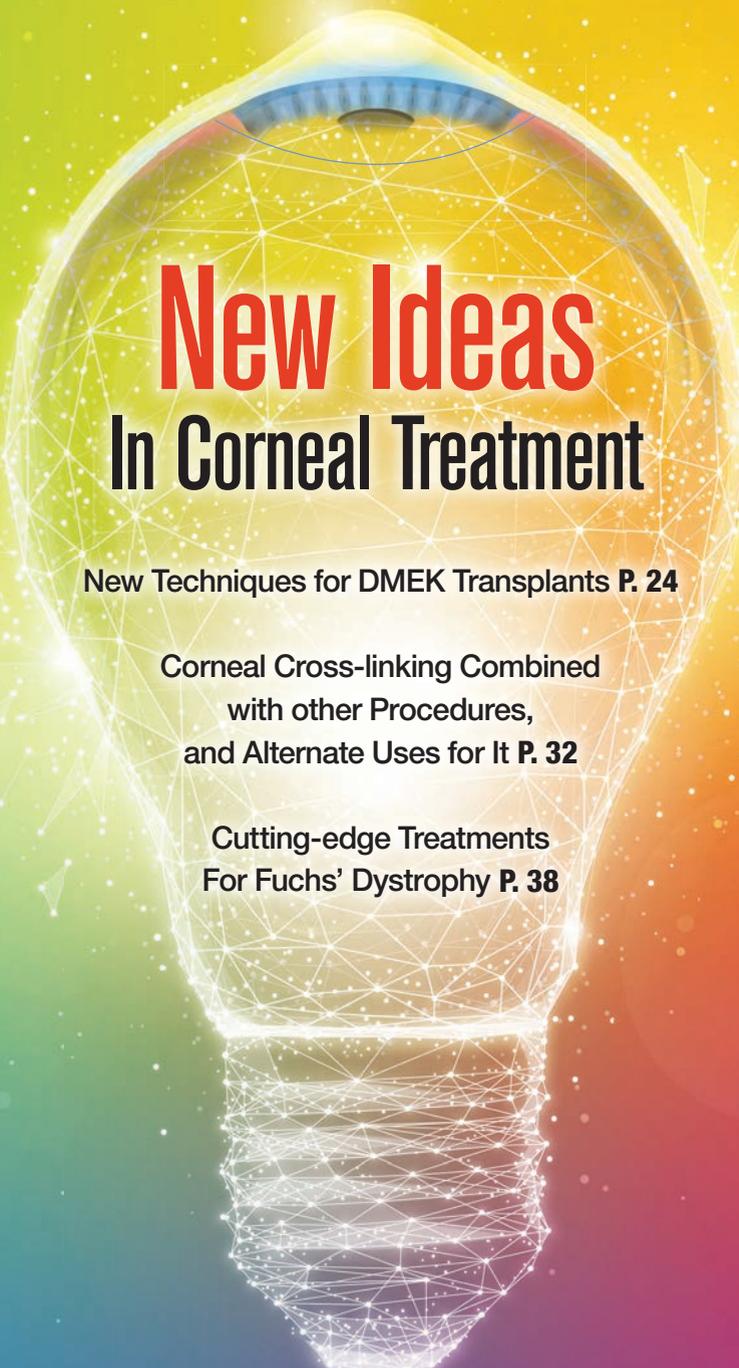


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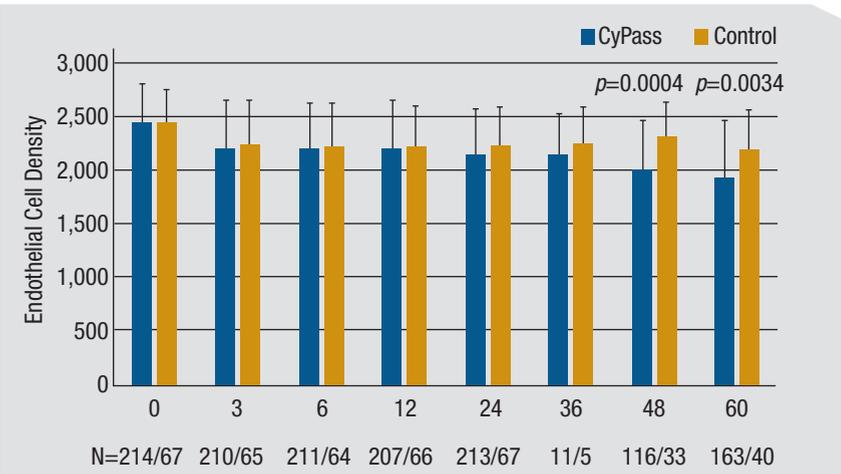
ASCRS Offers Guidance Following CyPASS Withdrawal

In late August, Alcon's CyPASS Micro-stent was suddenly withdrawn from the market due to significant endothelial cell loss seen in an extension of the study that won the device approval from the U.S. Food and Drug Administration. Since then, more information about what triggered the product withdrawal has become available, and the American Society of Cataract and Refractive Surgery has released guidelines for surgeons whose patients have already been implanted with the device.

The original COMPASS study compared the safety and efficacy of implanting the CyPASS device at the time of cataract surgery, to cataract surgery alone. Although the study's two-year follow-up didn't find a statistically significant difference in endothelial cell loss between the control group and CyPASS group, that changed by the five-year follow-up in the COMPASS-XT study. At five years, the mean endothelial cell count in the control subjects had dropped from 2,434 at baseline to 2,189, a 10-percent drop; but in the CyPASS patients, the ECC dropped from 2,432 at baseline to 1,931—a 21-percent drop. (Fortunately, despite the losses of endothelial cells, all corneas remained clear and no eyes required corneal surgery at five years.) However, this loss was not found uniformly among the CyPASS patients, leaving researchers to search for an explanation.

As it turned out, anterior chamber pictures from the COMPASS-XT

Statistically Significant Difference in Endothelial Cell Density Between CyPass and Control at Months 48 and 60



study revealed differences in how deeply the device was implanted, and that correlated with the likelihood of increased endothelial cell loss. The device has three retention rings on its collar; implants that had no rings showing in the anterior chamber following implantation had a mean endothelial cell loss of 1.39 percent per year; implants that had one ring visible had a loss rate of 2.74 percent per year; and those with two or three rings visible had a loss of 6.96 percent per year. (For comparison, eyes in the control group had a mean loss of 0.36 percent per year, a much lower rate than historic norms for healthy eyes following cataract surgery.) However, even this correlation wasn't perfect: Some eyes with multiple rings visible have had minimal endothelial cell loss.

Given this information, on October

4, ASCRS issued an official statement making the following recommendations for patients who already have an implanted CyPASS:

- Monitor these patients at appropriate intervals, including performing gonioscopy to check the position of the implant. Because eyes with multiple rings visible did not all experience a high rate of endothelial cell loss, no action beyond monitoring is recommended unless you find evidence of corneal decompensation—although increasing the frequency of corneal evaluation could be considered. (Alcon recommends periodic assessments of endothelial cell density using specular microscopy.)

- If more than one ring is visible and corneal decompensation

(Continued on page 6)

2CTech: A Case Study in a Retina Start-Up

In Ocular Product Development Insights, we've discussed broad product-development topics that are especially relevant to physician entrepreneurs who are at the early stage of an investment opportunity and/or starting up a business. In prior columns, we've covered case studies and discussed issues like the proper selection of a drug's indications, the pathway to proof-of-concept studies, ex-U.S. regional deals, financing, intellectual property and strategic relationships. This month we provide an overview of a company that originated from a physician scientist. The company's subsequent development incorporates key examples and lessons from many of the prior articles.

The company is called 2CTech (Irvine, California), and its initial concept came out of individual work by Jeff Olson, MD, a retinal specialist at the University of Colorado, as well as from a collaboration with his department chair, Naresh Mandava, MD. Dr. Olson wanted to see if it would be possible to take a retinal implant that provides electrical stimulation to the cells and "grind it up" into millions of small stimulation devices that are spread throughout the retinal layers. He subsequently learned that materials of the type he imagined already exist in the nanotechnology world, and are called Quantum Dots (QDs).

QDs are biocompatible crystalline nanoparticles a few nanometers wide, engineered to be sensitive to energy of different wavelengths. QDs behave like mini solar cells, producing energy in response to light. When excited by light, electrons inside the QD are boosted to a higher level and, when they return to a lower level, the QDs emit energy in the form of photons. Each QD contains a crystalline core that's encapsulated in an inert shell and surrounded by a hydrophilic coating that enables the material to be supplied as a colloidal solution of semiconductor nanocrystals. This combination of coatings is used to protect the core/shell from oxidative damage, enhance the efficacy of the particle, allow the particle to be suspended in water and to sequester the heavy-metal core from the environment. 2CTech has been developing QD technology with the intention of delivering photovoltaic stimulation to the retina in patients with retinal degenerative diseases,

with the ultimate objective of improving light sensitivity and visual function.

The QD particles can be introduced into the vitreous via a routine intravitreal injection, at which point they diffuse through the retina. The particle emissions result in direct stimulation of the neural retina, and also elicit the release of growth factors that could amplify or extend the duration of effect. The intended result would be a periodically administered treatment that could preserve or enhance vision in patients with degenerative diseases.



Selecting an Indication

The manner in which the product can induce electrical stimulation of photoreceptors has implications across multiple retinal diseases, ranging from inherited retinal diseases (IRD) such as retinitis pigmentosa and Stargardt's, to diabetic retinopathy, dry age-related macular degeneration and even glaucoma (via neuroprotection). While the largest market is arguably dry AMD, multiple factors led 2CTech to choose RP as the lead indication. As an orphan indication, the studies are smaller in size and there are clear, accepted, validated endpoints available for IRD, thanks to the approval of Luxturna (Spark) for RPE-65-mediated LCA-2. The intention is that RP serves as proof-of-concept for retinal degeneration as a whole.

There are multiple drug development programs in the pipeline that focus on IRD, many with potentially exciting gene-therapy and nucleic-acid-based approaches that target specific genetic variants of the IRDs. RP as a broad classification is an orphan condition, and consists of many genetic variants—more than 80 genes associated with RP and LCA

encode proteins for phototransduction. Generally, many of these therapeutic approaches target specific variants. 2CTech is taking the approach that the QDs may stimulate photoreceptors regardless of which genetic variant caused the disease, and potentially could also be used in conjunction with future gene therapies, other neurostimulation devices or other retinal treatment modalities. In addition, other work with electrical stimulation of the neuroretina (such as Second Sight's Argus II) has shown that electric stimulation generated by implants can also generate visual improvements, and this serves as an additional "reason to believe" in the general concept. Investors and industry also view programs in IRDs as indications that can drive investment in their companies, as well as transactions with other pharma and bio-tech entities (see Allergan/Editas, and Novartis/Spark). Therefore, a therapeutic technology with an effectiveness that can span genetic variants would certainly be supported by the commercial model that many other companies are pursuing for individual variants.

Financing

The initial work of 2CTech was financed by a convertible loan from the University of Colorado, plus two grants from the state of Colorado. An investment (both equity investment and an additional convertible note) from a strategic partner (Hoya, Japan) further comprised the Series A financing. Hoya was motivated by the prospect of nanotechnology applied to retinal disease, with a goal of making an initial financial investment in a project that had a clear path to the next steps. Such an investment gains the partner early visibility in an area of strategic interest. The investment by this company was made without reserving any specific rights to the product. (Note that in some situations where a strategic partner has exclusive access, potential future investors may see such a deal as having a potential cap on its upside for them, and thus would want to see appropriately structured terms for that access.) This Series A helped 2CTech accomplish key items of preclinical work, and an early human feasibility clinical trial.

A preclinical study was conducted in a relevant rat model, and demonstrated safety, efficacy and pharmacokinetics. The studies showed a clear benefit associated with the semiconductor particles and no evident negative effect on photoreceptor cells. In addition, a rabbit study was conducted, demonstrating clearance of quantum dots in the vitreous through the retina. Manufacturing capability was also secured with this early funding round.

With the initial funding, 2CTech then performed an early, small, clinical pilot study outside the United States. Several more goals remained at this stage, namely: formally meeting with the FDA in order to define the pathway; defining the ideal patient population and inclusion/exclusion criteria for the planned clinical trial; and securing access to the dots.

The first tranche of the Series B (B-1) was then brought together with additional investment from Hoya of \$4 million. This funding enabled 2CTech to achieve key milestones that checked off several items that would be required for additional funding (a planned B-2 round): generating valuable pre-treatment clinical data; securing a supply of materials; confirming a clinical-regulatory pathway with the FDA; and engaging advisors and key opinion leaders.

2CTech was able to secure an application-specific and exclusive license-and-supply agreement for quantum dots—representing an IP enhancement—and the funding of Series B-1 enabled the purchase of a quantity of quantum dots sufficient for the upcoming trial(s). Work was completed to define the regulatory pathway with the FDA, and thanks to this round of financing the company was able to conduct a clinical trial (pre-treatment).

Clinical Program & Endpoint Selection

After the FDA's review of the protocol and study plan, the pre-treatment clinical trial was conducted at Baylor University in collaboration with our retina group at our development firm, Ora (Andover, Massachusetts). This pretreatment feasibility study assessed the impact of different acuities and visual fields of RP subjects on their ability to navigate specific navigation courses, because potential improvements in vision after therapy may be characterized by improvements in the ability to navigate different mobility courses at low ambient

light levels. In order to best demonstrate improvement following quantum-dot therapy, at baseline the subject population should be unable to navigate a particular course at low light levels in order to support the objective of demonstrating an improvement in mesopic navigation following treatment. Therefore, courses at various difficulties are desired. Ora has developed and operates four separate mobility courses consisting of up to 21 different course/light level combinations for patients with inherited retinal diseases to assess differing levels of visual function (called the Visual Navigation Course or VNC). By running this study early, 2CTech identified which patients should enter into the eventual treatment trial, established patient baseline performances on the test, and confirmed that the test protocol can determine a range of potential improvement in visual function generated by the treatment.

A unique feature of Ora's mobility courses is their modular nature, which specifically facilitates multicenter studies. Identical mobility courses can be installed and validated at any clinical site and, as a result, 2CTech's follow-on study can leverage the same general protocol methods and identical courses to those tested in the feasibility trial, increasing the likelihood of replicating results.

Once the second tranche of the Series B is funded, 2CTech will be primed with quantum-dot supplies, a protocol, an accepted endpoint and a patient population, which will allow it to proceed rapidly into the controlled-treatment proof-of-concept study.

In conclusion, the case example of 2CTech demonstrates a program initiated by a physician-scientist that created a reason-to-believe with early funding, identified key issues that future investors would want to see resolved, and subsequently resolved many of these issues in order to de-risk the program. The case of 2CTech is also an example of the value of a pre-treatment study for identifying the population and criteria once full funding is in place for the treatment evaluation. With a relatively small amount of early funding, 2CTech is now poised to validate a novel technology for retinal degenerative conditions.

Mr. Chapin is senior vice president of corporate development at the research and development firm Ora Inc. He welcomes your comments or questions regarding product development. Send correspondence to mchapin@oraclinical.com or visit oraclinical.com.

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develops, trimming the proximal end of the device appears to be the least-risky intervention. (Repositioning or removing the device can be problematic, due to likely fibrosis around, and possibly through, the filtration holes of the device.) Alcon notes that there's limited clinical data regarding the impact of trimming the device, so when deciding whether or not to proceed, surgeons should consider the possibility of causing further endothelial cell trauma. The ASCRS statement notes that in the absence of clinical sequelae, device adjustment or removal isn't recommended.

- In terms of notifying patients already implanted with the device, ASCRS recommends checking the policies of your practice, hospital and/or ASC regarding what to do when an implant has been voluntarily withdrawn from the market.

Atlanta glaucoma specialist Reay Brown, MD, who participated in the COMPASS study, says he was very surprised that there was any problem with the device. "It's small and stable," he notes. "I haven't seen any cornea problems in my patients, and I have patients from the study who are more than seven years out. All of their endothelial cell counts have been fine."

Dr. Brown is skeptical that Alcon will be able to reintroduce the device with different guidelines in the future. "I thought it was terrible that the CyPASS wasn't approved for use in pseudophakes," he says, "After all, we always put the CyPASS into the eye after the cataract surgery has been completed, so we're already putting it in pseudophakic eyes. But it was made clear to me that the FDA will only approve devices based on studies. So without further studies, I'd be surprised to see any new approval—especially now that the endothelial cell loss issue has been discovered."



An image of the CyPASS glaucoma micro-stent following implantation. The device was withdrawn from the market due to issues with long-term endothelial cell loss.

Dr. Brown says that he recommends staying positive and upbeat with CyPASS patients—especially if everything is going well. "If a tube is obviously malpositioned, or something bad is happening such as local corneal opacity or a significant loss of endothelial cells, then I would trim or remove it," he says. "Otherwise, intervention or worrying the patient will probably be counterproductive."

Yutiq Wins Approval to Treat Uveitis

In October, the FDA approved EyePoint's sustained-release implant Yutiq (fluocinolone acetonide intravitreal implant) 0.18 mg for the treatment of non-infectious posterior uveitis. The implant is designed to deliver the drug for 36 months.

According to the company, Yutiq's first Phase III trial met its primary efficacy endpoint at six months, with a uveitis recurrence of 18.4 percent for Yutiq versus 78.6 percent for control. The company says results through 12 months were similar, (intent-to-treat analysis; recurrence of 27.6 percent for Yutiq versus 85.7 percent for control). Yutiq was generally well tolerated through 12 months of

follow-up with a mean IOP elevation of 1.3 mmHg compared to 0.2 mmHg in the sham. Cataract surgeries were performed in 33.3 percent of patients receiving Yutiq, compared to 4.8 percent for sham.

In Yutiq's second Phase III trial uveitis recurred in 21.8 percent of Yutiq cases versus 53.8 percent of control cases at six months.

Similar to the first Phase III clinical trial, in the second trial, Yutiq was well tolerated with a mean IOP elevation of 2 mmHg compared to no change in the sham. Cataract surgeries were performed in 18 percent of patients receiving Yutiq compared to 8.6 percent for sham.

The company plans to launch Yutiq in the first quarter of 2019.

Raindrop's Haze Risk

In late October, the FDA issued a warning that patients already implanted with the mothballed Raindrop corneal inlay are at increased risk for corneal haze, based on results from a post-approval study (PAS).

According to the agency, of the 150 patients in the PAS, 23 percent (35 patients) had to have the Raindrop removed. Of these, 31 percent (11 patients) required removal due to haze, and 28 percent (10 patients) were removed due to inflammation. One patient even developed haze six months after device removal, and in other cases, the haze persisted even after removal.

