better at some tasks than others, but both are valuable imaging technologies.

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This article is based on Dr. Shields’ presentation at the American Academy of Ophthalmology’s 2019 annual meeting. Dr. Shields has no financial interest in this subject matter.
Change the outlook for dry eye disease

INDICATIONS AND USAGE
CEQUA™ (cyclosporine ophthalmic solution) 0.09% is a calcineurin inhibitor immunosuppressant indicated to increase tear production in patients with keratoconjunctivitis sicca (dry eye).

IMPORTANT SAFETY INFORMATION
WARNINGS AND PRECAUTIONS
Potential for Eye Injury and Contamination: To avoid the potential for eye injury and contamination, advise patients not to touch the vial tip to the eye or other surfaces.
Use with Contact Lenses: CEQUA should not be administered while wearing contact lenses. If contact lenses are worn, they should be removed prior to administration of the solution. Lenses may be reinserted 15 minutes following administration of CEQUA ophthalmic solution.

ADVERSE REACTIONS
The most common adverse reactions reported in greater than 5% of patients were pain on instillation of drops (22%) and conjunctival hyperemia (6%). Other adverse reactions reported in 1% to 5% of patients were blepharitis, eye irritation, headache, and urinary tract infection.

Please see brief summary of Full Prescribing Information on the adjacent page.

Brief Summary of Prescribing Information for CEQUA™ (cyclosporine ophthalmic solution) 0.09%, for topical ophthalmic use

CEQUA™ (cyclosporine ophthalmic solution) 0.09%
See package insert for Full Prescribing Information.

INDICATIONS AND USAGE
CEQUA ophthalmic solution is a calcineurin inhibitor immunosuppressant indicated to increase tear production in patients with keratoconjunctivitis sicca (dry eye).

CONTRAINDICATIONS
None.

WARNINGS AND PRECAUTIONS
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Use with Contact Lenses
CEQUA should not be administered while wearing contact lenses. If contact lenses are worn, they should be removed prior to administration of the solution. Lenses may be reinserted 15 minutes following administration of CEQUA ophthalmic solution.

ADVERSE REACTIONS
Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In clinical trials, 769 patients received at least 1 dose of cyclosporine ophthalmic solution. The majority of the treated patients were female (83%).

The most common adverse reactions reported in greater than 5% of patients were pain on instillation of drops (22%) and conjunctival hyperemia (6%). Other adverse reactions reported in 1% to 5% of patients were blepharitis, eye irritation, headache, and urinary tract infection.

USE IN SPECIFIC POPULATIONS
Pregnancy
Risk Summary
There are no adequate and well-controlled studies of CEQUA administration in pregnant women to inform a drug-associated risk. Oral administration of cyclosporine to pregnant rats or rabbits did not produce teratogenicity at maternally toxic doses of 30 mg/kg/day in rats and 100 mg/kg/day in rabbits, as indicated by increased pre- and postnatal mortality, reduced fetal weight, and skeletal retardations. These doses (normalized to body weight) were approximately 3200 and 21,000 times higher than the maximum recommended human ophthalmic dose (MRHOD) of 1.5 mcg/kg/day, respectively. No adverse embryofetal effects were observed in rats or rabbits receiving cyclosporine during organogenesis at oral doses up to 17 mg/kg/day or 30 mg/kg/day, respectively (approximately 1800 and 6400 times higher than the MRHOD, respectively).

An oral dose of 45 mg/kg/day cyclosporine (approximately 4800 times higher than MRHOD) administered to rats from Day 15 of pregnancy until Day 21 postpartum produced maternally toxicity and an increase in postnatal mortality in offspring. No adverse effects in dams or offspring were observed at oral doses up to 15 mg/kg/day (approximately 1600 times greater than the MRHOD).

Lactation
Risk Summary
Cyclosporine blood concentrations are low following topical ocular administration of CEQUA. There is no information regarding the presence of cyclosporine in human milk following topical administration or on the effects of CEQUA on breastfed infants and milk production. Administration of oral cyclosporine to rats during lactation did not produce adverse effects in offspring at clinically relevant doses. The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for CEQUA and any potential adverse effects on the breastfed child from cyclosporine.

Pediatric Use
The safety and efficacy of CEQUA ophthalmic solution have not been established in pediatric patients below the age of 18.

Geriatric Use
No overall differences in safety or effectiveness have been observed between elderly and younger adult patients.

PATIENT COUNSELING INFORMATION
Handling the Vial
Advise patients to not allow the tip of the vial to touch the eye or any surface, as this may contaminate the solution. Advise patients also not to touch the vial tip to their eye to avoid the potential for injury to the eye.