Because of these results, the FDA advises not to implant the device, and is working to recall all remaining devices. Doctors should carefully monitor Raindrop patients, and these patients should seek evaluation sooner if they develop any visual symptoms, the FDA says. **REVIEW**



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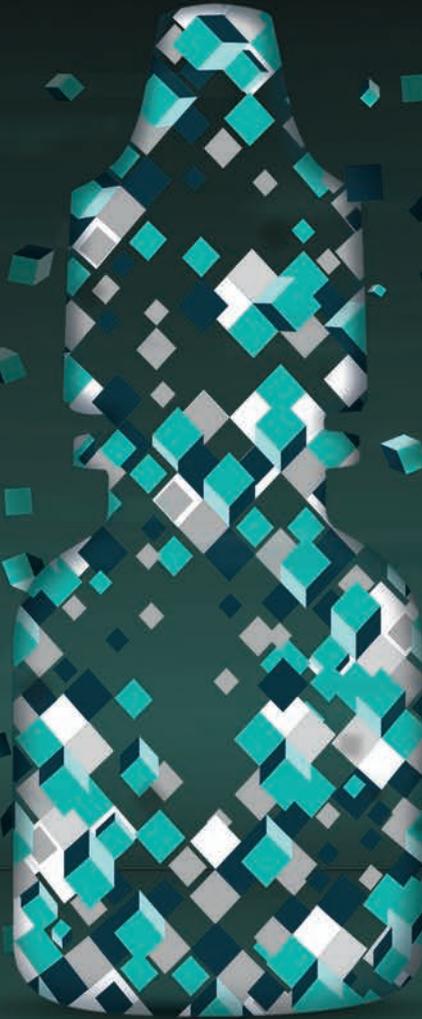
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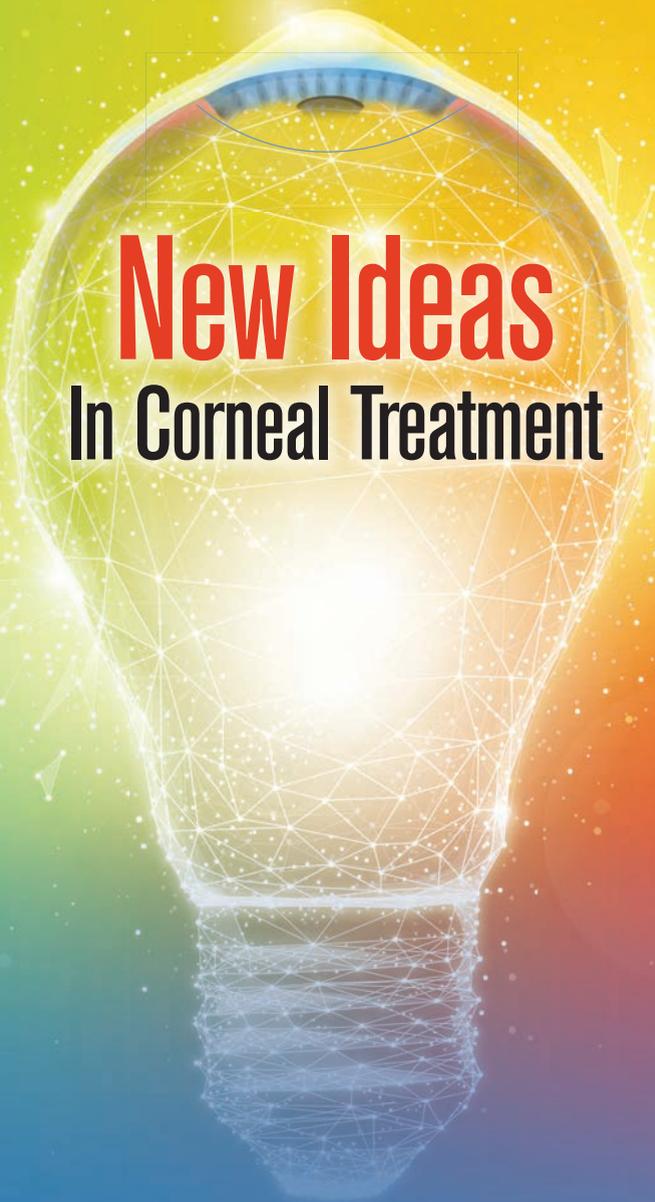
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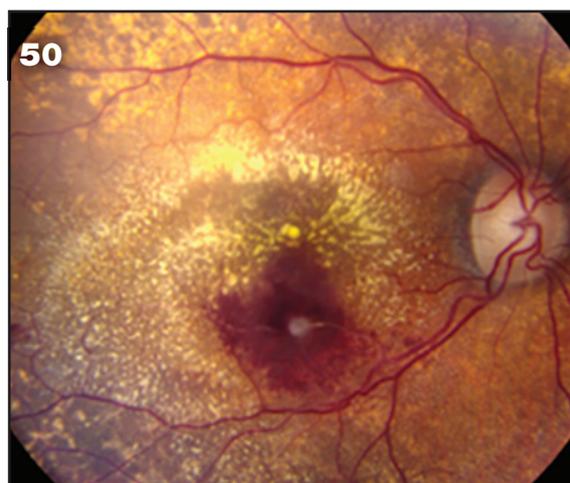
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Retinal Prostheses: A Second Chance for Eyes?

A look at how two retinal prostheses—one approved and one investigational—work and whom they might help.

Kristine Brennan, Senior Associate Editor

Hereditary retinal dystrophies can do their worst just when patients are trying to live their fullest lives, leaving them with no useful vision at the most advanced stages. The Food and Drug Administration's approval of Luxturna (Spark Therapeutics; Philadelphia), a gene therapy injected subretinally, offers hope to patients with mutations to the RPE65 gene. Retinal prosthetic devices are a concept that both pre-dates gene therapy and continues apace with it. Here's an update on two such devices currently being implanted to address blindness from advanced retinitis pigmentosa.

The Argus II

The Argus II Retinal Prosthesis (Second Sight; Sylmar, Calif.), CE-marked in 2011 and FDA-approved for humanitarian use in 2013, consists of a pair of glasses with a video camera mounted in the center and an external coil on the sidearm, and a portable, battery-powered video processing unit that wirelessly transmits electronic pulses to a tiny, 60-channel electrode chip implanted epiretinally, via a cable that enters the eye from

the housing of the chip. "The Argus II is a device that restores sight to patients with certain types of retinal blindness, particularly patients who suffer from inherited retinal degeneration that leads to loss of photoreceptors," says Mark Humayun, MD, PhD, co-inventor of the Argus series of retinal implants.

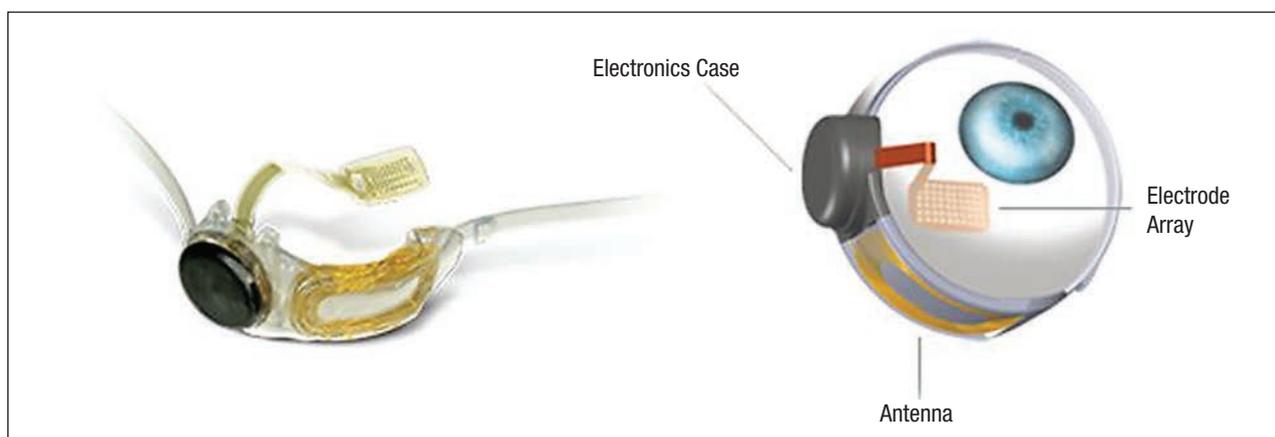
"In addition to the wearable components, the implanted component is a computer chip that receives the information; the chip's delicate electrode array converts that information into controlled electrical pulses that stimulate the ganglion cells in the retina and send the information to the optic nerve," Dr. Humayun explains. "So it's basically a camera system, wirelessly connected to implanted electronics, that jumpstarts the otherwise blind eye. It bypasses the function of the lost or damaged photoreceptors. It provides that information to the retina, and then the retina relays it to the brain."

According to Dr. Humayun, the success of the cochlear implant for deafness was a source of inspiration for the Argus retinal implant. "Wireless links like the one in Argus have

been used extensively in cochlear implants and elsewhere in the body. We have decades of experience with that technology," he says.

Dr. Humayun says that the implantation procedure for the Argus II is well within the skill set of a retina-trained surgeon. "Most of the steps of the surgical procedure could easily be done by a retinal surgeon," he says. "There are certain parts, such as attaching the electrode array to the retina, that the surgeon has to learn." The surgeon must create a retinal detachment to insert the electrode array epiretinally, and affixing it in place is one tricky element of the procedure, he says. "You have to use a tiny tack to attach the chip to the back of the eye," he notes. "That's a step you normally don't do, but it's easily learned. More than 200 patients have been implanted in 30 countries worldwide, including Europe, the United States, Canada, the Asia Pacific region, the Middle East, Russia and even Iran."

In a study of 30 blind retinitis pigmentosa patients implanted with the Argus II and followed for 36 months, all those who reported that their vision negatively affected their quality



The ocular-implant component of the Argus II Retinal Prosthesis System, outside and inside the eye. The sheet of microelectrodes receives information from the antenna, which gets the signal from a camera housed in the recipient's glasses after an external, wearable video-processing unit processes the original image captured by the glasses-mounted camera. The electrodes then emit pulses that bypass damaged photoreceptors to stimulate remaining cells in the retina, which transmit the pulses to the optic nerve and then the brain. Patients must learn how to interpret the pulses as visual patterns of light, contrast and pixelated shapes.

of life with respect to getting injured, meeting life's demands and fulfilling life roles reported improvement across those dimensions.¹

"Whether it occurs at the retinal level or at the brain level, adaptation is key [to these improvements]," says Dr. Humayun. "When we implant the device we see a learning effect. The patient is now using the eye's remaining cells after perhaps decades of complete blindness, and suddenly getting used to this type of stimulation. It's very different from what we normally see, because electrodes from the chip are stimulating groups of neurons; whereas light can stimulate single rods and cones.

"In the eye, initially the input is different, maybe just spots of light," he continues. "Eventually, however, the patient learns to use the signals to recognize objects." after Argus implant surgery, patients may be able to see light and motion, and may also become able to do things like sort laundry or follow lines in crosswalks and avoid obstacles while walking; some may even be able to read very large letters close up or sort laundry visually, according to the Second Sight website's FAQ page for patients (second-sight.com). Dr. Humayun says that

the Argus II's software code is more sophisticated and better presented than in the earlier version of the device, and is therefore more "readable" by the patient, resulting in meaningful visual gains sooner for those who take the time to practice with the system after implantation. "We didn't fully understand the code early on, but as we understand it more and we know how to present it better, the acclimation process is down to months, as opposed to years," he notes.

Retina Implant Alpha AMS

The Retina Implant Alpha AMS (Retina Implant AG; Reutlingen, Germany), CE-marked in 2013, is an investigational device in the United States, and is currently intended to treat patients with blindness due to retinitis pigmentosa. The Alpha AMS doesn't require an external camera. It's a 1,600-pixel microphotodiode array implanted subretinally, relying on light to stimulate the optic nerve via remaining RPE cells.

"In retinitis pigmentosa, when the retinal pigment epithelium sustains damage, those cells are no longer able to take care of the rods and the cones, and the rods and the cones and the

photoreceptors get damaged," explains Sunir J. Garg, MD, principal investigator and chief surgeon for the current feasibility trial (ClinicalTrials.gov Identifier: NCT03629899) at Wills Eye Hospital in Philadelphia. "The chip implant goes underneath the retina, with the photodiodes directly touching the rod and cone cells. An electrical signal stimulates those rods and cones. We're basically replacing or supplementing the RPE cells, helping to rev up the cells that are still functional but weakened. Then the electrical signals go through the normal pathway: through the retina and the optic nerve and to the brain."

The implant includes a handheld component about the size of a cell-phone that holds batteries and transmits energy via magnetic induction to a ceramic-housed coil implanted under the skin behind the ear. The patient can also adjust for brightness and contrast using the handheld device. "They can tweak it, but some of the tweaking is also done by us in our laboratory," says Dr. Garg.

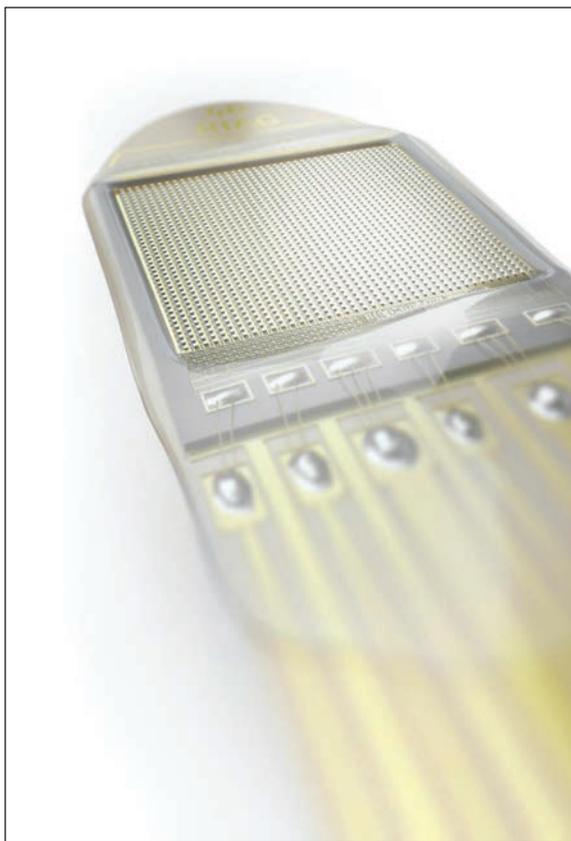
Since the Alpha AMS doesn't require an external camera to gather information, patients glance around by moving their eyes, rather relying on

head movement to accommodate a limited visual field. “One of the neat things about this particular implant is that there’s no camera,” Dr. Garg says. “The patient is looking through his or her own eye; light’s coming in through the pupil just like it always did. It’s being focused on the retina just like it always has been. Once light hits the implant, the implant does what the damaged cells can’t do, which is provide stimuli.”

As with the Argus II, Dr. Garg says that retinal surgeons can master the skills needed to implant the Alpha AMS. “The implantation techniques are essentially techniques that vitreoretinal surgeons are comfortable with, including vitrectomy, creating a retinal detachment and doing scleral cut-downs.” There are a few caveats, though. “The surgical skills are combined in a way that’s very different than what we’re used to, however. In order to get comfortable with the procedure, I think people will have to spend time in a training laboratory setting, under the mentorship of people who’ve done it several times,” Dr. Garg continues. “It’s not as simple as watching a video once or twice and figuring that you can do it. It does require dedicated time under supervision in a practice lab to learn.”

The other added consideration when implanting an Alpha AMS is that the procedure takes what Dr. Garg calls “one big OR day” working together with colleagues from other surgical specialties. “There’s a battery pack that’s implanted behind the ear, similar to the way a cochlear implant battery pack goes behind the ear: That requires the expertise of an ENT sur-

geon or a neurosurgeon, just because they’re the ones with experience doing cochlear implants. There’s also wire that’s tunneled from behind the ear to the orbit; that wire is placed underneath the skin. An ophthalmologist person generally does that. You need a team of experts working together. Some facilities may be more readily equipped than others to assemble that team,” he acknowledges.



Close-up view of the photodiode array of the RI Alpha AMS. The array replaces degenerated RPE. The chip is 3.2 x 4 mm and 70 µm thick. The photodiodes convert light that enters the eye into an electrical signal that the functional retinal cells amplify; and the signal then travels through the optic nerve to the brain.

Although Dr. Garg and colleagues haven’t yet implanted any patients with the device, he reports a lot of interest. He hopes to operate on his first patient by the end of 2018 or early 2019, although other patients have received the device outside of

the United States. “From a clinical perspective, we’re looking for patients who have either bare light perception or no light perception,” he says of the screening process. “But what’s interesting about these patients is that even though they have no light perception when we measure in the clinic, they can still have some of their retinal cells functioning; and if you do electrical stimulation studies and ultra low-vision testing, you can still detect that the retina is functional. Although we’re looking at people who have profound vision loss, we want to make sure the retina is at least somewhat functional for them to be in the trial. We’re also currently working with patients who are middle-aged (50 years) or older.”

The Retina Implant Alpha AMS seems to help end-stage RP patients with their light perception and high-contrast object recognition. Five of six Alpha AMS recipients demonstrated improved visual functioning with the implant turned on versus off for up to 24 months. (One patient had to be explanted at three months due to iatrogenic damage to the device and incorrect implantation.)²

“We’re still learning how all the neurons and synapses interact with each other,” Dr. Garg notes. “I guess I’m surprised—but not too surprised—to see that if you re-establish pathways that have been dormant for awhile, the body is going to try to make the best of the hand that it’s been dealt. So this device is pretty good. Although I’ve seen some variable results, when patients have a good result, it can really be quite spectacular. These are people who’ve literally been in the dark for years. One

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patient who has received the implant is able to look at his child and see her face; he's able to reach out and touch her nose. Another patient was able to notice that one of his kids was wearing a bracelet, and could reach out and touch it. The resolution's clearly not as good as the Retina display in your iPhone, for example, but it's definitely better than some of the pixelated images we've seen with some of the other technologies. So for some patients, I think it can really offer them meaningful visual perception and information that they haven't had in a long time."

Pros and Cons

Dr. Humayun and Dr. Garg both acknowledge that there are pros and cons to both retinal prostheses, with the placement of the electrode and photodiode arrays in the respective devices being a prime example. "The Argus II goes on top of the retina, so it's stimulating the cells, but it's doing so in a slightly different place than they would normally be stimulated. Therefore, the Alpha AMS implant may be more directly targeting the affected cells," says Dr. Garg.

While the Alpha AMS more directly stimulates the photoreceptors by virtue of where it's implanted, the cells most proximal to the implant may not be the best carriers of stimuli in the setting of disease, Dr. Humayun notes. "Theoretically, the subretinal device is closer to the next cell in line, which is potentially advantageous, but a lot of aberrant rewiring occurs in the retina. A subretinal device may end up stimulating the next cell in line, but it may be aberrantly rewired so you lose that benefit," he says. "Whereas the epiretinal device stimulates the ganglion cells, which are less prone to rewiring."

Some patients seeking to restore visual functioning through these technologies may find that they're

not suitable candidates for one type of implant or the other, right out of the gate. Dr. Humayun contrasts the anatomical requirements for the Alpha AMS and the Argus II, the latter of which entails a lensectomy during the implantation surgery. "A photodiode array gets its information through light, so it has the advantage of conveying information without a cable," he says. "But in the Argus II, there's a cable going from the implanted chip to the electrode. The photodiode array doesn't have that cable, but it does require a clear cornea and lens, which is not necessary for the Argus to work."

"One of the other big things to keep in mind is that these devices are not suitable for everybody," says Dr. Garg. "Patients have to really want to be involved in a trial, and have to want to be explorers who are willing to try something new to help drive the field forward and help us learn. That's an important thing to keep in mind that we don't traditionally think about with clinical trials. After the implant is done, patients have to spend a reasonable amount of time in rehabilitation, learning how to use the device and integrate it into their daily activities."

Future Advances

Dr. Garg is optimistic that as retinal implants improve, surgeons will be able to help more patients to a greater degree. "My hope is that, just as computer technology keeps on getting better, faster, smaller and cheaper, we'll be able to see those types of advances with these implants. As time goes on and we have more experience with the Alpha AMS trial and we overcome some of the technological limitations, I hope that the implants will keep getting better. There are certain diseases, such as geographic atrophy from macular degeneration or central vi-

sion loss from Stargardt's disease, and others, that may benefit from these types of technologies in the future. We're not there now, but I'm hopeful that things will improve faster and faster, to the point where we'll be able to help those patients as well in the near future."

To that end, a feasibility study of the Argus II is underway to evaluate its use in dry AMD patients (ClinicalTrials.gov Identifier: NCT02227498). Dr. Humayun also notes that Second Sight is launching a new device that may broaden the indications for the implantable devices by working around the retina and optic nerve altogether. "We just launched the Orion Visual Cortical Prosthesis System, a cortical implant device that goes directly into the vision center of the brain," he reports. "So far, five subjects have been implanted. It still has a camera and wireless transmission. But instead of going into the retina, the electrodes go into the brain."

The Orion won FDA clearance for a feasibility trial late last fall (ClinicalTrials.gov Identifier: NCT03344848). Because its electrode array goes on the surface of the visual cortex, it may be suitable for completely blind patients whose vision loss stems from trauma, DR, glaucoma or other conditions. **REVIEW**

Dr. Humayun holds equity in Second Sight and receives patent royalties for his work on the Argus Series I and II.

Dr. Garg is the principal investigator and chief surgeon of the current feasibility trial for the Retina Implant Alpha AMS, but receives no remuneration in this role.

1. Duncan IL, Richards TP, Arditi A, et al. Improvements in vision-related quality of life in blind patients implanted with the Argus II Epiretinal Prosthesis. *Clin Exp Optom* 2017;100:2:144-50.
2. Edwards TL, Cottrill CL, Xue K, et al. Assessment of the Electronic Retinal Implant Alpha AMS in restoring vision to blind patients with end-stage retinitis pigmentosa. *Ophthalmology* 2018;125:432-43.

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References: 1. Yong JJ, Scott IU, Greenberg PB. *Ophthalmology*. 2015;122(3):595-599. 2. Age-Related Eye Disease Study 2 Research Group. *JAMA*. 2013;309(19):2005-2015.

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Thyroid Eye Disease: Its Causes and Diagnosis

In Part 1 of a two-part series on TED, an oculoplastics specialist explains the disease and its manifestations.

Sathyadeepak Ramesh, MD, Philadelphia

Thyroid eye disease can be an extremely distressing condition that affects both men and women, primarily in their formative years. Fortunately, our understanding of the disease process has increased dramatically of late, allowing for targeted treatments that have the potential to change the course of the disease. Here, I'll discuss the epidemiology of TED, the anatomy involved, how it affects the eye and how to best diagnose it.

Pathophysiology

The thyroid gland, located in the neck, is chiefly responsible for secreting thyroid hormones. These hormones are integrally involved in almost every process of the body, including regulation of the heart, lungs, brain and metabolism.

If the thyroid produces too much of the hormone thyroxine, hyperthyroidism occurs. Hyperthyroidism leads to cell growth, both via the effects of the hormone and via the IGF-1 (insulin-like growth factor) pathway, which is connected to the thyroid hormone receptor. Activation of these two pathways leads to growth of fat, muscle and

fibrous cells, causing the characteristic clinical manifestations of thyroid eye disease. There are many obvious effects of hyperthyroidism, such as increased heart rate with palpitations, increased respiratory rate, diarrhea and increased metabolism leading to resorption of bone and fat. Hypothyroidism can also occur, leading to fatigue, weight gain or gastric dysfunction. In addition, equally important but subtler symptoms can occur in both kinds of thyroid disorder, such as cognitive dysfunction, depression, poor memory, numbness and tingling.

Thyroid disorders are generally diagnosed by detecting abnormalities in a patient's blood work. Thyroid-stimulating hormone (TSH) and thyroid hormones (T3, T4) can be altered in ways that allow the physician to tell if the body is secreting more or less hormone than normal. During treatment, these hormone levels may also be tracked to determine if the therapy is controlling the hormone levels.

In general, between 25 and 50 percent of patients with a thyroid problem (hyper- or hypothyroidism) will go on to develop some form of TED,¹ with roughly 5 percent having a moderate to severe form of the disease that can affect vision. Interestingly, once

TED starts, it's a separate process from the initial thyroid abnormality, with very little interaction between the two. Specifically, once patients develop TED, having well-controlled thyroid hormone levels won't make the eye disease better, although hav-

ing poorly-controlled thyroid hormone levels may make it worse. Though strides are constantly being made, it's still unclear exactly why patients with a thyroid-hormone abnormality develop the eye disease.

Epidemiology

Different factors influence a patient's development of TED:

- **Type of thyroid disorder.** While



Figure 1. Superior limbic keratopathy in early inflammatory thyroid disease, highlighted by rose bengal stain.

the majority of patients who develop TED are hyperthyroid (~80 percent), a small percentage are hypothyroid (~10 percent), and an even smaller percentage (5 to 10 percent) may be euthyroid, without any previously diagnosed thyroid abnormality. The disease is primarily a young person's disease, affecting patients in their 30s, although there is another peak in the late 60s.² It disproportionately affects young women, for whom it can be mild, though if young men or older men and women develop the disease they tend to have a more severe course.^{2,3}

TED results in changes to the eyes' appearance, and since the eyes and face are the most unique and scrutinized part of the body, any changes to them—particularly in young adulthood when patients are advancing in their careers and starting families—can be particularly distressing. Fortunately, the disease spontaneously improves or stabilizes in the great majority of patients, with only a very small percentage (~15 percent) experiencing progressive worsening.⁴

Dr. Francis Rundle first described the clinical course of TED in the early 20th century, with a famous graph depicting two phases of the disease: active and stable. Dr. Rundle observed that TED tends to be "active" at first, with inflammation and worsening for the first 18 to 36 months of the disease, followed by a gradual improvement into a "stable" phase.^{1,5} Roughly 10 percent of patients may have reactivation of disease at some point in their life, and this may be precipitated by surgery. Older patients may not have a pronounced active phase with severe inflammation, but may have a slow, subtle and fibrotic course that's very difficult to treat.

In general, treatment centers around managing inflammatory symptoms and improving quality of life in the active phase, and surgery to restore the cosmetic and functional outcomes in the stable phase.

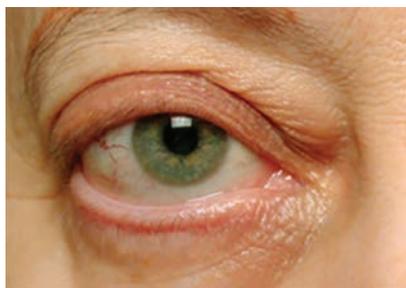


Figure 2. Exposure keratopathy from lower eyelid retraction in TED's stable phase.

• **Genetics.** Genetic factors clearly play a role in the development of TED. Graves' disease itself is known to have a hereditary component; twin studies have shown that monozygotic (identical) twins have a much higher incidence of Graves' (~30 percent) compared to dizygotic (fraternal) twins, at 3 percent.⁶ Furthermore, when asymptomatic family members of patients with TED were examined, many had early signs of TED without any systemic thyroid abnormalities.⁷ Scientists are spending a great deal of time identifying which genes in particular may cause someone to be susceptible to developing TED, in the hopes that this may help with prognosis and early treatment. However, the specific genetics of TED are still poorly understood.

• **Environmental factors.** Smoking is perhaps the biggest environmental risk factor that can trigger TED. TED is a disease of orbital inflammation, and the additional inflammatory molecules in tobacco smoke have been proven to significantly worsen disease⁸

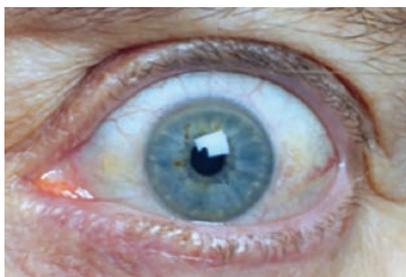


Figure 3. Upper eyelid retraction causing abnormal opening of the eyes.

by up to 700 percent, possibly due to the creation of free radicals and reactive oxygen species. This risk is directly related to the number of cigarettes smoked and is reversible—smoking cessation can lead to milder disease and visual improvement—so it is never too late to stop.

The gut microbiome has also been implicated in TED pathogenesis. Certain bacteria that colonize the intestines, such as *Yersinia enterocolitica*, create proteins that appear to be very similar to thyroid-related proteins. When the immune system mounts an attack against such bacteria, the antibodies can cross-react with the thyroid gland and related tissues, leading to worsening of disease.⁹

• **Nutrition factors.** Finally, various vitamins and minerals may be deficient in patients who develop TED. Selenium, a trace mineral important in the function of anti-inflammatory proteins, has been found to be deficient in patients with Graves' disease, hypothyroidism and TED,¹⁰ and selenium supplementation has been shown to reduce the symptoms of mild TED.¹¹

Vitamin D is also reduced in many autoimmune states, including Graves' disease, and may also be related to an anti-inflammatory effect that's still unclear.¹² Either a pre-existing vitamin deficiency has caused the development of TED, or the development of TED has consumed these vitamins and minerals such that the low levels reduce the production of anti-inflammatory proteins. In either scenario, supplementation of these factors may improve the course of TED.

Other Factors

Circulating antibodies to various thyroid-related proteins are responsible for the manifestations of Graves' disease, which results in hyperthyroidism. There have been several well-described antibodies that are relevant both to systemic Graves' and TED,

including anti-TSHR (thyroid-stimulating hormone receptor), anti-TPO (thyroid peroxidase) and anti-Tg (thyroglobulin) antibodies. These antibodies target thyroid-related proteins which

are present both in the thyroid gland and the orbit, as well as other connective tissues in the body such as the shins (leading to swelling, or pretibial myxedema).

Antibodies against TSHR are particularly important and can be further categorized as TSHR-binding (TBII), TSHR-stimulating (TSI) or TSHR-blocking.¹³ TSI seem to be particularly important, as the levels of TSI are directly correlated with clinical severity in TED, with a level greater than 400 suggesting moderate-to-severe disease.^{14,15} TSI may also help predict the development and severity of TED in both adults and pediatric patients.^{16,17}

Hyperthyroid Treatment

Physicians have several tools to treat hyperthyroidism, including oral anti-thyroid medicine (methimazole, propylthiouracil), radioactive iodine and surgical thyroidectomy. Oral medicine blocks formation of hormones in the thyroid, but doesn't alter antibody levels. Given the importance of TSI in the development of TED, it stands to reason that oral anti-thyroid medicine doesn't prevent the development of TED. Radioactive iodine treatment consists of administration of an iodine molecule that's absorbed by any cell that imports iodine internally, i.e., cells in the thyroid gland and the orbit. This leads to a powerful inflammatory response that



Figure 4. A possible symptom of thyroid eye disease is the inability to close the eyes even with forceful blinking, known as lagophthalmos.

can both worsen existing TED and increase the probability of development of TED in patients who don't have any ocular manifestations.¹⁸ Pre-treatment with steroids can reduce the risk of worsening TED.¹⁹

Surgical thyroidectomy is removal of the entire thyroid gland by a qualified head-and-neck surgeon. Risks such as vocal cord dysfunction, persistent calcium abnormalities or intraoperative bleeding or thyroid storm are low, and thyroidectomy may provide the quickest route to control of the thyroid hormones. While having excellent thyroid hormone control doesn't improve the course of TED, having poor thyroid hormone control may worsen TED (possibly by increasing the TSI level), so quickly and consistently achieving control of thyroid hormone levels is important.

Clinical Manifestations of TED

Thyroid eye disease has several characteristic manifestations, although the disease is notoriously asymmetric and variable in presentation. By far, ocular surface disease and eyelid changes are the most common, present in



Figure 5. Inwardly crossing left eye (esotropia) as a result of thyroid eye disease.

more than 90 percent of patients with TED. Proptosis is present in 70 to 80 percent of patients, and strabismus (extraocular muscle changes with double

vision) occurs in roughly 50 percent of patients. True sight-threatening disease is rare, on the order of 2 to 5 percent. Following is a detailed discussion of these manifestations.

- **Ocular surface disease.** Ocular surface disease encompasses all symptoms that relate to poor function of the eyelid-tear-cornea interface. These symptoms can include light sensitivity, gritty or painful eyes, tearing and blurry vision when reading, driving, working on the computer or watching TV. These symptoms may be worsened in windy, dry or low-humidity conditions.

Ocular surface disease in TED has two main causes: ocular inflammation and ocular exposure. In the first 12 to 18 months of TED, when the disease is in the active phase, inflammatory molecules can attack the mucous-producing cells, tear gland and the corneal surface, and cause breakdown of the tear film (*Figure 1*). In the stable phase, inability to close the eye completely due to eyelid changes can lead to chronic exposure of the inferior portion of the cornea, leading to dryness (*Figure 2*). It's important to distinguish between the two causes, as the treatments differ. Inflammatory

dry eye demands control of the inflammation, either via control of the thyroid disease itself or with topical steroid drops. Dry eye from chronic exposure can be treated with artificial tears and other forms of ocular lubrication, as well as orbital decompression.

sion or eyelid surgeries. The two types of dry eye often coexist, and it's important to perform a careful evaluation to address each patient's unique condition.

- **Eyelid.** Thyroid eye disease primarily causes upper and/or lower lid retraction (Figure 3). This disturbs the normal blink reflex and can lead to inability to close the eye, or lagophthalmos (Figure 4). This is caused by fibrosis, or scarring in the muscles that maintain the eyelid position. Some form of eyelid retraction is present in more than 90 percent of patients with TED, and it can be very asymmetric. Eyelid surgery can often improve the cosmetic and functional aspects of these eyelid changes.

- **Extraocular muscles.** Strabismus, or misalignment of the eyes, is a common finding in TED, and is present in roughly half of patients (Figure 5). Enlargement of the extraocular muscles that move the eyeball leads to inability of these muscles to relax, pulling the eye away from the neutral gaze. Double vision resulting from strabismus can be one of the most debilitating consequences of TED, impairing the ability to drive, read or work. Pressure on the eyeballs from these enlarged muscles can also lead to increased intraocular pressure and glaucoma. Strabismus surgery or prisms in spectacles can help improve double vision, although a small amount of diplopia in extreme positions of gaze often remains.

- **Orbit.** Growth of fat, muscle and fibrous tissue leads to an increased volume of orbital soft tissue, while the bony confines of the orbit don't change. Like a scoop of ice cream on a cone that's too small, the eyeball can be pushed forward, known as proptosis (Figure 6). This bulging of the eyes is cosmetically dis-



Figure 6. Proptosis, or bulging of the right eye, due to growth of tissue behind the eyeball in thyroid eye disease.

figuring and causes dry eye, eye pain and other disturbances in visual function. The overall tightness of the orbital tissues also causes congestion and poor blood flow, which leads to swelling, redness and a dull ache behind the eye (Figure 7). If the tightness is severe enough, patients may even experience vision loss due to corneal ulceration or lack of blood flow to the optic nerve. Patients need a combination of medical and surgical therapies for rehabilitation after these conditions develop.

Currently, a thorough understanding of the molecular basis of thyroid eye disease has allowed for earlier diagnosis with more accurate prognostication. Much research still needs to be done, however, since it's unclear exactly which factors trigger the onset of TED in a patient with Graves' hyperthyroidism. Elucidating these factors may allow accurate prediction and allow for earlier treatment. In Part 2 of this series on thyroid eye disease, which will appear in the next installment of Plastic Pointers, we'll delve into ways of managing TED. **REVIEW**

Dr. Ramesh is a clinical assistant professor of ophthalmology at Sidney Kimmel Medical College at Thomas Jefferson University, and a member of



Figure 7. Orbital congestion with redness, swelling and retrobulbar ache in thyroid eye disease.

the Wills Eye Hospital Orbital and Oculoplastic Surgery Service. He practices at Eye and Facial Plastic Surgery Consultants in Langhorne, Pennsylvania. His areas of interest include TED, facial trauma and cosmetic facial and eyelid procedures.

1. Wang Y, Smith TJ. Current concepts in the molecular pathogenesis of thyroid-associated ophthalmopathy. *Invest Ophthalmol Vis Sci* 2014;55:3:1735-48.
2. Bartley GB. The epidemiologic characteristics and clinical course of ophthalmopathy associated with autoimmune thyroid disease in Olmsted County, Minnesota. *Trans Am Ophthalmol Soc* 1994;92:477-588.
3. Bartley GB, Fatourech V, Kadrmas EF, et al. Chronology of Graves' ophthalmopathy in an incidence cohort. *Am J Ophthalmol* 1996;121:4:426-34.
4. Shan SJ, Douglas RS. The pathophysiology of thyroid eye disease. *J Neuroophthalmol* 2014;34:2:177-85.
5. Rundle FF, Wilson CW. Development and course of exophthalmos and ophthalmoplegia in Graves' disease with special reference to the effect of thyroidectomy. *Clin Sci* 1945;5:3-4:177-94.
6. Brix TH, Kyvik KO, Christensen K, Hegedus L. Evidence for a major role of heredity in Graves' disease: A population-based study of two Danish twin cohorts. *J Clin Endocrinol Metab* 2001;86:2:930-4.
7. Ardley M MT, Lahooti H, Champion B, Wall JR. Eye findings and immunological markers in probands and their euthyroid relatives from a single family with multiple cases of thyroid autoimmunity. *Thyroid Res* 2012;5:4.
8. Bahn RS, Heufelder AE. Pathogenesis of Graves' ophthalmopathy. *N Engl J Med* 1993;329:20:1468-75.
9. Luo G SG, Niesel DW. Purification and characterization of Yersinia enterocolitica envelope proteins which induce antibodies that react with human thyrotropin receptor. *J Immunol* 1994;152:2555-61.
10. Liu Y, Liu S, Mao J, et al. Serum trace elements profile in Graves' disease patients with or without orbitopathy in northeast China. *Biomed Res Int* 2018;2018:3029379.
11. Marcocci C, Kahaly GJ, Krassas GE, et al. Selenium and the course of mild Graves' orbitopathy. *N Engl J Med* 2011;364:20:1920-31.
12. Planck T, Shahida B, Malm J, Manjer J. Vitamin D in Graves disease: Levels, correlation with laboratory and clinical parameters, and genetics. *Eur Thyroid J* 2018;7:1:27-33.
13. Diana T, Kahaly GJ. Thyroid stimulating hormone receptor antibodies in thyroid eye disease—methodology and clinical applications. *Ophthalmic Plast Reconstr Surg* 2018;34:4S (Suppl 1):S13-S9.
14. Lytton SD PK, Kanitz M, et al. A novel thyroid stimulating immunoglobulin bioassay is a functional indicator of activity and severity of Graves' orbitopathy. *J Clin Endocrinol Metab* 2010;95:2123-31.
15. Ponto KA, Kanitz M, Olivo PD, et al. Clinical relevance of thyroid-stimulating immunoglobulins in Graves' ophthalmopathy. *Ophthalmology* 2011;118:11:2279-85.
16. Kampmann E DT, Kanitz M, et al. Thyroid stimulating but not blocking autoantibodies are highly prevalent in severe and active thyroid-associated orbitopathy: A prospective study. *Int J Endocrinol* 2015;2015:678194.
17. Diana T BR, Bossowski A, et al. Clinical relevance of thyroid-stimulating autoantibodies in pediatric Graves' disease - a multicenter study. *J Clin Endocrinol Metab* 2014;99:1648-55.
18. Bartalena L, Marcocci C, Bogazzi F, et al. Relation between therapy for hyperthyroidism and the course of Graves' ophthalmopathy. *N Engl J Med* 1998;338:2:73-8.
19. Tallstedt L, Lundell G, Topping O, et al. Occurrence of ophthalmopathy after treatment for Graves' hyperthyroidism. The Thyroid Study Group. *N Engl J Med* 1992;326:26:1733-8.

DMEK: New Insights, Emerging Advances

Kristine Brennan, Senior Associate Editor

While approaches to DMEK are still being standardized, even newer techniques and alternatives are on the way.

“There was a time when the only treatment for corneal edema we had was full-thickness corneal transplantation,” recalls Lorenzo Cervantes, MD, of Connecticut Eye Specialists in Shelton. In recent years, however, Descemet’s membrane epithelial keratoplasty has been taking over as the treatment of choice for many patients with corneal endothelial dysfunction. DMEK is an anatomical endothelium-to-endothelium transplant that requires less recovery time, achieves more predictable refractive outcomes and has lower rejection rates than other endothelial keratoplasty techniques. Here, experienced DMEK surgeons describe its benefits and explore emerging techniques that may soon make this beneficial but tricky procedure easier to perform and potentially suitable for more patients.

“In many respects, going from full-thickness keratoplasty to DSEK was one of the biggest game changers in the world of cornea,” Dr. Cervantes continues. “DSEK was leaps and bounds better than full-thickness corneal transplantation or full-thickness keratoplasty. But DMEK has become more and more mainstream for several reasons. DSEK involves transplanting endo-

thelium, but we’re also transplanting the posterior 20 percent of the donor cornea. With DMEK, there’s no stroma-to-stroma interface. That is leading to better-quality vision, and the recovery is even faster than after DSEK. A lot of my patients notice improved quality of vision by one to three months. The refractive results are much more predictable, to the point at which we can do DMEK together with advanced-technology IOL implantation. The rejection rates that we’re seeing are even lower than with DSEK: on the order of 1 to 2 percent over the course of a patient’s lifetime. For those reasons, I offered DMEK to my patients as soon as I was able to learn it.”