Use with Contact Lenses
CEQUA should not be administered while wearing contact lenses. Patients with decreased tear production typically should not wear contact lenses. Advise patients that if contact lenses are worn, they should be removed prior to the administration of the solution. Lenses may be reinserted 15 minutes following administration of CEQUA ophthalmic solution.

Administration
Advise patients that the solution from one individual single-use vial is to be used immediately after opening for administration to one or both eyes, and the remaining contents should be discarded immediately after administration.

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Gene therapy zeroes in as LHON treatment

Research indicates positive results in patients receiving treatment

By Lynda Charters; Reviewed by Jiajia Yuan, PhD

Gene therapy for Leber’s hereditary optic neuropathy (LHON) seems to be the first promising treatment for the disease.

LHON, a maternally inherited disease, causes optic nerve atrophy that in most cases results in simultaneous or sequential bilateral visual loss. Disease onset typically happens in patients between 14 to 21 years of age.

The most frequently occurring offending mutation is ND4 that appears in about 90% of Chinese patients and in about 50% to 60% of U.S. patients, according to Jiajia Yuan, PhD, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei, China.

No treatment is currently available for this disease.

**LHON TREATMENT**

Dr. Yuan and colleagues initially treated nine patients with LHON with gene therapy in 2011. With this first attempt, she reported seven of the nine patients had a significant improvement of 0.3 logarithm of the minimum angle of resolution (logMAR) VA at 36 months in the best-corrected visual acuity (BCVA).

“We saw a durable response in six of these patients out to 75 to 90 months after treatment,” she said. “In addition, a bilateral improvement was achieved, as also was observed by other groups investigating gene therapy.”

**GENE THERAPY TRIAL**

These promising results prompted a second multicenter gene therapy trial that began in 2017 that includes 149 Chinese patients and 10 Argentinean patients.

According to Dr. Yuan, the patients, who ranged in age from 7 to 45 years, received a fixed dose of 1 x 10^10 mg/eye for all patients, regardless of age, Dr. Yuan explained.

**PROMISING RESULTS**

“The treatment was found to be well tolerated and no severe adverse effects occurred,” she said.

Keratitis developed in one eye at one month and anterior inflammation in one eye at three months that were both considered to be unrelated to the treatment.

Ocular hypertension was the most common adverse event that developed in 27.04% of eyes that decreased slowly over time after cessation of the steroid.

A significant improvement in the BCVA occurred in 63.21% (67 of 106 patients) at 12 months. The rest of the patients had not reached the 12-month time point at the time of this report. Similar to the initial study, the patients showed bilateral improvement.

“This is a real-world study, in that there was no specific patient selection. The patients’ ages spanned a wide range as did the time of disease onset and the pretreatment BCVA.”

Dr. Yuan explained. “The patients’ ages spanned a wide range as did the time of disease onset and the pretreatment BCVA.”

An evaluation of only the Argentinean patients showed that all had improvement in the BCVA.

“These patients fared better overall than the other patients in the group, with the average improvement in the treated eye was 0.6 logMAR and the average improvement in the untreated eye was 0.9 logMAR,” Dr. Yuan pointed out.

Importantly, this improvement in the BCVA is highly relevant for the ability of patients to function well during everyday tasks.

And the researchers saw results with the patients that were treated.

Dr. Yuan related that three months after treatment, a patient was able to cook and watch sporting events on the computer.

Dr. Yuan noted that gene therapy is a promising approach for patients with LHON.

“Nine patients were treated in 2011 to 2012 and we continue to follow them. This is the longest term data from human gene therapy to date.”

“Nine patients were treated in 2011 to 2012 and we continue to follow them. This is the longest term data from human gene therapy to date.”

**TAKE-HOME**

- Gene therapy for Leber’s hereditary optic neuropathy appears highly promising for increasing the best-corrected visual acuity in this patient population.

**CONCLUSIONS**

According to Dr. Yuan, nearly two-third of 106 patients who reached the 12-month follow-up point achieved a clinically significant improvement in the BCVA.

“Importantly, no serious adverse events occurred in the real-world studies,” she said. “We are very excited about the potential impact of gene therapy on this disease.”

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This article is based on Dr. Yuan’s presentation at the American Academy of Ophthalmology’s 2019 annual meeting. Dr. Yuan has no financial interest in any aspect of this report.
Gene therapy offers treatment for X-linked retinitis pigmentosa
Research finds the highest doses had best responses with no retinal toxicity

By Lynda Charters; Reviewed by Paulo E. Stanga, MD

THE RESULTS OF treatment of X-linked retinitis pigmentosa (XLRP) with AAV8-RPGR gene therapy proved to be early and effective with durable improvements in vision occurring as early as one month following treatment.