Preloaded Tissue

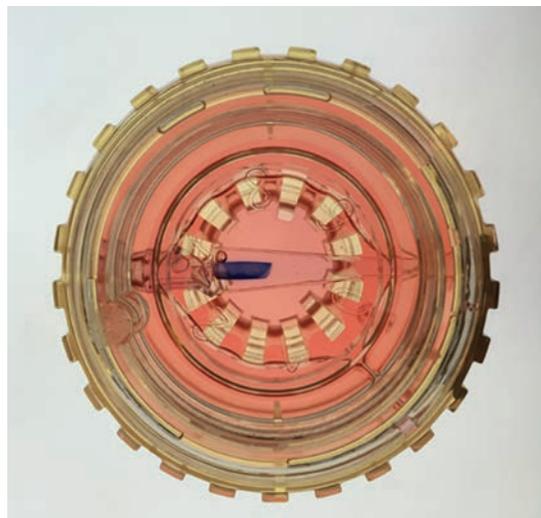
One of the original arguments against widespread DMEK adoption, according to Peter Veldman, MD, assistant professor, residency program director and vice chair for education, Department of Ophthalmology and Visual Science at the University of Chicago, was that the delicate and time-consuming nature of graft preparation made the procedure less efficient than DSAEK. “A few years back, many established DSEK surgeons would

talk about how quickly they could do a DSAEK—in 10, 15, or 20 minutes—and they were hesitant to transition to a surgery that would take perhaps an hour in the surgery center to achieve results that were believed to be equivalent at that time,” he says. The advent of Descemet’s grafts from eye banks that are trephined to order, pre-punched, pre-stained, stamped with an orientation mark and then loaded into an injector tube has changed that. “I think it took an average of 15 minutes off of my cases when I made the transition to patient-ready DMEK,” Dr. Veldman estimates. He serves on the medical advisory committee

(uncompensated) of Lions Vision-Gift eye bank in Portland, Oregon.

Michael D. Straiko, MD, associate director of corneal services at Devers Eye Institute in Portland, and an associate medical director (uncompensated) at Portland’s Lions VisionGift eye bank, says that orientation marks on donor tissue help eliminate a major source of error in DMEK. “Because one of the main causes of primary graft failure can be an upside-down graft, having these grafts marked with an ‘S’ or an ‘F’ or some other kind of really intuitive mark helps avoid that complication, which takes some of the fear out of it for the surgeon and increases the success rate,” he notes. “Our eye bank’s partners have taken it even one step further: Not only do they prepare the tissue, they measure the epithelial cell density and inspect it at the slit lamp after they measure it. Then they preload and pre-stain the graft so that it comes to you in the injector tube ready to be implanted into the patient.”

“Stamping is so helpful,” adds Dr. Cervantes, who is medical director (uncompensated) at Eversight eye



View of a preloaded, stained DMEK graft inside the glass Straiko modified Jones tube. Preloaded donor tissue can dramatically reduce time in the OR for DMEK.

bank in Connecticut. “We used to have to rely on the way that the graft unfolds under the microscope for orientation; this can be very difficult if your view is poor. The S-stamp really saves time and gives the surgeon confidence that what they’re doing is correct. The most common way of orienting the tissue is by the placement of an ‘S’ stamp, using a little printing-press stamp at the end of a handle dipped in gentian violet. They stamp the stromal side of the transplant with an ‘S’ so when you’re looking at it, if you see the letter ‘S,’ the graft is oriented correctly. But if you see the number ‘2,’ that means you’re upside down and you’ve got to flip the graft,” he explains.

Dr. Veldman says that F-stamping, in addition to S-stamping, is becoming commonplace. “You want a definitive orientation mark, like a stamp, done utilizing a validated technique that minimizes endothelial damage,” he says. “Having a definitive reference mark takes you over that last hurdle by eliminating the number-one cause of iatrogenic primary graft failure: putting a graft in upside down. I also think for sur-

geons looking to incorporate DMEK, eliminating that fear of putting the graft in upside down is a huge confidence booster. I’ve heard that countless times from colleagues.”

Dr. Veldman adds that orientation marks aren’t just for beginning DMEK surgeons. “If you talk to any experienced DMEK surgeon, they will on occasion open up a graft that they believed was right side up, only to see that the ‘S’ or the ‘F’ is backwards. That’s happened to me many times. Once recognized, it’s quite easy then to flip the graft over to the proper orientation, preventing what would have otherwise certainly resulted

in graft failure,” he says. “Published studies have shown that upside-down graft implantation occurs up to 10 percent of the time—and although the actual incidence is likely significantly less than that as surgeons gain experience, it is still far from zero.”

“Preloaded tissue appeals to surgeons because the technicians who process those grafts do it all day, every day,” concurs Dr. Cervantes. “When Eversight began promoting their preloaded DMEK tissue, I was one of the first ones to adopt it. I was comfortable preparing my own tissue, but I’m only doing a certain number of DMEK transplant procedures a month, whereas they’re processing a lot of donor tissue every day. Our eye bank started offering preloaded tissue in the fall of 2017. In the fourth quarter of 2017, about 8 percent of DMEK tissue was pre-processed; in the first two quarters of 2018, 30 percent was pre-processed. In this third quarter, about 58 percent of our DMEK tissue is now preloaded.”

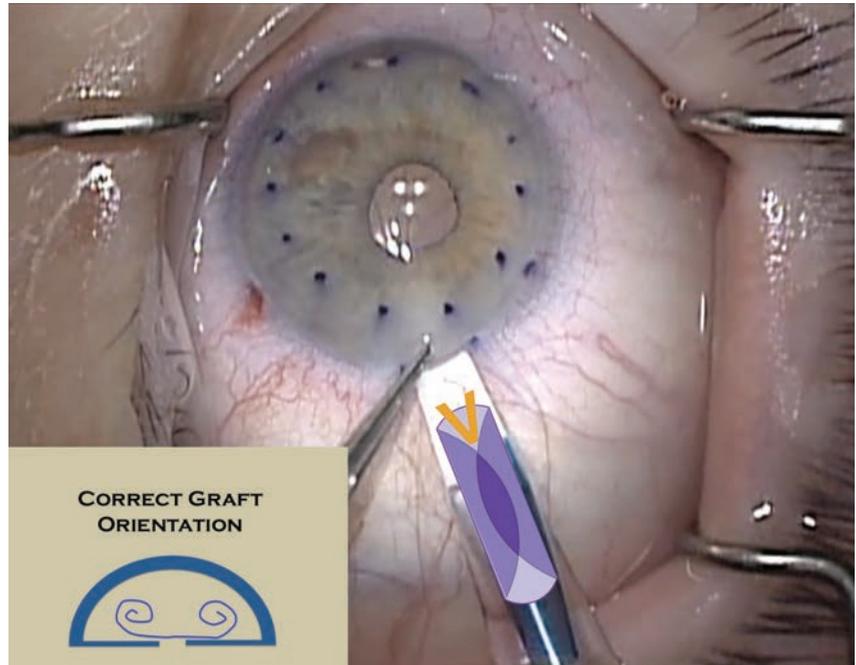
The rise of preloaded DMEK tissue brings attention to concerns

All images: Michael D. Straiko, MD

about eye banks' ability to select suitable donor tissue¹ and to meet the Eye Bank Association of America's requirements for post-processing assessments, however.² "Though I've been using the preloaded tissue, that decision to adopt it isn't universal," notes Dr. Cervantes. "I know some surgeons who prefer to prepare their own tissue, and their reasons are valid. In preparing DMEK tissue, the surgeon has the opportunity to see if there's been any endothelial cell damage prior to graft preparation. They can pick which part of the cornea they want to use. They might punch or prepare the tissue away from any areas of endothelial cell loss for improved quality. Perhaps the biggest reason not to use preloaded tissue, according to other surgeons, is probably the opportunity to assess the quality of the tissue before they prepare it and transplant it."

"There are surgeons who prepare DMEK tissue themselves to varying degrees," adds Dr. Veldman. "There is a billable code for tissue preparation in the OR [CPT code 65757]. For me, however, the time involved, as well as the risk of damaging the tissue, canceling a case and being out about \$3,000 for a lost graft doesn't stack up favorably against being able to bill for prep in the OR. Additionally, I feel very comfortable with the skillful tissue preparation techniques utilized by my partnering eye-bank technicians who do this for their profession."

Drs. Veldman's and Straiko's preloaded DMEK tissue comes in Straiko modified Jones tubes (Gunther Weiss Scientific Glassblowing Co., Portland, Oregon). Dr. Straiko came up with the idea for this glass injector after ample trial and error. "We were using IOL cartridge-based injectors, and I used a whole lot of different types of injectors, some that I'd cobbled together in the



A donor graft that is double scrolled, with both scrolls pointed upwards towards the stromal surface, is optimally placed for "dancing" the graft into proper position via external taps that take advantage of fluidics in the eye.

OR. But sometimes the graft tissue sticks to the plastic, or the plunger can damage the graft. I've also occasionally noted striations in the endothelial-cell mosaic with plastic, where you can tell that the graft was actually scraped on the way out of the injector. I haven't ever seen that with glass," he says. "I was trying to come up with something that was glass, about the right size and shape and already FDA-approved. I came up with using Jones tubes because they met these criteria, and when I googled 'Jones tubes,' I found out that they're actually made in Portland, not more than 15 miles from my office." He contacted the manufacturer, and the Straiko modified Jones tube was developed.

"A lot of people use the Straiko modified Jones tube," Dr. Cervantes notes. "It fits well through a 2.4-mm incision: This makes it very useful for when I combine DMEK with cataract surgery, which I can do through the same incision. There

are other glass injectors that will work through even smaller incisions, but they might not be useful when you're combining DMEK with cataract surgery."

Practice Aids

Regardless of whether you prepare your own DMEK tissue or what type of injector you use, surgeons agree that it's crucial to practice before attempting this tricky transplant on your own patients. Dr. Cervantes and Dr. Straiko recommend a modified artificial anterior chamber devised by Christopher Sáles, MD, to practice manipulating the graft.

"It's a really good training tool that uses an artificial anterior chamber that's been partitioned with a latex diaphragm. You put a corneal scleral cap on top, and then use that for practicing DMEK surgery," says Dr. Straiko, who was also an author on Dr. Sáles' paper describing the practice model.³ Dr. Straiko adds that he

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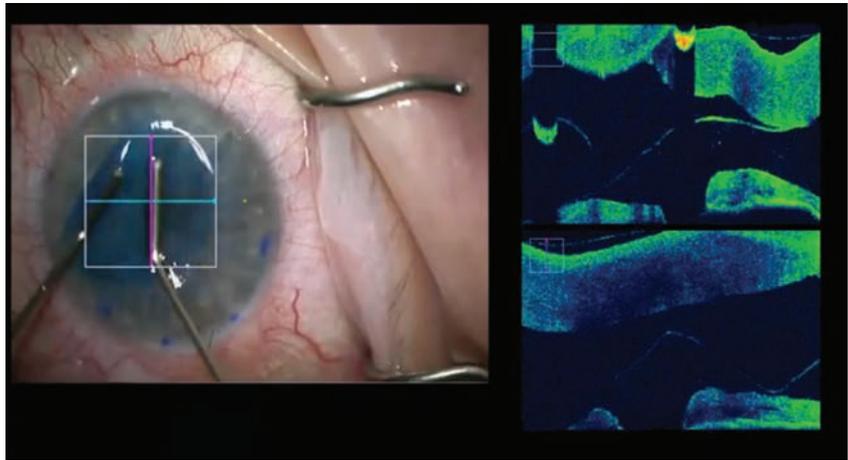
just observed its use at the Cornea Society’s educational summit for fellows in September. “It worked really well for training young surgeons to do DMEK,” he reports.

“It works so much better than cadaveric eyes, which are what we used to use,” says Dr. Cervantes. “Cadaver eyes get mushy and soft, and their corneas become hazy and cloudy. They definitely don’t behave like eyes that are full of life. But these artificial-chamber eyes do behave like actual eyes. Dr. Sáles’ practice model uses an artificial chamber to create the same type of fluid dynamics that we encounter during actual DMEK surgery, and it has been very well received.”

Dr. Straiko adds that the artificial anterior chamber may give surgeons an edge prior to attempting DMEK on patients. “Although it’s a very realistic model, I find that the surgery on real patients is a little bit easier, just because of the way the iris behaves in the model. But it’s still much better than practicing on a cadaver eye or a pig eye,” he says. He also recommends teaming up with a seasoned DMEK surgeon for your early cases.

Patient Selection

Once you’re ready to perform your first DMEK cases, patient selection is key to early success, says Dr. Straiko. “The other tip for people just getting started is that they should really look for eyes that have a normal lens-iris diaphragm and a normal anterior chamber depth. Shallow anterior chambers are okay, but you want to avoid hyper-deep chambers or any special circumstances, such as iris defects, unstable lens implants or prior vitrectomies. Those eyes are just more difficult to operate on; you’ll want to pick up your earliest experiences with DMEK in relatively normal eyes.”



Intraoperative OCT guidance can assist surgeons with decision making in real time and may reduce the risk of iatrogenic graft failure.

Dr. Cervantes adds that for all of DMEK’s potential benefits, there are some patients even experienced surgeons might want to offer other procedures. “There are instances where DMEK is not the best option,” he says. “For example, if a patient has a lot of corneal scarring in addition to corneal edema; a patient who has more complicated anterior segment anatomy due to the presence of glaucoma tubes or shunts; patients who’ve got anterior chamber intraocular lenses; patients who are aphakic; patients who’ve had a vitrectomy—these patients don’t make good DMEK candidates; their complex anatomy can interfere with the unscrolling and the unfolding of the DMEK graft. But a DSEK graft could do well in those eyes because it’s sturdier and easier to unfold inside the eye.”

DMEK Dancing

Dr. Cervantes says, “Universally, I think the hardest part of DMEK is learning how to unfold the graft. It’s unlike any other procedure that we do. It’s a series of tapping or corneal manipulations that creates fluid waves within the eye, affectionately known as the ‘DMEK dance,’ to unfold and move the graft around without directly touching it. There are all

sorts of different techniques and nuances to it. It’s very difficult to explain verbally or by reading; It’s probably best learned by seeing surgeons do it, and by practicing it before attempting it with a live patient.”

Dr. Straiko reiterates the need to practice dancing the graft into place until you understand it intuitively. “I think it’s important to partner up with a surgeon who’s experienced, so you can get a feel for how hard you tap and where you tap. It’s not just random beating on the cornea: It’s really directed taps, used to direct fluid currents in the eye to dance the graft open and into position,” he explains.

Dr. Veldman notes that managing unfolding of the graft warrants careful study. “When you’re learning DMEK early on and watching videos, it can just seem like a lot of tapping and cannulas flying around, and then suddenly, the graft is open. But really, if you break it down, an experienced surgeon is quickly recognizing what conformation the graft is in, and drawing upon their experience to choose a technique to open it. There are really only a handful of orientations a DMEK graft can be in once it’s in the eye. To be able to reliably and efficiently open a DMEK graft, you have to have a clear strategy for each possible orientation, quickly

assessing whether it's a simple fold, a double scroll or a single scroll, for example. What's the most likely strategy to work? The second? The third? What's the next conformation it's likely to go into? You can really be almost algorithmic about opening grafts," he says, adding that he recently spoke about standardizing one's graft-opening technique at the American Academy of Ophthalmology meeting in Chicago.

Sulfur Hexafluoride

Once you get the graft into place, surgeons differ as to whether to use air or 20% sulfur hexafluoride (SF6) gas to make it stick. "Some surgeons do well using just air for the fill at the end of the procedure; whereas others feel that air alone might not be enough to keep the transplant stuck for long enough," says Dr. Cervantes. "The SF6 stays in the eye longer and is safe for the transplant. But there's debate on its use, and there's variability in the rate of metabolism of the gas from patient to patient," he says.

Dr. Straiko, who currently uses SF6 in all his cases, says that bubble size matters when it comes to optimizing DMEK outcomes. "It's been reported by Friedrich Kruse's group, and has been validated by other studies, that bigger bubbles are better," he says. "You really want to have at least an 80-percent anterior chamber fill at the conclusion of the case to provide adequate graft support. There's also data that indicates that using SF6 gas can decrease the risk of rebubble procedures and graft detachments.

"I like the pressure to be elevated to about 40 mmHg for approximately two minutes, then I restore it to normal physiologic intraocular pressure," Dr. Straiko continues. "If I'm leaving a patient phakic, I want to avoid high pressures, since that could cause cataracts. For most patients I make sure to never go above 40; for others, that's not quite as critical. Obviously, if the patient has advanced glaucoma, you also want to avoid any high intraocular pressures, even transiently."

Pull-through Techniques

Compared to other keratoplasty procedures, DMEK is still relatively novel; as surgeons master protocols and they become somewhat standardized, innovation also continues apace. Bimanual pull-through techniques may expand the indications for DMEK, according to Dr. Straiko and Dr. Veldman.

"Pull-through methods hold a lot of promise for more complicated eyes," says Dr. Straiko, "including eyes with hardware from glaucoma surgery or anterior chamber IOLs, for example. Our standard DMEK techniques



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The circled area shows a region on a donor DMEK graft damaged by a plastic injector. Some surgeons think glass injectors are potentially less damaging to endothelial cells.

may not work or may cause too much damage to the graft in those patients. Pull-through techniques are a little more complicated because they rely on an anterior chamber maintainer, which can cause the fluidics in the eye to make the graft difficult to handle. But when they work, they can work very well, even in complicated eyes.”

As opposed to the push-through method technique using a glass tube or IOL-cartridge-based injector and no touching, pull-through DMEK requires the donor graft to be on a substrate of some kind that goes into the eye, and then comes back out without the graft, while the surgeon pulls the graft into place with forceps through a clear corneal incision. Dr. Straiko credits Massimo Busin, MD, with first reporting the use of a pull-through technique for graft insertion in DMEK, adding, “At Singapore National Eye Centre, Drs. Donald Tan and Jod Mehta have been working on modifying the EndoGlide (Network Medical; N. Yorkshire, U.K.) for DMEK.” Dr. Tan developed the EndoGlide, a dispo-

able plastic pull-through insertion aid; Dr. Busin has also been using the Busin glide for pull-through of corneal donor tissue for many years. Other conveyances include contact lenses or corneal lenticules. “Initially Dr. Tan was using the EndoGlide for putting a graft on a contact lens, or on a corneal lenticule,” says Dr. Straiko. “But now, they’re working on modifying it so that it doesn’t require any substrate: it just goes into the glide and the DMEK graft is pulled into the eye without any carrier tissue or contact lens.”

Dr. Straiko says that early data on various DMEK pull-through techniques suggest that they produce similar outcomes to standard DMEK techniques. “We’re currently working on a DMEK pull-through technique that we hope will make the procedure easier,” he says.

Because of the potential to use pull-through DMEK on more complex eyes, Dr. Straiko cautions about measuring pull-through outcomes against standard push-through DMEK with external tapping. “One caveat to keep in mind is to com-

pare pull-through DMEK to similar cases,” he emphasizes. “If you’re using pull-through DMEK for complex cases, you should expect higher complication rates and ECL rates just because of the nature of the eyes that get this technique done.”

Dr. Veldman also thinks that pull-through DMEK may open the procedure to eyes that are poor candidates for injector-based DMEK techniques and external tapping of the cornea. “There are situations where standard DMEK is not your best procedure, for example, in eyes with prior vitrectomy or unicameral eyes. If you utilize a pull-through, where you have complete control of the graft, it may open up these indications,” he says. “One of the things I’m looking forward to is the further simplification of the pull-through techniques. One thing that’s on my timeline right now is to let the dust settle a little on the validation of the various pull-through techniques, and then incorporate one into my practice for use in cases where a patient may be a less-than-ideal candidate for my routine external-tapping techniques.”

In addition to pull-through DMEK techniques, some promising treatments for corneal endothelial decompensation are noninvasive alternatives to DMEK, Dr. Veldman notes. “Another interesting emerging option is Desecemet’s Stripping Only, and what implications that will have for the number of DMEKs we’re doing,” he says. “It’s certainly a very promising technique for the right patients, but I don’t think we know yet exactly who the right patients are. My impression is that the ideal candidate is likely to be an individual with a relatively small amount of central Fuchs’ disease.” He also notes the emergence of Rho kinase inhibitor eye drops as a potential treatment to heal the corneal endothelium.⁴ “This medication may prove a useful adjunct for increasing the success and



A gentian violet “S” or “F” stamp helps beginning and seasoned DMEK surgeons alike ensure that the donor graft is right side up.

potentially expanding the indications for Descemet's Stripping Only. That said, it is important to note that this is an off-label therapy at present,” he says. (For a discussion of these new techniques, see “The Newest Treatment Options for Fuchs’” on p. 38.)

Although new DMEK techniques and even alternatives to transplantation loom on the horizon, surgeons say that mastering the currently prevalent push-through technique is well worthwhile to give select patients the best visual outcomes possible right now. “It does require an investment of time and effort to master it, but it's very worthwhile for the sake of your patients,” says Dr. Cervantes. Standardization is a double-edged sword, he adds. “I think that different parts of the procedure can be standardized to a degree, but they're also very much guided by surgeon preference, and they're also dependent on the individual patient's eye. From the size of the eye to previous eye disease, to how fast they metabolize the gas that we use at the end of surgery, every case is going to be a little bit different. We're all going to react to those factors differently as well.” **REVIEW**

Dr. Cervantes, Dr. Veldman and Dr. Straiko report no relevant financial disclosures. Dr. Straiko receives no remuneration or royalties for the Straiko modified Jones tube.

1. Vianna L MM, Stoeger CG, Galloway JD, et al. Risk factors for eye bank preparation failure of Descemet membrane endothelial keratoplasty tissue. *Am J Ophthalmol*. 2015;159:5:829–34.e2.
2. Eye Bank Association of America. 2016 Medical Standards. Washington, DC: Eye Bank Association of America; 2016.
3. Sáles CS, Straiko, MD, Fernandez AA, Odell K, et al. Partitioning an artificial anterior chamber with a latex diaphragm to stimulate anterior and posterior segment pressure dynamics: The “DMEK practice stage,” where surgeons can rehearse the “DMEK dance.” *Cornea* 2018;37:2:263–66.
4. Moloney G, et al. Descemetorhexis without grafting for Fuchs' endothelial dystrophy—supplementation with topical ripasudil. *Cornea* 2017;36:642–48.

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Making the Most of Corneal Cross-linking

Christopher Kent, Senior Editor

Many surgeons are using this procedure in ways that go beyond the current FDA approval.

It's very well established that corneal collagen cross-linking is an effective way to strengthen the cornea and prevent the progression of keratoconus and ectasia. However, cross-linking appears to be potentially useful in several other ways as well.

The U.S. Food and Drug Administration approval of epi-on cross-linking is relatively limited in scope; it applies only to the UV light system and riboflavin solutions designed by Avedro, and only gives approval to its use in patients over the age of 14 who have been shown to have progressive keratoconus or post-surgical ectasia. Those limitations, of course, are the result of the nature of the studies upon which the approval was based. Meanwhile, outside of the United States other uses for cross-linking are common, and new ones are under investigation. In fact, many surgeons in the United States are using the procedure in ways that go beyond the officially sanctioned indications.

Here, surgeons with experience using cross-linking in off-label ways discuss their experiences and share what alternate uses currently look most promising.

Treating Young Patients

The FDA approval states that kera-

toconus patients receiving this treatment should be 14 years or older and have disease that's progressing. However, many surgeons are treating patients younger than that—and they're not waiting for clinical proof that the patient's disease is progressing.

Parag A. Majmudar, MD, is associate professor of ophthalmology at Rush University Medical Center in Chicago and president and chief medical officer of Chicago Cornea Consultants. Dr. Majmudar began performing cross-linking in 2010; he's done hundreds of cross-linking procedures, especially treating post-LASIK ectasia, and has worked with Roy Rubinfeld, MD, on the development of an effective epi-on cross-linking procedure. Dr. Majmudar notes that his practice has never worried too much about documenting progression before treating a patient. "After all the years that cross-linking has been done internationally, we really believe in the technology," he says. "We know it's going to help prevent problems, so we haven't necessarily wanted to withhold treatment until progression has been documented. If a 14-year-old patient comes in with vision suddenly getting worse because of keratoconus, I don't see any reason to wait and have him come back three months later."

Dr. Majmudar also says his practice

will treat patients as young as 8 years old. “The youngest keratoconus patient I’ve treated myself was 10 years old,” he says. “These are cases that are perfect for cross-linking because we’re seeing the patients when they’re just starting to show signs of the disease. I think if we fast-forward 10 or 20 years after cross-linking, we’ll find that these individuals in their 30s and 40s are still maintaining stable topography and very good uncorrected or best corrected visual acuity, compared to what we’ve seen in patients who weren’t treated early. I’ve examined patients I treated six or seven years earlier when they were in their teens, and they’re still doing extremely well.”

A. John Kanellopoulos, MD, a clinical professor of ophthalmology at NYU Medical School in New York City and medical director of the Laservision.gr Institute in Athens, Greece, agrees that waiting for proof of progression can be counterproductive in young patients. “Cross-linking is globally acceptable for patients under 25 years old who have symptoms of visual change and keratoconus,” he says. “Most surgeons experienced with cross-linking would offer it as a means of stabilizing these corneas, even in the absence of enough follow-up to prove progression. In younger patients, keratoconus can progress rapidly, and the opportunity to address this and avoid a possible future transplant may be critical.”

William B. Trattler, MD, director of cornea at the Center for Excellence in Eye Care in Miami, agrees. (Dr. Trattler has been involved with corneal cross-linking since participating in the 2008 FDA clinical trial, and has done extensive work with Dr. Rubinfeld, Doyle Stulting, MD, and other surgeons on developing an effective epi-on cross-linking protocol as part of CXLUSA.) “Keratoconus is a progressive disease, and our experience is that children with keratoconus are likely to progress more quickly than adults,”



Corneal collagen cross-linking is showing potential far beyond simply mitigating the progression of keratoconus and ectasia.

he says. “When a child or teenager develops keratoconus, the general recommendation is to consider treatment with cross-linking at that time rather than wait for progression. I have one 10-year-old patient whose mom wanted her son to wait for spring break to undergo the cross-linking procedure. The family waited three months. During this time, the child’s corneal shape and vision declined. If the patient had undergone cross-linking within a few weeks, progression could have been avoided.

“Fortunately,” he adds, “not all young patients have rapid progression. But since it can be difficult to determine which young patients are most likely to progress rapidly, it’s helpful to provide cross-linking shortly after diagnosis rather than waiting to document progression.”

Treating Older Patients

Although the FDA didn’t place any upper age limit on treatment, older individuals are less likely to progress, making their treatment off-label. So, deciding whether to treat—and whether to wait for proof of progression—is a somewhat different problem when the patient is older.

“As the patient’s age at the time of the initial encounter increases—for instance, when treating a patient age 25 to 35—evidence of progression is

probably prudent prior to performing cross-linking,” says Dr. Kanellopoulos. “In general, patients over 40 are rarely found to progress, but we should never exclude that possibility. We recently encountered a patient in his 60s who, after many decades of a stable cone and without any specific explanation such as a recent increase in eye-rubbing, had increased progressive ectasia and had to be cross-linked.”

“We do have some elderly keratoconus patients,” says Dr. Majmudar. “Most of the time, patients who have keratoconus or ectatic disorders are going to slow down and stabilize by their mid 40s or so—although pellucid marginal degeneration may have a little bit longer time horizon.” Dr. Majmudar says he doesn’t put much stock in the idea of looking for proof of progression in older patients. “I don’t think that has any scientific merit,” he says. “The technology is so safe and effective—especially when you’re talking about epi-on technology—that we haven’t had a single complication in more than 2,500 cases. I don’t see any downside to doing it.

“However,” he continues, “there’s an out-of-pocket cost to the patient because insurance probably won’t cover it. That’s problematic, because if I’m asking someone to pay out-of-pocket, I want some sort of reassurance that they’ll see a clinically significant benefit. If an older patient hasn’t progressed in 10 years, I’m not going to ask him to spend money on a procedure that may or may not do anything for him. So in that situation, we suggest waiting. Even if there is progression, it will occur slowly.”

However, preventing progression isn’t the only consideration. Dr. Trattler points out that the idea that cross-linking only stabilizes the cornea is a misconception. “The cross-linking procedure also reshapes the cornea over time,” he explains. “The cornea will gradually become flatter, as happened in the FDA clinical trial, and

best-corrected vision can potentially improve as a result.

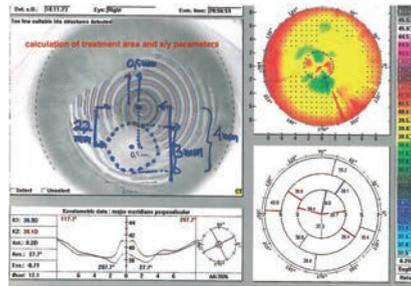
“For example, consider a 65-year-old patient with keratoconus who can achieve 20/20 with scleral contact lenses, but his best visual acuity with spectacles is 20/50,” he says. “Even though progression is uncommon in patients in their 60s, it can occur, and the cross-linking procedure will prevent that. More importantly, he could improve from a BCVA of 20/50 to 20/30 over two or three years.”

In fact, Dr. Majmudar says his practice sees a few older patients who just want to have cross-linking to see if it might have a positive effect on their topography. “We have seen improvements in a certain segment of the population at that age,” he notes. “They may not have been progressing, but after cross-linking, six months or a year later we see some corneal flattening and improvement in vision. It seems reasonable to us to do this and stabilize their corneas because they’re likely to have other surgeries such as cataract surgery in the future. So we haven’t limited ourselves to patients in a certain age range.”

Cross-linking with LASIK

One promising possibility for cross-linking is combining it with refractive procedures such as LASIK and PRK, potentially stabilizing the altered cornea and possibly offsetting any corneal weakness induced by cutting a flap.

Dr. Kanellopoulos says that his group has demonstrated that the use of cross-linking along with refractive procedures such as LASIK and PRK can be beneficial. “We’ve shown that cross-linking works synergistically with a partial topography-guided PRK normalization in keratoconus patients, using the Athens Protocol,” he says.^{1,2} “This approach has become the standard of care globally. In addition, the use of cross-linking along with LASIK may be viewed as a means to offset the



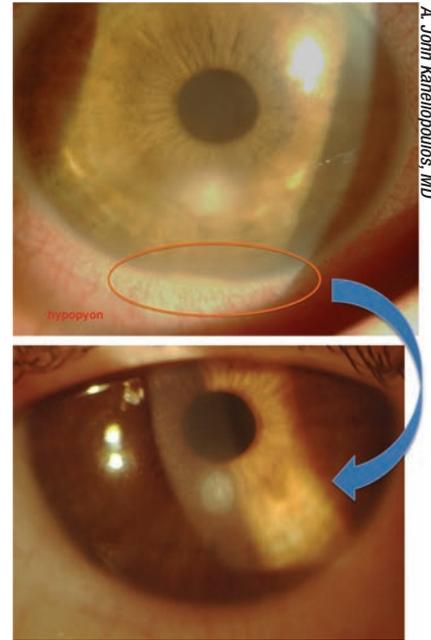
A case of infectious keratitis in a 38-year-old female, post-RK. A customized, variable-fluence, variable-pattern cross-linking treatment helped to address the infection.

reduction in biomechanical stability of the cornea caused by LASIK.”³⁻⁵

Some surgeons, however, are skeptical of combining cross-linking with LASIK. “In the international space there’s been discussion about a procedure called ‘LASIK Xtra,’ where the surgeon performs LASIK on a patient who may have a higher risk for ectasia,” notes Dr. Majmudar. “At the time of the LASIK procedure, the surgeon applies riboflavin to the stromal bed, replaces the flap, and then performs UVA light application to complete the cross-linking process. To me, this doesn’t seem like a great idea. If you have a patient who may be at risk for developing ectasia, I’m not sure I’d recommend doing LASIK in the first place. I’d do PRK instead. In fact, combining PRK with cross-linking may make more sense in some of these situations.

“Of course, if a post-LASIK patient has developed ectasia, treating it with cross-linking is appropriate—we’ve been able to demonstrate very successful outcomes, comparable to those seen in keratoconus patients,” he adds. “But as a routine procedure on a new patient who’s never had LASIK before, I don’t think performing LASIK and cross-linking at the same time makes sense.”

Dr. Trattler reports that he also is not a fan of combining LASIK and cross-linking. “If a patient is interested in undergoing laser vision correction,



A. John Kanellopoulos, MD

and during the preoperative evaluation keratoconus is identified, that patient should undergo cross-linking, not LASIK or PRK,” he says. “If the patient is found to have mild keratoconus and has good BCVA and a low refractive error, the patient can consider PRK. It’s simpler than a combination procedure. Simpler is often better, and PRK can provide very good visual outcomes.”

Dr. Kanellopoulos agrees that questions about combining LASIK and cross-linking remain. “Those questions include: Which eyes require this? And, should this approach be used in LASIK cases that are considered high-risk, such as high myopes or lower-age patients?” he says. “Of course, this should not be taken as an endorsement of performing LASIK in corneas that are suspicious for ectasia, such as forme fruste keratoconus.”

Cross-linking with PRK

Combining cross-linking with PRK is becoming popular outside the United States, especially when the PRK is topography-guided. “There’s still a very large segment of the keratoconus

population that has been left with a fairly irregular cornea which results in some refractive morbidity,” says Dr. Majmudar. “They can’t see well without a rigid or scleral contact lens. I think the next phase of treatment will be to take these irregular corneas and make them more regular by doing topography-guided PRK and combining that with cross-linking. This will allow patients to be less dependent on customized rigid lenses.

“I’d like to explore what’s already being done internationally—a protocol that combines topography-guided PRK and cross-linking, so we can treat patients who have these irregularities and rehabilitate them—not just try to prevent them from getting worse,” he says. “Most of the patients who have keratoconus are fed up and miserable with their contacts. Rehabilitating these patients is the holy grail in the field of keratoconus treatment.”

Dr. Majmudar notes that this could also help individuals who are early in the disease and hoping to get refractive surgery. “When one of these patients comes in and you’re not sure that operating on that eye is a good idea, topography-guided PRK combined with cross-linking to stabilize it might be a good solution,” he says. “These are patients who have funny-looking corneas—maybe not frank keratoconus, perhaps forme fruste keratoconus—but have pretty good visual acuity with glasses or contacts. We should be able to help them, either with a standard PRK plus cross-linking, or a topography-guided PRK if they have already developed some irregularity. That’s where we’re going to try to find a synergy between these two modalities.”

Dr. Kanellopoulos says his group has reported extensively on this type of work. “Last year at the American Academy of Ophthalmology meeting we introduced 10-year data on combining customized, topography-guided partial PRK with cross-linking

using the Athens protocol in eyes with ectasias and keratoconus,” he says. “This was a means to not only stabilize corneal ectasia, but also dramatically improve visual function.”



*Other applications
that are showing
promise include
using CXL to address
refractive error.*



Dr. Trattler, however, says he’s not a big fan of performing PRK and cross-linking simultaneously. “There’s an increased risk of corneal haze as well as other complications,” he points out. “For my keratoconus patients, I feel the more effective option is to perform cross-linking as a primary procedure. Over the next one to four years the corneal shape will improve. Then, at some point during the postoperative course, the patient may become a candidate for PRK to potentially further improve his vision and reduce the need for contact lenses or glasses.

“These are typically patients who start off with less-severe keratoconus,” he notes. “For patients with more advanced keratoconus, the advantage of performing cross-linking first is that the corneal shape can improve, and the cornea will have become stronger. Patients can then become candidates for topography-guided PRK. Of course, if there are any signs of keratoconus recurrence after PRK, they’ll need to undergo a second cross-linking procedure.

“When cross-linking is performed first, I recommend waiting six months to four or five years before performing PRK,” he adds. “The longer the time frame, the greater the improvement in corneal shape. In some cases

of mild keratoconus with a low refractive error and BCVA of 20/25 or better, rather than combining PRK and cross-linking, surgeons can perform PRK alone for refractive purposes and then observe patients on an annual basis during the postoperative period. If ectasia were to develop, the cross-linking could be performed at that time. Fortunately, in patients with mild keratoconus and low levels of myopia, the risk of ectasia after PRK is low.”

Treating Corneal Infections

Dr. Kanellopoulos notes that there have been several studies reporting that the use of corneal cross-linking can be effective for treating bacterial infections.⁶⁻⁸ “Obviously, the use of antibiotics is still considered standard of care,” he says. “However, cross-linking may help, in a bimodal way. First, it may reduce the occurrence of corneal melt and the spread of the infection within the corneal stroma by increasing the cornea’s rigidity. Second, it appears to have a direct bactericidal effect. It remains to be determined whether cross-linking will change the bioavailability of topical or oral antibiotics within these corneas, which could impact their efficacy, but the preliminary data shows that cross-linking can be an effective means to address some types of corneal infection.

“Along those lines, we recently submitted a report of a study in which we used customized, variable-fluence and variable-pattern cross-linking to pinpoint and topographically guide a spot of cross-linking on the infiltrate,” he says. “This approach was relatively successful at reducing the infiltrate size. Of course, this was done along with the use of topical antibiotics.”

Dr. Trattler reports that he has had some limited personal experience with treating corneal infections with cross-linking. “We treated one patient who had fungal endophthalmitis and developed a full-thickness fungal corneal

infection,” he says. “The cross-linking treatment didn’t work, which was most likely due to the fact that the cross-linking therapy couldn’t reach the deeper portions of the cornea.”

Dr. Majmudar says that he hasn’t tried using cross-linking to treat problems such as fungal or bacterial post-infectious keratitis, but he believes it may have value. “The main issue is that when you have an organism like a bacteria or fungus, collagenases—enzymes that break down collagen—are part of the defense mechanism your body uses to try to eradicate the organism,” he explains. “Unfortunately, collagenases can destroy normal corneal tissue as well. However, if the cornea has been strengthened using cross-linking, that might help to minimize the damage to the cornea itself. It’s also possible that the UV light itself may have a sterilizing effect. There’s definitely enough there to warrant further investigation.”

Combining CXL with Intacs

Dr. Majmudar says that combining cross-linking with Intacs has been a useful option. “I’ve done a fair amount of that,” he says. “Most of the time, we find that cross-linking gives us a significant amount of corneal flattening, but there are patients who still have to wear contacts, and they’re still unhappy. In the past, when we didn’t have the option of topography-guided PRK, all we had to help them was Intacs. Typically, my protocol was to wait about six months after cross-linking and then perform Intacs to see what additional impact we could have.

“The issue with Intacs has been that there’s a fair amount of variability in terms of the effect we get,” he continues. “In the United States we’re also limited in terms of what sizes of rings are available. For the longest time, we only had two ring thicknesses. The larger, 0.45-mm ring, did give us a little bit more flattening, but the results

Cross-linking for Post-RK Diurnal Fluctuation?

Parag A. Majmudar, MD, president and chief medical officer of Chicago Cornea Consultants, says he has tried using cross-linking for post-RK diurnal fluctuation, although only in a handful of cases. “That’s not enough to draw a meaningful conclusion,” he admits. “Nevertheless, we thought cross-linking might be effective for this purpose, but my sense is that it doesn’t work the way we’d like—the way it does for keratoconus or post-LASIK ectasia. There’s something in the mechanism of post-RK diurnal fluctuation that doesn’t lend itself to being limited by the cross-linking process.

“Others in our group have done a more extensive evaluation of this,” he adds. “Their conclusion is the same—that we can’t get a reproducible effect on post-RK corneas at this time.”

—CK

were still more variable than what we were seeing in other countries that had access to more ring options.

“As a result, we tended to favor sequential treatment rather than doing Intacs and cross-linking simultaneously,” he says. “Even so, we still had a fair amount of variability in our results, so it kind of fell out of favor in our practice. Perhaps the most significant factor was problems with reimbursement. Insurance companies rarely reimbursed us for the Intacs; a lot of times it was out of pocket for the patient. Since the results were not reproducible, it was hard for us to ask patients to pay for the procedure.”

Dr. Trattler says he’s aware of keratoconus patients who have undergone cross-linking combined with Intacs. “My understanding is that surgeons create the Intacs channels, and then inject riboflavin solution into the channels so the riboflavin can spread within the cornea,” he says. “Following treatment with the UV light, the Intacs segments can be placed.” Dr. Trattler notes that this can have another benefit. “At centers where effective epi-on riboflavin solutions are not available, using the Intacs channels for riboflavin placement can allow for an epi-on procedure,” he says. “That has a lower risk profile than epi-off cross-linking.”