XLRP, a rare disease that comprises 10% to 20% of RP worldwide, affects mostly males, and 70% of the cases are caused by RPGR gene mutations and 60% of those are caused by gene mutations in RPGR-ORF15. In this form of RP, the median age of blindness is 45 years, which is younger than the other forms. Disease progression occurs in stages, with nyctalopia manifesting in the early stage, peripheral visual field constriction in the middle stage, and central visual deterioration and visual loss in the end stage, according to Paulo E. Stanga, MD, professor of Ophthalmology and Retinal Regeneration, Manchester Royal Eye Hospital and University of Manchester, London, UK.

The RPGR mutations cause abnormal transport across the cilium, where RPGR is located, and this abnormal transport results in photoreceptor death. "Obviously, this leads to loss of retinal sensitivity across the visual field and loss of visual acuity," he said.

The RPGR mutations cause abnormal transport across the cilium, where RPGR is located, and this abnormal transport results in photoreceptor death. "Obviously, this leads to loss of retinal sensitivity across the visual field and loss of visual acuity," he said.

Dr. Stanga recounted.

The patients underwent a surgical procedure that included creation of a bleb followed by injection of the virus vector within the bleb.

"The investigators evaluated the early effects of changes in the retinal sensitivity in the central retina using microperimetry (Maia, Centre-Vue). The central 16 retinal loci represent 8 degrees of vision; an improvement of five of the central 16 loci equals a 30% improvement in the central visual field. An improvement of 7 dB represents five times greater light sensitivity, he explained."

One month after treatment, Dr. Stanga reported that there was a significant improvement in microperimetry in six of the 12 treated eyes in cohorts 3 to 6 that occurred at one month after vector injection; these cohorts received therapeutic doses. Cohorts 1 and 2, which received subtherapeutic doses, showed no changes.

Cohort 3 showed a mean improvement in the mean retinal sensitivity of 5 to 6 dB in the central 16 retinal loci between the treated and untreated eyes. The improvement became apparent as early as one month after vector injection; these cohorts received therapeutic doses. Cohorts 1 and 2, which received subtherapeutic doses, showed no changes.

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Cohort 3 showed a mean improvement in the mean retinal sensitivity of 5 to 6 dB in the central 16 retinal loci between the treated and untreated eyes. The improvement became apparent at one month and remained relatively stable at three and six months, Dr. Stanga reported.

According to Dr. Stanga, these changes in retinal sensitivity differed from those observed in untreated eyes in the central 16 retinal loci. The untreated eyes showed decreases in retinal sensitivity over time.

The investigators also reported that they also determined that the gene therapy with AAV8-RPGR gene therapy for XLRP was generally well tolerated.

No patients left the study and no dose-limiting toxicities were readily apparent. Transient inflammation developed in the higher cohorts that responded to systemic steroid therapy. Two ocular adverse effects were related to the procedure or drug.

"We aim for yields of high expression levels that are four times higher than the expression levels of the wild-type RPGR," he explained.

"We demonstrated proof with durable dose-related improvements that appeared as early as one month after treatment across multiple microperimetry analyses."

- Paulo E. Stanga, MD

The treatment that Dr. Stanga and colleagues devised has the goal of correcting the full length of the RPGR-ORF15 mRNA.

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COMING SOON

DURYSTA™
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Improving DR outcomes through comprehensive medical management

Ophthalmologists tackling diabetes-related blindness at ground level

By Mark Ruchman, MD; Special to Ophthalmology Times

Diabetes currently affects more than 30 million Americans (about 9.4% of the population). The American Diabetes Association estimates that more than seven million people are not even aware that they have this debilitating disease. While many people with diabetes learn they have the disease via a high-fasting blood glucose test, fully 20% discover they are diabetic as a result of an eye exam. 1

FROM DIABETES TO BLINDNESS

Diabetes may be associated with systemic co-morbidities including kidney disease, peripheral neuropathy and vasculopathy. Additionally, untreated diabetics are at risk for the disabling consequences of diabetic retinopathy, cataract and glaucoma. Approximately 30% of people with diabetes have retinopathy; fortunately, early detection and treatment can reduce the risk of blindness by 95%. 2 Recent advances offer hope to those at risk from the devastating effects of this disease. Aiello and colleagues at the Diabetes Control and Complications Trial, found the risk of developing diabetic retinopathy was reduced by 76% and progression slowed by 54% in response to intensive treatment. 3

Early intervention is central to successful treatment of diabetic retinopathy. In its early stages, however, when treatment has the greatest likelihood of success, patients are typically asymptomatic. Thus, an annual eye exam – combined with a robust medical management program – is a critical component of any health and wellness program to reduce blindness from this disease.