CXL for Refractive Correction

Other applications that are showing

promise include the use of customized, variable-pattern, variable-fluence cross-linking to address refractive error, based on topography. “This is called refractive cross-linking,” says Dr. Kanellopoulos. “This includes the concept of treating corneal irregularity with a higher refractive correction than standard cross-linking.

“We reported the first clinical experience with this back in 2013,^{9,10} but it has yet to become mainstream,” he notes. “That’s partly because other options such as using a laser to treat refractive error are more time-proven. In the future, however, I wouldn’t be surprised to see cross-linking used as a means to modulate corneal biomechanics and generate slight refractive corrections. By then, the efficacy and safety track record of this type of procedure will be established.”

Dr. Majmudar says while he finds the idea of using cross-linking to produce a refractive correction plausible, he’s skeptical that it will work well. “I’m not sure you can tailor it precisely enough to get the exact effect you need to correct a refractive error,” he says. “Furthermore, how long will the change last? And is it reproducible? These are questions that need to be answered.”

Dr. Majmudar also points out that corneal changes associated with cross-linking that impact refraction are not the same from patient to patient. “I’ve seen some keratoconus corneas flatten

quite a bit after treatment, but I've also had patients with mild keratoconus who had virtually no flattening, at least with our type of cross-linking," he says. "In our experience, the higher the degree of irregularity in keratoconus, the more flattening we see. Of course, these treatments did not involve focal cross-linking, directed at a specific part of the cornea, and it's possible that changing the parameters might cause a greater effect. But I still believe that most 'normal' corneas are not going to get a significant refractive shift—certainly not more than 2 or 3 D at the most. So I doubt that it will replace a procedure like LASIK. I don't think it's precise enough to rely on, even in a keratoconus patient—at least not today."

It's Still Early in the Game

It's clear that corneal cross-linking is likely to end up being used in a number of ways. However, it's still early in the game, and much more research needs to be done. Not only do we need to know more about how to perform some of these procedures effectively, we need to know more about the cornea and how its characteristics make cross-linking useful—or a waste of time.

Dr. Kanellopoulos agrees. "A key piece of information needed to justify using cross-linking in a broader number of patients is missing," he says. "Until we have a metric to measure corneal biomechanical properties and what the threshold is for eyes to develop ectasia, we'll probably treat more corneas than actually need the treatment. We still don't really know which corneas require cross-linking prophylactically." [REVIEW](#)

Dr. Trattler has a financial interest in Avedro and CXL Ophthalmics. Dr. Kanellopoulos is a consultant for Avedro and Alcon. Dr. Majmudar is an investor in CXLO.

1. Kanellopoulos AJ. Comparison of sequential vs. same-day simultaneous collagen cross-linking and topography-guided PRK for treatment of keratoconus. *J Refract Surg* 2009;25:9:S812-8.
2. Kanellopoulos AJ, Asimellis G. Corneal refractive power and symmetry changes following normalization of ectasias treated with partial topography-guided PTK combined with higher-fluence CXL (the Athens Protocol). *J Refract Surg* 2014;30:5:342-6.
3. Kanellopoulos AJ, Asimellis G, Karabatsas C. Comparison of prophylactic higher fluence corneal cross-linking to control, in myopic LASIK, one year results. *Clin Ophthalmol* 2014;8:2373-81.
4. Kanellopoulos AJ, Kontos MA, Chen S, Asimellis G. Corneal collagen cross-linking combined with simulation of femtosecond laser-assisted refractive lens extraction: An ex vivo biomechanical effect evaluation. *Cornea* 2015;34:5:550-6.
5. Kanellopoulos AJ, Asimellis G, Salvador-Culla B, Chodosh J, Ciolino JB. High-irradiance CXL combined with myopic LASIK: Flap and residual stroma biomechanical properties studied ex-vivo. *Br J Ophthalmol* 2015;99:6:870-4.
6. Müller L, Thiel MA, Kipfer-Kauer AI, Kaufmann C. Corneal cross-linking as supplementary treatment option in melting keratitis: A case series. *Klin Monbl Augenheilkd* 2012;229:4:411-5.
7. Makdoui K, Mortensen J, Crafoord S. Infectious keratitis treated with corneal crosslinking. *Cornea* 2010;29:12:1353-8.
8. Zlot O, Barequet IS, Weissman A, et al. Does PACK-CXL change the prognosis of resistant infectious keratitis? *J Refract Surg* 2018;34:8:559-563.
9. Kanellopoulos AJ, Dupps WJ, Seven I, Asimellis G. Toric topographically customized transepithelial, pulsed, very high-fluence, higher energy and higher riboflavin concentration collagen cross-linking in keratoconus. *Case Rep Ophthalmol* 2014;5:2:172-80.
10. Kanellopoulos AJ, Asimellis G. Hyperopic correction: Clinical validation with epithelium-on and epithelium-off protocols, using variable fluence and topographically customized collagen corneal crosslinking. *Clin Ophthalmol* 2014;8:2425-33.



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The Newest Treatment Options for Fuchs'

Michelle Stephenson, Contributing Editor

A look at the cutting-edge treatments in development.

Fuchs' endothelial corneal dystrophy is the most common indication for corneal transplantation in the United States, and surgical management of this disease has undergone a revolution during the past 20 years.¹ Though endothelial keratoplasty is a highly effective treatment, investigators are searching for alternative treatment options because of the worldwide shortage of donor corneas and the risks associated with donor transplantation.

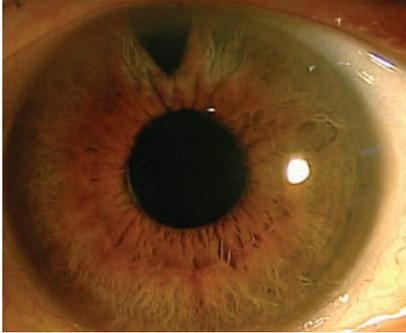
"Standard of care is partial-thickness corneal transplantation, typically the endothelium only," says Kathryn Colby, MD, PhD, chair of ophthalmology at the University of Chicago. "We still do way more Descemet's stripping endothelial keratoplasty (DSEK) in the United States than Descemet's membrane endothelial keratoplasty (DMEK). In 2014, I performed my first case of Descemet's stripping only (DSO), and we published our initial case series in 2016. Since then, it has really taken off. This is a simple technique, which involves removing the dysfunctional central corneal endothelial cells to allow healthier peripheral cells to migrate in. There is no long-term steroid use, no glaucoma and no chance of rejection. It's a really wonderful technique."

Descemet's Stripping Only

Although early case series on Descemet's stripping have yielded variable results, many more positive than negative outcomes have now been published, suggesting that this is indeed a promising technique for the treatment of Fuchs' endothelial corneal dystrophy, which would reduce the rate of surgical complications, eliminate the risk of rejection and lessen the demand for donor tissue.²

Dr. Colby's initial case series found that repopulation of the central corneal endothelium with corneal deturgescence can occur after deliberate central Descemet's stripping in patients with Fuchs' endothelial dystrophy who underwent cataract removal.³

In this retrospective case series, patients with Fuchs' endothelial dystrophy and visually significant cataract underwent phacoemulsification. After intraocular lens insertion, 4 mm of the central Descemet's membrane was stripped and removed. Vision assessment, corneal pachymetry and confocal imaging of the endothelial anatomy were performed preoperatively and 1, 3, 6 and 12 months postoperatively. Patients were classified as fast responders, responders, slow responders or nonresponders on the basis of postoperative time to resolution of corneal



All images: Kathryn Colby, MD, PhD

Figure 1. Slit lamp photo of a Descemet's stripping patient more than four years after surgery.

edema with demonstration of a visible central endothelial mosaic.

The study included 13 eyes of 11 patients, who ranged in age from 51 to 91 years. Preoperatively, no eyes had countable central endothelial cells by confocal imaging, and visual acuity ranged from 20/25 to 20/400. At days one and seven postoperatively, all corneas showed stromal and microcystic edema in the area of Descemet's stripping. Four eyes demonstrated resolution of corneal edema with a visible central endothelial cell mosaic (range: 410 to 864 cells/mm²) by postoperative month one, with visual acuity ranging between 20/25 and 20/40. Four additional eyes demonstrated a similar response by postoperative month three, and an additional two eyes had resolution of corneal edema with an intact central endothelial mosaic at postoperative month six or later. Cell counts (range: 428 to 864 cells/mm²) were maintained in all 10 responders at the last follow-up visit, which occurred between postoperative months six and 24. Final vision ranged from 20/15 to 20/20 in these 10 eyes, with the exception of two eyes with retinal pathology. Three eyes required endothelial keratoplasty. Dr. Colby's first Descemet's stripping patient will reach the five-year mark in January 2019 and is still doing well with no signs or symptoms of endothelial dysfunction.

According to Christopher J. Rapuano, MD, chief of the cornea

service at Wills Eye Hospital in Philadelphia, surgeons are still trying to determine the best instrumentation and candidates for this technique. "It works great, but it may not work forever. After a few years, the cells may die off, and patients may need an endothelial keratoplasty. However, there is a benefit to delaying it even a few years, and you can always do DSEK or DMEK later on," he says.

Adjunctive Use of ROCK Inhibitors

Rho kinase (ROCK) inhibitors have been used in combination with Descemet's stripping. A recent study comparing Descemet's stripping and DMEK included three patients who elected to apply a topical ROCK inhibitor (riipasudil 0.4%), which could potentially improve healing.²

The study found that Descemet's stripping effectively treats select patients with mild to moderate Fuchs' dystrophy, with visual outcomes equivalent to DMEK. While the recovery time with Descemet's stripping may be longer, these patients had fewer adverse events and less need for additional procedures. Additionally, they didn't need long-term immunosuppression or donor corneal tissue.

This retrospective comparative cohort study included 27 eyes with mild to moderate Fuchs' dystrophy (with corneal guttae/edema limited to the central cornea with relatively clear periphery). All procedures were performed at the University of Pittsburgh Medical Center between 2015 and 2017. Fifteen patients underwent DMEK, and 12 patients underwent Descemet's stripping.

At the end of phaco, 4 mm of diseased Descemet's membrane was removed. Visual acuity was measured using the Snellen chart and then converted to logMAR for analysis.

The average postoperative pinhole visual acuity was 20/25-1 (logMAR 0.16 ±0.09) for DMEK eyes and 20/30+1

(logMAR 0.13 ±0.10) for Descemet's-stripping eyes. The average time to 20/40 vision was 2.2 ±2.8 weeks for DMEK eyes and 7.1 ±2.7 weeks for Descemet's-stripping eyes. In the DMEK group, adverse events included: seven had increased intraocular pressure, one had anterior chamber inflammation, and one had graft nonadherence, with one patient (6.7 percent) requiring anterior chamber paracentesis and another (6.7 percent) requiring a rebubbling procedure. Patients in the Descemet's-stripping group experienced no adverse events.

Another Descemet's-stripping study included two cases that had been rescued by topical ripasudil.⁴ This Australian study found that descemetorhexis without grafting is a viable procedure for patients with Fuchs' dystrophy with visual degradation due to central guttae. While careful patient selection is required, the researchers note that the advent of topical ripasudil as a salvage agent suggests that a broader application of the surgery may be possible.

This study included 12 eyes of 11 patients who underwent central descemetorhexis that didn't exceed 4 mm. All patients had visual symptoms that were a result of Fuchs' dystrophy. Corneal status and visual parameters were recorded monthly until corneal clearance was observed. After corneal clearance, they were recorded every six months. Cases that failed to clear by month two were considered for salvage treatment,

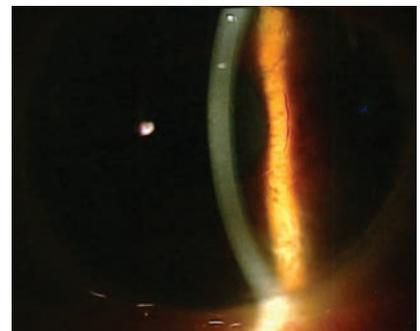


Figure 2. An image of the same patient from Fig. 1, showing the edge of Descemet's stripping and clear cornea.

which consisted of a ROCK-inhibitor eye drop. Endothelial keratoplasty was planned as the final salvage procedure in unsuccessful cases.

Of the 12 eyes, nine (75 percent) cleared spontaneously between two and six months. One eye failed to clear by month five, and the investigators administered topical Y-27632, a compounded ROCK inhibitor, without success. Endothelial keratoplasty was performed.

In two eyes, corneal healing stalled at two and three months. In both cases, complete corneal clearance was achieved by administering topical ripasudil six times a day for two weeks. In cases achieving corneal clearance, best-corrected visual acuity improved from a mean of 0.26 to 0.125 (log-MAR) with subjective improvement in quality of vision.

Cultured Cells + ROCK Inhibitor

Another new procedure is the injection of cultured cells in combination with a ROCK inhibitor.⁵ This procedure has been investigated by Japanese surgeon Shigeru Kinoshita, MD, PhD, and colleagues.

“It’s been performed in a variety of ways over the years, in animals and then in early human studies,” Dr. Rapuano explains. “Endothelial cells are taken from a donor or from the patient undergoing treatment, and brought into the lab. Then, a ROCK inhibitor is used to help multiply the cells. You can take a small number of cells and expand them many times. They can then be implanted in multiple patients. The cells are injected into the patient who then has to lie face down for a few hours. Theoretically, gravity forces those cells to stick onto the endothelium and then grow and repopulate to eliminate Fuchs’ dystrophy corneal edema.”

This same concept can be applied to cells from other parts of the body. “This can theoretically also be done

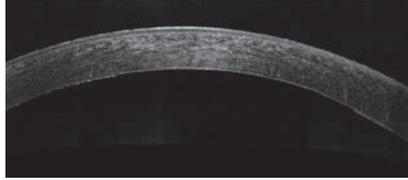


Figure 3. Anterior segment OCT showing the edge of Descemet's stripping.

with skin cells or lip cells. Additionally, to avoid rejection, the patient’s own cells can be harvested and expanded in the lab. Once you’ve expanded a few cells to hundreds or thousands of cells, you can put all of them back in the eye. There is no chance of rejection and no need for long-term steroids,” he adds.

Dr. Kinoshita recently published a study that found that the injection of human corneal endothelial cells supplemented with a ROCK inhibitor resulted in an increase in corneal endothelial cell density after 24 weeks in 11 people with bullous keratopathy.⁵ It’s well known that corneal endothelial cell disorders, such as Fuchs’ endothelial corneal dystrophy, induce abnormal corneal hydration that results in corneal haziness and vision loss, known as bullous keratopathy.

In Dr. Kinoshita’s study, the bullous keratopathy patients had no detectable corneal endothelial cells. Human corneal endothelial cells were cultured from a donor cornea. The researchers supplemented a total of 1×10^6 “subcultured” cells with a ROCK inhibitor and injected the cells into the anterior chamber of the eye that had been selected for treatment (subculture is used to prolong the life and/or expand the number of cells or microorganisms in the culture). Patients then remained in a prone position for three hours. The primary outcome was restoration of corneal transparency, with a corneal endothelial cell density of more than 500 cells per square millimeter at the central cornea at 24 weeks after cell injection. Secondary outcomes included corneal

thickness of less than 630 μm and improvement in best-corrected visual acuity equivalent to two lines or more on a Landolt C eye chart at 24 weeks after cell injection.

At 24 weeks after cell injection, all of the treated eyes had a corneal endothelial cell density of more than 500 cells/ mm^2 (range: 947 to 2,833), and 10 eyes had a corneal endothelial cell density exceeding 1,000 cells/ mm^2 . Ten of the 11 treated eyes achieved a corneal thickness of less than 630 μm (range: 489 to 640), and nine of the eyes achieved an improvement in BCVA of two lines or more.

The Future

According to Dr. Colby, even with these exciting new treatment options, endothelial keratoplasty is here to stay. “For other forms of endothelial dysfunction besides Fuchs’, either a tissue or a cell transplant will be required,” she says. “Additionally, patients who have advanced Fuchs’ will not be able to be successfully treated with Descemet’s stripping, because the disease is just too far gone. These patients don’t have enough healthy peripheral cells to repopulate.”

Another important area of research is the pathogenesis of Fuchs’ corneal endothelial dystrophy.¹ A better understanding of the pathogenic mechanism of the disease will hopefully allow for the development of medical therapies to treat or prevent this condition in the future, experts say. **REVIEW**

1. Sarnicola C, Farooq AV, Colby K. Fuchs endothelial corneal dystrophy: Update on pathogenesis and future directions. *Eye & Contact Lens*. July 12, 2018. E-pub ahead of print.
2. Huang MJ, Kane S, Dhaliwal DK. Descemetorhexis without endothelial keratoplasty versus DMEK for treatment of Fuchs endothelial corneal dystrophy. *Cornea*. September 14, 2018. E-pub ahead of print.
3. Borkar DS, Veldman P, Colby KA. Treatment of Fuchs endothelial dystrophy by Descemet stripping without endothelial keratoplasty. *Cornea* 2016;35:10:1267-1273.
4. Moloney G, Petsoglu C, Ball M. Descemetorhexis without grafting for Fuchs endothelial dystrophy—Supplementation with topical ripasudil. *Cornea* 2017;36:6:642-648.
5. Kinoshita S, Koizumi N, Ueno M, et al. Injection of cultured cells with a ROCK inhibitor for bullous keratopathy. *New England Journal of Medicine* 2018;378:11:995-1003.

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Everything You Need to Know About GATT

Gonioscopy-assisted transluminal trabeculotomy is showing efficacy for treating many glaucomas—even at advanced stages.

Davinder S. Grover, MD, MPH, and Ronald L. Fellman, MD, Dallas

Right now, there's a revolution taking place in glaucoma surgery centered around minimally invasive glaucoma surgeries, or MIGS. The overarching theme behind MIGS is safety, but as the popularity of MIGS increases, efficacy and cost effectiveness are also becoming an issue. Here, we'd like to provide an update on the MIGS procedure known as gonioscopy-assisted transluminal trabeculotomy, or GATT. GATT shows promise in all three areas—safety, efficacy and cost effectiveness.

The History of Trabeculotomy

The idea that a trabeculotomy might cause a drop in IOP first came to the fore back in the 1950s, when Morgan Grant, MD, hypothesized that 75 percent of resistance to aqueous outflow was inherent in the trabecular meshwork—and that it could be eliminated by creating an opening between the anterior chamber and Schlemm's canal.¹ Many years later, working with more sophisticated technology, David Epstein, MD, redid those studies and found that the

resistance produced by the trabecular meshwork was actually somewhere in the 60-percent range.² Despite the difference in the numbers, the conclusion was clear: The majority of resistance to aqueous outflow in POAG is caused by the trabecular meshwork. (This is often true in the secondary glaucomas as well.)

Using a trabeculotomy to restore flow through the patient's natural drainage system was a great idea; previous surgical alternatives involved creating an entirely different outflow pathway via options such as trabeculectomy or a tube shunt. (Those options don't involve the patient's natural drainage system at all. Moreover, shunting aqueous away from the natural drain may further contribute to the eye's impaired outflow capacity.)

One of the pioneers of this type of approach was Redmond Smith, MD, who published his initial description of the *ab externo* technique of trabeculotomy using a nylon filament in 1969.³ Initially, his version of the procedure generated a lot of interest because it showed great promise as a means to lower intraocular pressure,

especially in primary congenital and juvenile open-angle glaucoma. The idea that a trabeculotomy could potentially eliminate 75 percent of the outflow resistance was very appealing, so many surgeons were eager to try this in their POAG patients. However, his approach had several drawbacks and limitations that caused it to eventually drop in popularity:

- **It takes a long time to do.** Even in the best hands, this procedure takes 30 to 60 minutes or longer.

- **It violates the conjunctiva.** Performing a trabeculotomy *ab externo* requires a large conjunctival dissection, a large scleral flap and several scleral sutures. Surgeons didn't want to violate the superior conjunctiva and the sclera because it would make any subsequent surgery less likely to be effective.

- **The pressure drop wasn't as great as that obtained with a trabeculectomy or tube shunt.** Especially when trabeculectomy was performed with mitomycin-C, it produced a more significant pressure drop than *ab externo* trabeculotomy.