HIGH COSTS

Diabetes costs the United States an estimated $327 billion annually, with $237 billion coming from direct medical costs and $90 billion coming from decreased productivity. 4 And with nearly 30% of diabetics suffering from retinopathy, 5 diabetes-related visual impairments can total more than $500 million per year. 6

A study by Zhang and colleagues found that medical costs for diabetics were significantly higher for those with diabetic retinopathy (DR) than those without retinopathy (DR). 7 Specifically, those diabetics with even moderate diabetic retinopathy had notably higher medical costs than who did not have retinopathy, but had other diabetes-related conditions, such as neuropathy, vasculopathy and chronic kidney disease. 8

A similar study by Schneir and colleagues published in Retina looked at the costs associated with diabetic retinopathy in the Medicare population. 9 Researchers examining 5% Medicare claims data from 1997 through 2004 identified 178,383 controls (people with diabetes but no evidence of diabetic retinopathy), 33,735 cases of nonproliferative diabetic retinopathy (NPDR) and 6,138 cases of proliferative diabetic retinopathy (PDR). They found that average annual Medicare payments for care, as well as the average payments for ophthalmic care, were significantly higher for both the NPDR and PDR cases compared to diabetic patients without retinopathy.

MANAGING DIABETES, DR.

To reduce the risk for and/or severity of diabetic eye disease, it is crucial to create a program of community outreach overseen by healthcare experts dedicated to the management of the disease. In my experience, there are three key ways to accomplish this.

1. ENHANCED DATA COLLECTION VIA EYE CARE PROFESSIONAL PORTALS

In eye care professional (provider) portals, when claims are submitted, ask a number of diabetes-related questions to stratify risk. For those members known to have diabetes, include several retinopathy-related questions the eye care professional needs to answer.

In cases where no diabetes is indicated, include a series of questions and conditions indicative of diabetestes to help identify patients who may be at risk for the disease and require more intensive oversight.

2. PERSONALIZED DIABETES OUTREACH

Establish a system to identify diabetics who have not yet had an annual dilated retinal examination and remind them to get a retinal exam every year to monitor and track the progression (or lack thereof) of their disease. In this way, you can craft individual outreach solutions for each patient based upon their particular circumstances. This leads to improved patient care and better patient outcomes; an important metric for health plan HEDIS and STAR measures.

3. MEDICAL MANAGEMENT

Medical management is key for patients with or at risk for diabetes. With comprehensive medical management, you can track the entire spectrum of eye health and vision services. You can then utilize predictive analytics to convert data to actionable strategies to enhance early interventions and improve patient outcomes while ensuring that patient funds and health plan resources are used prudently.

By aggregating the collective experience of an extensive eye care professional network, diabetic outreach program and medical management team, you have the opportunity to provide the intellectual and operational infrastructure for new insights in the management of diabetic eye disease.

And that can save money as well as lives. ■

REFERENCES


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Gender disparities in surgical experiences a hurdle for residents

Operating room performance improves with more surgeries

By Lynda Charters

THERE IS no argument with the old adage that practice makes perfect, and this is particularly true for ophthalmology residents.

The results of studies both older and more recent all point in the same direction: Operating room performance by ophthalmology residents improves as they perform more surgeries.

One study, however, found that female residents performed significantly fewer cataract surgeries and a significantly lower total number of procedures compared with male residents from 2005 to 2017 (p < 0.001 for both comparisons).

The disparity comes even as the number of male and female residents was similar in ophthalmology programs during the period. As a result, it must be considered that if the numbers of men and women in the residency training programs were similar, why was the surgical experience not the same?

This finding emerged from a retrospective longitudinal analysis of recent case logs performed by Dan Cong, MD, a vitreoretinal surgery fellow at Massachusetts Eye and Ear, and colleagues.

The research team asked 119 ophthalmology residency programs in the United States to participate.

Participation was anonymous and data collected for each graduating resident included graduation year, resident gender, number of cataract procedures performed as the primary surgeon, total number of procedures performed, and parental leave status. The main outcome measures were the mean volumes of cataract surgeries and total procedures, resident gender, and maternity or paternity leave.

Of the programs contacted, 24 (20.2%) residency programs provided data on 1,271 residents, of which 815 (64.1%) were men and 456 were women (35.9%) who graduated from 2005 to 2017.

The authors reported that the male residents performed more cataract surgeries than the female residents (mean, 176.7 versus 161.7, respectively); the male residents also performed a higher mean number of total procedures (509.4 versus 451.3, respectively). Eighty-five male residents and 71 female residents took parental leave.