Ironically, we now know part of the reason for this: Many surgeons

GATT Outcomes in Patients with Different Surgical Status, with or without Cataract Extraction*

Surgical status**	POAG	POAG: GATT w/CE	POAG: prior CE	SOAG	SOAG: GATT w/CE	SOAG, prior CE
Months followed mean (SD)[range]	24.6 (6.1) [6-33]	24.5 (5.1) [6-31]	25.5 (6.4) [9-35]	25.5 (6.3) [6-32]	22.8 (6.4) [8-36]	25.7 (7.0) [9-43]
Number of patients requiring further IOP-lowering surgery	15 (33%)	3 (8%)	16 (43%)	9 (30%)	4 (16%)	4 (17%)
Number of patients at each follow-up						
Baseline	46 (100%)	36 (100%)	37 (100%)	30 (100%)	25 (100%)	24 (100%)
12 months	36 (78%)	33 (92%)	29 (78%)	25 (83%)	20 (80%)	18 (75%)
24 months	26 (57%)	27 (75%)	19 (51%)	19 (63%)	13 (52%)	17 (71%)
IOP, mean (SD)						
Preop	26.0 (6.9)	22.5 (5.4)	24.7 (6.2)	30.9 (10.0)	25.7 (6.3)	26.8 (7.9)
12 months	16.4 (6.4)	15.2 (4.3)	16.3 (4.4)	14.5 (5.1)	14.1 (2.9)	12.2 (2.8)
24 months	15.6 (5.7)	14.1 (3.2)	15.8 (7.4)	13.8 (4.5)	14.5 (4.4)	13.4 (4.7)
Number of medications, mean (SD)						
Preop	3.2 (1.1)	2.9 (1.1)	2.6 (1.1)	3.6 (1.2)	3.0 (1.3)	3.5 (0.8)
12 months	1.9 (1.6)	0.7 (1.0)	1.7 (1.3)	1.5 (1.5)	0.9 (1.3)	1.6 (1.1)
24 months	1.8 (1.5)	1.0 (1.1)	1.6 (1.4)	1.6 (1.8)	1.2 (1.6)	1.4 (1.1)

** POAG: Primary open-angle glaucoma. SOAG: Secondary open-angle glaucoma. CE: Cataract extraction.

* Based on Grover DS, Smith O, Fellman RL, et al. Gonioscopy-assisted transluminal trabeculotomy: An ab interno circumferential trabeculotomy: 24 months follow-up. J Glaucoma 2018;27:5:393-401.

performed *ab externo* trabeculotomy using metal trabeculotomes to open the canal. Because of the limitations associated with this approach, they were only opening the superior nasal and temporal parts of the meshwork. Anatomic studies have revealed that most of the outflow in the eye occurs inferonasally.⁴ So, not only was a significant amount of the trabecular meshwork not being opened, the sections that were being opened weren't as effective for drainage.

The impact of this on the effectiveness of the procedure was supported by a study published in 2012, in which eyes treated with a 360-degree trabeculotomy created with a nylon suture under a scleral flap (25 eyes with POAG and 18 eyes with secondary open-angle glaucoma) were compared retrospectively with 16 POAG and 19 SOAG eyes treated with metal trabeculotomes.⁵ At 12 months, the POAG patients' success rate was 84 percent using the sutures vs. 31 percent using the trabeculotome; it was 89 percent vs. 50 percent in the SOAG group. This demonstrates the

comparative power of opening up 360 degrees of the trabecular meshwork rather than, say, 120 to 180 degrees. The more of the angle you open, the greater the pressure decrease you get. (We see this same trend in the other MIGS surgeries currently available.)

Trabeculotomy: Previous Data

Before we discuss the details of performing the GATT procedure, let's review what some of the previously published data says about the effectiveness of trabeculotomy.

- A 2004 Japanese retrospective review included 149 eyes with primary congenital and juvenile open-angle glaucoma that received 360-degree *ab externo* trabeculotomy.⁶ The patients were followed for 9.5 ± 7.1 years; the data showed a success rate of nearly 90 percent at final follow-up. Mean IOP at that point was 15.6 ± 5.0 mmHg.

This supports the idea that circumferential 360-degree trabeculotomy is the gold standard for treating developmental glaucoma. We almost never see success rates in the

90-percent range with any glaucoma surgery, but we're seeing that with trabeculotomy in kids who have this type of glaucoma.

- Another Japanese study, published in 1993, looked at using *ab externo* 360-degree trabeculotomy in patients with open-angle glaucoma, POAG and pseudoexfoliation.⁷ Depending on which type of glaucoma the patient had, the three- and four-year success rates ranged from 60 to 70 percent. That's equivalent to the success rates found in the five-year Tube vs. Trab study.⁸ So there's significant long-term data showing that this type of surgery is equivalent to what major prospective studies have found with trabeculectomy and tube shunts.

- Another retrospective, multicenter study published in 2011 evaluated the surgical outcomes of trabeculotomy in 121 eyes that had steroid-induced glaucoma, comparing their outcomes to those in 108 eyes with POAG that underwent trabeculotomy and 42 steroid-induced glaucoma patients who underwent trabeculectomy.⁹ At three years, trabeculotomy was



A GATT procedure is performed. 1) Gonioscopic view showing the blunted prolene suture in the AC, filled with healon GV. A 25-ga. MVR blade has created a goniotomy. The back wall of Schlemm's canal (a white strip by the tip of the blade) is visible. 2) A blunted 5-0 prolene suture is used to cannulate Schlemm's canal. The tip is in the canal, confirmed by direct visualization. 3) The blue color of the prolene confirms placement of the suture through the entire canal. 4) The distal end of the prolene suture has circumnavigated the canal 360 degrees, and the tip is retrieved with microsurgical forceps. 5) Traction is placed on the proximal end of the suture. (Continued on facing page.)

significantly more effective at treating steroid-induced glaucoma than it was at treating POAG. However, the two surgeries were not significantly different when it came to treating steroid-induced glaucoma. This data suggests that, for treating this type of glaucoma, trabeculotomy is just as effective as trabeculectomy.

The Advantages of GATT

Over time, variations on the trabeculotomy procedure were developed. Then, about seven years ago, Dr. Fellman came up with the idea for GATT. As already noted, earlier methods for performing trabeculotomies were *ab externo*, requiring the creation of a scleral flap, with all of the associated problems. Some recent versions also used a catheter, which has a few drawbacks as well. The *ab interno* GATT procedure has eliminated many of those drawbacks while maintaining the advantages and remarkably good success rate that a complete, 360-degree trabeculotomy has to offer.

To perform a GATT, we begin by making a goniotomy in the nasal quadrant. We then cannulate the canal with a 5-0 prolene suture that's been blunted using low-temperature cautery, which allows it to go around the angle more easily. We pass the suture through the canal 360 degrees, retrieve the end and then pull the loop into the anterior chamber. (See example, above.) The result is that

we've treated 360 degrees of the angle with just two small paracenteses. This leaves a trabecular shelf.

Typically, our postoperative regimen is primarily concerned with keeping any inflammation under control. Patients are on steroids and antibiotics four to six times a day for the first week. If we see a steroid response and the IOP is 17 mmHg or higher, we'll add pilocarpine at night plus a beta-blocker; if it's 22 mmHg or above, we'll have the patient use pilocarpine twice a day throughout the follow-up period. At one week we stop the antibiotics but keep the patient on steroids until the eye is quiet; then we taper the steroids.

Sometimes we'll keep our patients on Pred Forte once a day, and possibly pilocarpine at night, for three to six months, just to theoretically inhibit any potential wound healing in the angle. (The goal of the surgery is not to get the patient off all drops; the goal is to decrease dependence on medications and lower the pressure.) We also have the patient follow hyphema precautions—primarily keeping the head of the bed elevated—until the hyphema is gone.

The advantages GATT include:

- It's much safer and less invasive than *ab externo* trabeculotomy; it only requires making two small paracenteses.
- It restores flow through the eye's natural drainage system.
- It takes much less time to perform than *ab externo* trabeculotomy.

- It doesn't violate the conjunctiva, so it doesn't limit future surgical options.

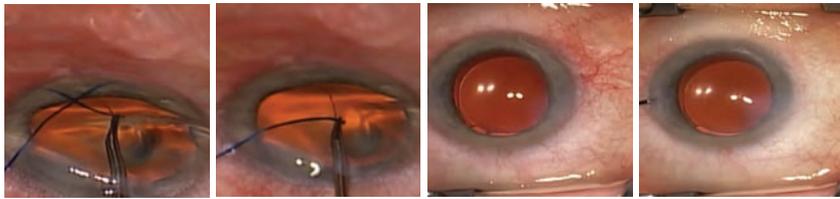
- It's cost effective and can be performed with a \$4 suture (5-0 prolene).
- It's very safe, with few complications. Those that do occur tend to be self-limiting with minimal consequences.
- Our data indicate that it's very effective. (More on that below.)

In terms of limitations, it's still true that a procedure such as a trabeculectomy might achieve a very low IOP such as 10 mmHg, which isn't likely to be achieved with a GATT. However, one reason that MIGS procedures have become popular is that surgeons have realized that not every patient requires a pressure that low.

What Our Data Show

In recent years we've conducted several studies to determine how effective the GATT procedure is when treating different types of glaucoma. The results indicate that it can be very effective, although its effectiveness varies with the type of glaucoma and its severity.

- In 2014 we published a study involving 85 eyes of 85 patients; 57 had POAG and 28 had secondary open-angle glaucoma.¹⁰ Both POAG and SOAG patients showed a significant and sustained drop in pressure and a significant, sustained decrease in dependence on drops. At 12 months the POAG patients



6 & 7) A complete 360-degree circumferential trabeculotomy is completed. 8) One can begin to see blood reflux into the anterior chamber. 9) With aggressive irrigation, balanced salt solution is used to lavage the downstream collector channels. A nearly 360-degree episcleral venous fluid wave confirms the patency of the downstream collector channels.

had an average IOP decrease of 11.1 mmHg (SD=6.1), with a reduction in medications of 1.1. The secondary-glaucoma group showed an IOP decrease of 19.9 mmHg (SD=10.2), with 1.9 fewer medications being used. Eight of the 85 patients (9 percent) were considered to have failed because they needed further glaucoma surgery.

- In 2015 we published a study examining the effectiveness of this surgery on children who had a dysgenic anterior segment angle and uncontrolled primary congenital glaucoma or juvenile open-angle glaucoma.¹¹ This was a retrospective chart review; patients ranged in age from 17 months to 30 years old. Fourteen eyes of 10 patients underwent GATT. We found that mean IOP decreased from 27.3 to 14.8 mmHg—a tremendous drop—and mean medication use decreased from 2.6 to 0.86 drops. This supports our belief that this technique (either *ab interno* or *ab externo*) is an excellent primary surgery for these types of glaucoma.

- In 2017 we published a study regarding the use of GATT in 35 eyes of 35 patients with prior incisional glaucoma surgery (mean age: 67.7 years; mean follow-up time: 22.7 months).¹² Nineteen eyes had a prior trabeculectomy; 13 had a prior glaucoma drainage device; four had a prior Trabectome; and five had prior endocyclophotocoagulation. Overall, IOP dropped from 25.7 mmHg to 15.4 mmHg; medication use dropped

from 3.2 meds to 2 meds ($p < 0.001$).

Traditional thinking has been that patients with a previous trabeculectomy or tube shunt would have a somewhat degraded natural drainage system, potentially minimizing the effectiveness of a trabeculectomy. However, the data for each group in this study showed that all patients benefited from the GATT surgery. Despite the fact that these patients had a prior failed trabeculectomy or tube, we were able to re-establish flow through their own drainage system.

Overall, at 24 months, in this refractory glaucoma group, about 60 percent of patients did well. (Keep in mind that these patients would be considered high-risk; they'd already undergone failed prior incisional surgery.) At 24 months only about 30 percent of eyes required further incisional surgery. Looking at the groups separately revealed that the prior-tube group did a little better with a GATT than the prior-trabeculectomy group. But even in the prior-trabeculectomy group, we were able to re-establish flow in a significant number of patients.

- In 2018 we published a report summarizing the two-year data from the original cohort of patients we treated when first developing the GATT technique.¹³ The data included 198 eyes of 198 patients with no prior incisional surgery; all of them had open-angle glaucoma with a mean pressure ≥ 18 mmHg. We divided the patients into categories based on their type of glaucoma and situation relative to cataract surgery, as follows:

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Pearls for First-timers

If you're trying GATT for the first time, surgeons advise:

- **Know your angle anatomy.** If you don't know the angle anatomy, you can't do this surgery.
- **Practice performing intraoperative gonioscopy.** Initially, just get used to holding the gonioscope on the eye and manipulating it. Get a sense of the spatial and tactile feedback so you'll be comfortable with it when you do the surgery.
- **Practice the type of moves you'll be making during the surgery.** The first way a surgeon can get used to doing angle surgery is to practice the hand motions with an uncomplicated cataract

surgery patient. After you put the lens in the bag, but before you wash out the Provisc, just tilt the head and the scope and put your second instrument in the angle. See what it looks like, see what it feels like. This will help you get used to doing that type of maneuver before you jump into doing any type of angle surgery.

- **Consider starting with a different MIGS surgery.** It may be easier to start by implanting a few iStents or using the Kahook Dual Blade or Trabectome while you're getting used to performing surgery in the angle.

—CK

patients with POAG; those who had phaco at the same time as GATT; pseudophakic patients; secondary open-angle glaucoma patients; SOAG patients who had phaco and GATT at the same time; and pseudophakic SOAG patients. (See table, page 43.)

Findings included:

— POAG patients overall had a mean decrease of 9.2 mmHg (37.3 percent), with a decrease of 1.43 medications.

— SOAG patients overall had an average decrease of 14.1 mmHg (49.8 percent), with a decrease of two medications.

— The cumulative proportion of failure at two years ranged from 0.18 to 0.48, depending on the group.

In terms of complications, the vast majority of these patients had a hyphema, most of which resolved at one week. None of these patients developed any significant or harmful complications. There was one case of choroidal detachment, and there were a handful of other isolated complications, but all were minimal and self-limited, and they resolved quickly. In terms of safety, this procedure is head and shoulders above trabeculectomies and tubes.

Choosing the Right Patients

There's a very important point to note here: It's crucial to pay attention to the status and condition of the individuals participating in any

study—particularly in terms of how sick the eyes are. This is especially true when the study concerns a MIGS procedure. For example, the COMPASS trial, iStent studies and Hydrus study were all done on patients with a Humphrey visual field mean deviation of 0 to -5 or so. In other words, the eyes being studied were fairly healthy.

In contrast, consider the eyes in the last study discussed above. They had pressures in the upper 20s on two to three medications, with mean deviations ranging from -6.5 to -11.8. In other words, the impressive results we obtained were in patients with advanced disease that could potentially blind them if not treated appropriately. This suggests that, unlike many MIGS procedures, GATT may be appropriate even in some eyes that have advanced disease.

It's also important to consider how different subgroups within a study responded to treatment. For whatever reason, the subgroup of patients who were pseudophakic in this study tended to do significantly worse than the other subgroups. Forty-three percent of them—almost half—were counted as failures because they needed further glaucoma surgery. At the same time, the data make it clear that the SOAG patients tended to do better. That makes sense, because most of the time their problems are associated with the trabecular meshwork, so removing the trabecular

meshwork works well for them. Overall, the POAG groups did pretty well; at 24 months the cumulative proportion of failure was anywhere from 10 to 30 percent. The subgroup that did the best was the patients who received GATT at the same time as cataract surgery.

The exception among the POAG patients was the pseudophakic group; they tended to be older, with a worse mean deviation, and they tended to do worse after GATT. About 40 percent of the pseudophakic POAG patients needed further surgery at 24 months. GATT did lower their pressure; it just wasn't sufficient for this group of patients, who needed an IOP in the low teens.

The data also made it clear that patients with the most serious disease are unlikely to get enough help from an angle procedure. Our criteria for failure was very similar to the Tube vs. Trab study, and at six months, almost 90 percent of POAG patients with a mean deviation of -15 dB or worse failed. (Notably, this paper was one of the first to demonstrate a correlation between phase of disease and outcome.) These patients should not have an angle surgery—including GATT. They have resistance to outflow at multiple layers, not just at the trabecular meshwork. To prevent further damage, they need a pressure of 11 or 12 mmHg—the kind of pressures you may only achieve with a trabeculectomy, tube shunt or pos-

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sibly a XEN45 implant, for example. They need more relief than any angle surgery will be able to give them. They need a new drain.

This was an important realization for us. When we first came up with the GATT procedure, we thought it was the best thing since sliced bread; we were doing it in everybody. Now we realize that as effective as GATT is, it's not going to be sufficient to rescue some patients. Knowing this is allowing us to tailor the surgery to the patient based on the stage of disease.

Despite this caveat, we believe the GATT procedure produces pretty impressive results. Of the original cohort—with the exception of the pseudophakic POAG patients—70 to 90 percent did not need a new trabeculectomy or tube after GATT. That's pretty powerful. In fact, in our clinical practice the GATT procedure has significantly decreased the number of patients that need a trabeculectomy or tube.

Strategies for Success

When performing GATT, these strategies will help ensure a good outcome:

- ***If the patient has a significant layered hyphema postoperatively, consider washing it out.*** Everyone has a different preference when it comes to something like this, but we believe that blood in the eye after surgery is a bad thing, so we're pretty aggressive. If the patient has a significant layered hyphema at the one-week point, we have a low threshold for washing it out.

- ***Patients with newly diagnosed severe glaucoma may do better with GATT.*** This is because years of drops can have a deleterious effect on the eye. In the United States, patients with very advanced glaucoma have usually been on drops for 10 or 20 years. In those rare cases in which an eye is newly diagnosed with advanced

glaucoma, however, the eyes tend to do better with angle surgery.

This is relevant because as previously noted, patients in the United States with a mean deviation of worse than -15 tend to do poorly with GATT. However, I've also done this surgery in developing countries. As the visiting doctor from America, I'm usually given the most advanced cases. Notably, however, these eyes have not been subjected to years of drops and preservatives. I was shocked to discover that despite their advanced disease, these virgin eyes did very well with GATT—much better than U.S. eyes that are in similar condition, but with years of exposure to eye drops.

We're still researching this, but I think it's going to have tremendous implications for our work in developing countries. In the meantime, it's challenged my understanding of glaucoma drops and lowered my threshold for doing nonmedical treatments for glaucoma, be it selective laser trabeculoplasty or a MIGS procedure.

- ***Advise patients who like to sleep on their side to sleep on the same side as the surgery.*** As already noted, the vast majority of outflow is in the nasal quadrant. If a patient lays straight back with the head elevated, the blood will settle down. However, if the patient is going to rest on one side or the other, we want her to turn toward the side of the surgery so that the blood pools temporally, not nasally. For example, if we perform GATT on the left eye, the patient should lean to the left. If the patient rests on the right side, the blood will pool nasally in the operated eye, in the part of the angle that's responsible for the greatest outflow.

This advice is the opposite of what the patient will expect, so it's important to mention it.

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patients, no matter what the surgery is—cataract surgery, tube shunts or angle surgery. Getting the head above the heart minimizes episcleral venous pressure and minimizes blood reflux. We believe this increases the safety of the surgery while helping to maintain visibility. (Of course, as with every anterior segment surgery, you must maintain the anterior chamber at all times to avoid complications.)

• **Base the direction of your approach on the eye you're treating (i.e., left or right).** In right eyes, we insert the suture going counterclockwise; in left eyes, we insert it going clockwise. The reason is that you're going to get the most resistance after the suture has been passed about 260 degrees into the canal. Using this approach, if the suture stops at 260 degrees, it will be at the 6 o'clock position; then you can go to the top of the bed and do a cut-down, or just pull on the suture. But if you start from the opposite side and the suture stops at 270 degrees, it will stop at the 12 o'clock position. You're not going to be able to access it without lying on top of the patient.

• **Leave some Healon in the eye, based on the amount of blood reflux and/or the episcleral venous fluid wave.** On the first day postop, patients will have a relatively low pressure because they still have glaucoma medications in their systems—aqueous suppressants, prostaglandin analogues and so forth. Until those medications are washed out, IOP may be lower than normal, and if the pressure's too low postoperatively the patient can have blood reflux. Ideally the pressure should be about 15 to 17 mmHg on the first day; you don't want a pressure of 5 or 6 mmHg at that point.