Interestingly, the research found the male residents who took parental leave performed a mean of 27.5 more cataract surgeries compared with the men who did not take parental leave, the female residents who took parental leave performed a similar number of surgeries to those who did not take parental leave.

Beginning in 2005, each subsequent year saw an increase in the number of cataract surgeries performed by each resident, although there was no significant (p = 0.11) gender difference identified. However, there was a significant (p = 0.008) gender difference in the total volume of procedures performed.

Over time, the male residents performed more surgeries than the female residents and that gap widened over time.


CONSIDERATIONS

The differences in the numbers of cataract surgeries performed by the female residents compared with the male residents ranged from 7.8 to 22.2 fewer, and the differences in the total numbers of procedures performed by the female residents ranged from 36.0 to 80.2 fewer.

The numbers of cataract surgeries performed by the male and female residents, however, more than met the requirements of the Accreditation Council for Graduate Medical Education, the authors pointed out.

The growing gap in the total number of procedures over time was of special interest to the study investigators.

“One concerning trend that deserves special mention is the growing gap in total procedural volume between male and female residents as time progresses,” they wrote. “Although we are encouraged that [the] overall case volume increased from 2005 to 2017, it is unclear why the increase asymmetrically affects male and female residents.”

The parental leave was found to have no affect the total numbers of procedures performed by the male and female residents.

The authors suggested that “if residents are more likely to take parental leave in their third year, taking leave would have less of an effect on procedural volume during the first and second years of residency when many laser and other procedures are performed.”

The investigators recommended that each residency program director evaluate the case volumes of the male and female residents and if there were differences found the directors should examine if the policies of the programs differ for men and women.

Some considerations could include the manner in which a program helps residents with their case volume when taking parental leave, adjusting rotation schedules based on the timing of the parental leave to minimize the disruptive effect on the residents’ education, and determining how and when the attendings pass on surgical cases to the residents.

CONCLUSION

The authors suggested that further studies with more participating residency programs be undertaken to confirm the current study data.

“Female residents performed 7.8 to 22.2 fewer cataract operations and 36.0 to 80.2 fewer total procedures compared with their male counterparts from 2005 to 2017, a finding that warrants further exploration to ensure that residents have equivalent surgical training experiences during residency regardless of gender,” the researchers wrote.
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Duties will include providing clinical care to neuro-ophthalmology patients, teaching the principles of ophthalmology to medical students and undergraduate students in Allied Health programs, providing teaching experience for residents in training, developing basic and/or clinical research, and performing additional departmental and/or sectional administrative duties as assigned by the Chair of the Department of Surgery.

This is a full-time, 12 month, salaried, faculty appointment and carries with it attending staff privileges at The University of Vermont Medical Center. Salary is competitive and commensurate with ability and experience.

Interested individuals should apply online at https://www.uvmjobs.com/postings/37767 (position number 000229). Inquiries may be directed to Dr. Brian Kim or Kristin Allard via Kristin.Allard@uvmhealth.org.

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Located in Burlington, the University of Vermont Medical Center serves as Vermont’s only academic medical center. Burlington is a vibrant community located on the shores of Lake Champlain, between the Adirondack and Green Mountains. With year-round recreational opportunities, safe communities and excellent schools, this progressive community has been frequently cited as one of the most livable cities in the U.S.

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The Division of Ophthalmology in the Department of Surgery at the Robert Larner, M.D. College of Medicine at the University of Vermont and its affiliated medical center, The University of Vermont Medical Center, is recruiting a full-time academic Comprehensive Ophthalmologist. This individual must have completed a board approved 3- or 4-year ophthalmology residency, be board certified or board eligible, and eligible for medical licensure in the State of Vermont. The candidate must have demonstrated interest and ability in teaching medical students and residents and be willing to participate in the surgical teaching programs. This academic appointment will be in the non-tenure clinical scholar pathway at the Assistant or Associate Professor level commensurate with experience and training.

This is a full-time, 12-month, salaried, faculty appointment and carries with it attending staff privileges at The University of Vermont Medical Center. Salary is competitive and commensurate with ability and experience.

Located in Burlington, the University of Vermont and the University of Vermont Medical Center serve as Vermont’s only academic medical center. It is the only ACS verified Level I trauma center in the state and provides tertiary care to patients from Vermont and Northern NY. Burlington is a vibrant community located on the shores of Lake Champlain, between the Adirondack and Green Mountains. With year-round recreational opportunities, safe communities and excellent schools, this progressive community has been frequently cited as one of the most livable cities in the U.S.

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