To help ensure that the pressure doesn't drop too low, we leave a little bit of Healon in the eye. How much we leave in the eye depends on how much blood reflux we see, and/or the

episcleral venous wave we see. If we see a huge wave and a lot of blood reflux, we may leave 40 percent of the Healon in the eye. If we see a minimal wave, we may leave 5, 10 or 20 percent in the eye.

• **Use a suture, not a catheter.** Using a suture is, in some ways, better than using a catheter. For example, if the suture stops, you can pull on it; it tears through the trabecular meshwork and treats the vast majority of the angle. If the catheter stops at 200 degrees and you pull on it, it just comes out.

Another reason to use a suture is cost: A GATT can be done using a \$4 suture, whereas a catheter may cost \$750. That's very significant for both the patient and the health-care system, in both the United States and worldwide.

What's Next?

GATT is a novel, safe, minimally invasive, conjunctiva-sparing surgery that comes with a lot of pre-existing data because it's a modification of a surgery that's been around for 60 years. Its mid-term success is similar to previously published results for *ab externo* trabeculotomy (the primary exception being POAG patients who need to end up with a pressure of 10 or 12 mmHg), but with far fewer issues of safety and complications. We believe it's unquestionably a surgery of choice for some types of glaucoma, such as uncontrolled primary congenital glaucoma or juvenile open-angle glaucoma, and it does very well treating secondary open-angle glaucomas where the primary problem lies in the trabecular meshwork.

GATT also promises to help our patients and the field of health care by keeping costs down. The fact that a GATT can be done using a \$4 suture rather than a \$750 catheter is important. The reality is, we're going

to increasingly be held accountable for the choices we make, not only in terms of outcomes, but also in terms of cost. A relatively inexpensive and very effective procedure has tremendous implications for health care in general and the field of glaucoma surgery in particular.

Currently, we're organizing a prospective GATT study, with the intention of generating data with a longer follow-up period. **REVIEW**

Neither Dr. Grover nor Dr. Fellman has any financial interests relevant to the subjects discussed in this article.

1. Grant W. Further studies on facility of flow through the trabecular meshwork. *Arch of Ophthalmology* 1958;60:523-33.
2. Rosenquist R, Epstein D, Melamed S, Johnson M, Grant WM. Outflow resistance of enucleated human eyes at two different perfusion pressures and different extents of trabeculotomy. *Current Eye Research* 1989;8:1233-1240.
3. Smith R. Nylon filament trabeculotomy. Comparison with the results of conventional drainage operations in glaucoma simplex. *Trans Ophthalmol Soc N Z*. 1969;21:15-26.
4. Dvorak-Theobald G. Further studies on the canal of Schlemm: its anastomoses and anatomic relations. *Am J Ophthalmol* 1955; 39:65-89.
5. Chin S, Nitta T, Shinmei Y, Aoyagi M, Nitta A, Ohno S, Ishida S, Yoshida K. Reduction of intraocular pressure using a modified 360-degree suture trabeculotomy technique in primary and secondary open-angle glaucoma: A pilot study. *J Glaucoma* 2012; 21:6:401-7.
6. Ikeda H, Ishigooka H, Muto T, Tanihara H, Nagata M. Long-term outcome of trabeculotomy for the treatment of developmental glaucoma. *Arch Ophthalmol* 2004;122:8:1122-8.
7. Tanihara H, Negi A, et al. Surgical effects of trabeculotomy ab externo on adult eyes with primary open angle glaucoma and pseudoexfoliation syndrome. *Arch Ophthalmol* 1993;111: 12:1653-61.
8. Gedde SJ, Schiffman JC, Feuer WJ, Herndon LW, Brandt JD, Budenz DL; Tube versus Trabeculectomy Study Group. Treatment outcomes in the Tube Versus Trabeculectomy (TVT) study after five years of follow-up. *Am J Ophthalmol* 2012;153:5:789-803. e2.
9. Iwao K, Inatani M, Tanihara H; Japanese Steroid-Induced Glaucoma Multicenter Study Group. Success rates of trabeculotomy for steroid-induced glaucoma: A comparative, multicenter, retrospective cohort study. *Am J Ophthalmol* 2011;151:6:1047-1056.
10. Grover DS, Godfrey DG, et al. Gonioscopy-assisted transluminal trabeculotomy, ab interno trabeculotomy: Technique report and preliminary results. *Ophthalmology* 2014;121:4:855-61.
11. Grover DS, Smith O, Fellman RL, et al. Gonioscopy assisted transluminal trabeculotomy: An ab interno circumferential trabeculotomy for the treatment of primary congenital glaucoma and juvenile open angle glaucoma. *Br J Ophthalmol* 2015;99:8:1092-6.
12. Grover DS, Godfrey DG, Smith O, Shi W, Feuer WJ, Fellman RL. Outcomes of gonioscopy-assisted transluminal trabeculotomy (GATT) in eyes with prior incisional glaucoma surgery. *J Glaucoma* 2017;26:1:41-45.
13. Grover DS, Smith O, Fellman RL, et al. Gonioscopy-assisted transluminal trabeculotomy: 24 months follow-up. *J Glaucoma*. 2018;27:5:393-401.

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Managing Retinal Macroaneurysms

Expert advice on how to diagnose and manage this rare retinal condition.

*Nandini Venkateswaran, MD, and Harry W. Flynn Jr., MD, Miami
Ella Leung, MD, Houston*

Retinal arterial macroaneurysms (RAMs) are rare in clinical practice. In this article, we'll describe the features of RAMs and how to respond if they are identified on clinical examination.

What are RAMs?

The distinct clinical entity of RAM, an aneurysmal alteration of the retinal arteries, has been described in clinical series.^{1,2} Specifically, RAMs are defined as fusiform or saccular dilatations of the retinal arteries, usually emanating from the first three branches of the arteriolar tree. They typically range from 100 to 250 μ m in diameter, commonly involve vessels along the superotemporal or inferotemporal retinal arcades, and often occur at arteriovenous crossings or bifurcation sites. RAMs are seen more often in women than men (ratio of 3:1), typically after 60 years of age, and with a medical history of systemic hypertension and/or arteriosclerotic vascular disease. Studies have shown that 10 percent of patients have bilateral disease and 20 percent have multiple macroan-

eurysms.¹⁻⁵ The term "simple RAM" refers to isolated vascular ectasia, while "complex RAM" is used when the ectasia is accompanied by hemorrhage.

Clinical Presentation

Patients with RAM can present with variable symptoms. Often, RAM is noted on clinical examination but the patient is asymptomatic. The involved artery may be narrowed proximally and distally to the macroaneurysm. In other instances, severe vision loss can occur from leakage of the aneurysm with resultant hemorrhage into the vitreous cavity, sub-

hyaloid space and/or intraretinally or subretinally. Many times, "hourglass hemorrhages," defined as the simultaneous presence of preretinal and subretinal hemorrhage, can be seen. Serous fluid can also collect intraretinally, producing diffuse or focal cystoid macular edema with or without the accumulation of lipid exudates. Secondary epiretinal membrane can form after the resolution of longstanding subhyaloid hemorrhage. In rare cases, large macroaneurysms occurring at an arteriovenous crossing can cause a secondary branch retinal vein occlusion.¹⁻⁶

RAM Pathogenesis

The pathogenesis of RAM is thought to be secondary to a combination of several mechanisms causing blood vessel wall weakness and subsequent aneurysmal dilatation. The main mechanisms thought to underlie RAM formation include focal ischemia to blood vessel walls, chronic hypertensive and arteriosclerotic vascular wall damage, and inherent structural defects in blood vessels. Histopathologically, RAMs

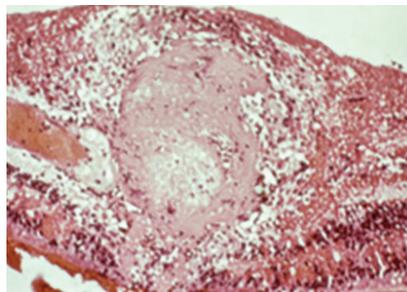


Figure 1. Histopathology of a ruptured RAM with preretinal, intraretinal and subretinal hemorrhage.

Table 1. Literature Review of Anti-VEGF Agents Used in the Treatment of RAM

Authors	Year of Publication	Treatment	# Pts	Pre BCVA	Post BCVA	Central macular thickness (µM)	# inj	Follow-up (months)
Chanana et al. ¹⁰	2009	Bevacizumab	1	20/400	20/50	607 to 173	2	1.5
Jonas et al. ¹¹	2010	Bevacizumab	1	0.40	0.8	“completely absorbed”	1	8
Jonas et al. ¹¹	2010	Bevacizumab	1	0.05	0.10	“completely absorbed”	1	3
Javey et al. ¹³	2010	Bevacizumab	1	20/400	20/20	--	2	12
Wenkstern et al. ¹⁴	2010	Ranibizumab + focal laser	1	20/50	20/25	510 to 148	2	5
Golan et al. ¹⁵	2011	Bevacizumab	1	20/160	20/20	364 to 248	2	13
Tsakpinis et al. ¹⁶	2011	Bevacizumab	1	0.3	0.8	--	2	39
Zweifel et al. ¹⁷	2011	Bevacizumab + Ranibizumab	10	20/100	20/50	366 to 266	3	6.1
Cho et al. ¹⁸	2013	Bevacizumab	23	0.26	0.34	384 to 265	1.42	10.8
Pichi et al. ¹⁹	2013	Bevacizumab	38	0.57	0.09	520 to 214	3	3
Erol et al. ²⁰	2015	Ranibizumab	7	1.09	0.67	427.5 to 208.7	2	10.8
Leung et al. ²¹	2015	Bevacizumab + focal laser	1	20/60	20/30	312 to 241	6	19
Bormann et al. ⁶	2017	Bevacizumab + focal laser	1	20/70	20/25	Not included	2	12
Bormann et al. ⁶	2017	Aflibercept	1	20/200	20/50	Not included	1	12

(Table modified from Leung et al.²¹)

are found to have arterial dilatation with variable degrees of artery wall hyalinization and surrounding retinal exudate or hemorrhage (Figure 1).⁷

Imaging of RAM

While the diagnosis of RAM is largely clinical, imaging—especially fluorescein angiography—can be a useful adjunctive tool. On FA, one can see immediate uniform filling of the macroaneurysm (Figure 2). Partial filling may be seen if the aneurysm is spontaneously involuting or is partially thrombosed. Many times, there can be no view of the RAM because it's hidden by hemorrhage overlying the macroaneurysm. Areas surrounding the RAM can show capillary microaneurysms, nonperfusion, intraretinal microvascular abnormalities and telangiectasis. Leakage can be seen if there is concomitant cystoid macular edema, and distortion of retinal architecture can be seen in the setting of ERM formation. OCT can be used for the identification of subretinal fluid and hemorrhage, macular edema and ERM formation and can be used to monitor the effects of therapy.^{1,6}

toid macular edema, and distortion of retinal architecture can be seen in the setting of ERM formation. OCT can be used for the identification of subretinal fluid and hemorrhage, macular edema and ERM formation and can be used to monitor the effects of therapy.^{1,6}

Treatment Options

The clinical course of RAMs can be variable. The majority of RAMs can be observed, and many will spontaneously involute. In a natural-history study, Cathleen McCabe, MD, and colleagues described a series of 41 patients with macular hemorrhages secondary to RAMs managed solely with observation. The patients' average visual acuity at baseline was 20/200 or worse. After an average follow-up of 15.7 months, 37 percent of eyes achieved a final visual acuity of

20/40 or better, 29 percent achieved 20/50 to 20/100, and 34 percent were 20/200 or worse. While good visual acuity outcomes can be achieved with observation alone, poorer visual acuity was associated with macular pigmentary changes after resorption of blood.⁸

However, intervention may be required in cases of exudative or hemorrhagic RAMs, or recurrent/persistent cystoid macular edema. Laser photocoagulation, first described by J. Donald M. Gass, MD, in 1976, was shown to reduce leakage in approximately 16 to 27 percent of RAMs. Laser of the artery and surrounding area may decrease flow and intraluminal pressure, thereby reducing the macroaneurysm. However, this therapy can be associated with the risk of vascular occlusion, early increase in exudates from selective reabsorption of fluid, arteriovenous shunts, macu-

lar pucker and scotomas.^{5,9}

Anti-vascular endothelial growth factor therapy has emerged as a useful treatment modality for RAMs (See table, p. 51). VEGF inhibition is thought to decrease vascular permeability, block angiogenesis to reduce further bleeding and exudation, and decrease the binding of pro-thrombotic VEGF receptor 2.^{5,10-21} Table 1 summarizes several articles in the

literature that analyzed anti-VEGF RAM therapy.

In 2009, Delhi, India's Bhuvan Chanana, MD, and co-workers published the first case report of a patient who received two intravitreal bevacizumab injections (at a concentration of 1.25 mg) for the treatment of cystoid macular edema in the setting of RAM; the patient's vision improved from 20/400 to 20/50 within six weeks

of treatment.¹⁰ Han Joo Cho, MD, and colleagues in the department of ophthalmology at the Myung-Gok Eye Research Institute in Seoul, South Korea, described a retrospective interventional case series of 23 patients with symptomatic RAMs who were either treated with intravitreal bevacizumab or observed. While both groups had statistically significant improvements in best-corrected visual

Case Report: Retinal Arterial Macroaneurysm

A 91-year-old Latino woman presented at the Bascom Palmer Eye Institute retina clinic in October 2017 with decreased vision OD. Her medical history included hypertension that was controlled with oral medications. Her ocular history was notable for pseudophakia OU. Visual acuity was counting fingers at five feet OD (from her baseline of 20/40) and 20/20 -2 OS. The anterior segment examination was within normal limits but the posterior segment exam was notable for bilateral drusen in the posterior pole and periphery, along with the presence of a retinal arterial macroaneurysm (RAM) and submacular hemorrhage OD in the foveal region (Figure 4A). Optical coherence tomography showed cystoid maculopathy with a neurosensory detachment (Figure 4B).

The differential diagnosis for a subretinal hemorrhage in this patient included exudative macular degeneration (given the findings of drusen bilaterally) versus a ruptured RAM (given the patient's age and history of hypertension). The patient underwent an intravitreal injection of aflibercept 0.05 mL OD. She subsequently underwent four monthly injections of aflibercept, and vision improved to 20/150 -2. An examination performed after four injections showed improvement in the subretinal hemorrhage with precipitation of macular exudates and the presence of a fibrosed RAM along the inferior arcade (Figures 5A and 5B). Due to an inflammatory reaction to intravitreal aflibercept, the patient was switched to intravitreal bevacizumab 1.25 mg/0.05 mL for two additional injections.

Her vision after a total of six injections remains 20/50 with no recurrence of hemorrhage or macular edema (Figures 6A and 6B). She continues to be followed in our clinic.

—NV, HF

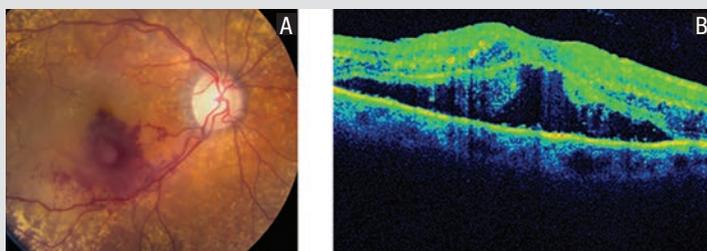


Figure 4A. Fundus photograph of the patient's submacular hemorrhage with the presence of a suspected RAM. Peripheral drusen are also noted. 4B: Retina OCT demonstrating subfoveal fluid exudation and hemorrhage.

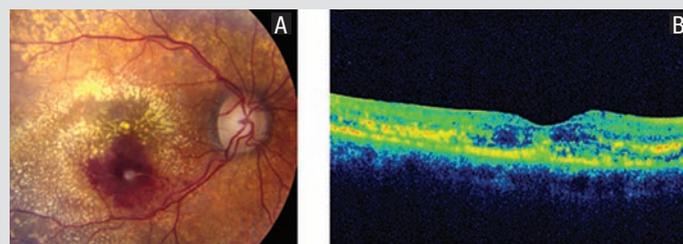


Figure 5A. Fundus photograph showing improving submacular hemorrhage and a sclerosed RAM. There is marked precipitation of exudates in the area of prior leakage. 5B: Retina OCT demonstrating resolution of cystoid macular edema but increased precipitation of exudates in the outer retinal layers.

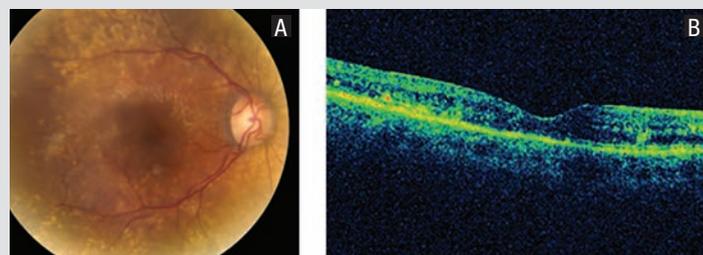


Figure 6A. Fundus photograph showing resolution of the submacular hemorrhage, sclerosed RAM along the inferior arcade, and drusen in the posterior pole and periphery. 6B: Retina OCT showing resolution of cystoid macular edema, subretinal fluid and exudates.

acuity and central macular thickness over a 10-month follow-up, the bevacizumab group, which received a mean of 1.4 injections, experienced more rapid improvement.¹⁸ Another prospective case series of 38 eyes (19 eyes with hemorrhagic RAM and 15 eyes with exudative RAM) found that three monthly injections of bevacizumab resulted in improved best-corrected visual acuity and macular thickness.¹⁹ One study of seven patients with either exudative or hemorrhagic RAMs treated with intravitreal ranibizumab reported significant anatomical and visual recovery after 10.8 months, with no associated complications.²⁰ A recent report demonstrated improvement of vision from 20/60 to 20/30 in a patient with a RAM and macular exudation after a series of six injections; however, ultimately focal laser photocoagulation was needed due to recurrence of CME with stabilization of vision at 20/30 at 19 months of follow-up.²¹ Our case (*See Case Report, p. 52*) also demonstrates the usefulness of various anti-VEGF agents in the treatment of leakage secondary to a RAM.

Other treatment options include pneumatic displacement of submacular hemorrhages and pars plana vitrectomy to clear persistent hemorrhages.^{22,23} In one study from 1998 Mark Humayun, MD, and co-workers described nine eyes with submacular hemorrhage secondary to ruptured RAMs, treated with submacular surgery with tissue plasminogen activator-assisted thrombolysis, with 89 percent of eyes achieving a corrected visual acuity of 20/60 or better.²³ These options are currently used less



Figure 2. Fluorescein angiography showing pooling within a RAM with blockage from submacular hemorrhage.

often with thin submacular hemorrhages, given the positive response with anti-VEGF agents.

In conclusion, RAMs are rare clinical findings occurring most often in older, hypertensive women. While anti-VEGF therapy can be a useful treatment option to improve vision and decrease macular edema, more complex RAMs may require laser photocoagulation and/or surgical intervention (*Figure 3*). **REVIEW**

Dr. Venkateswaran is a third-year resident at the Bascom Palmer Eye Institute in Miami. Dr. Flynn is a professor at Bascom Palmer and the Donald M. Gass Distinguished Chair in Ophthalmology at The University of Miami, Miller School of Medicine. Dr. Leung is an assistant professor at the Cullen Eye Institute at the Baylor College of Medicine in Houston.

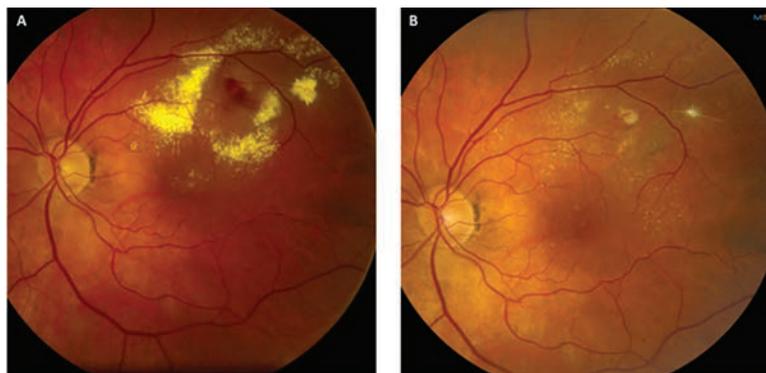
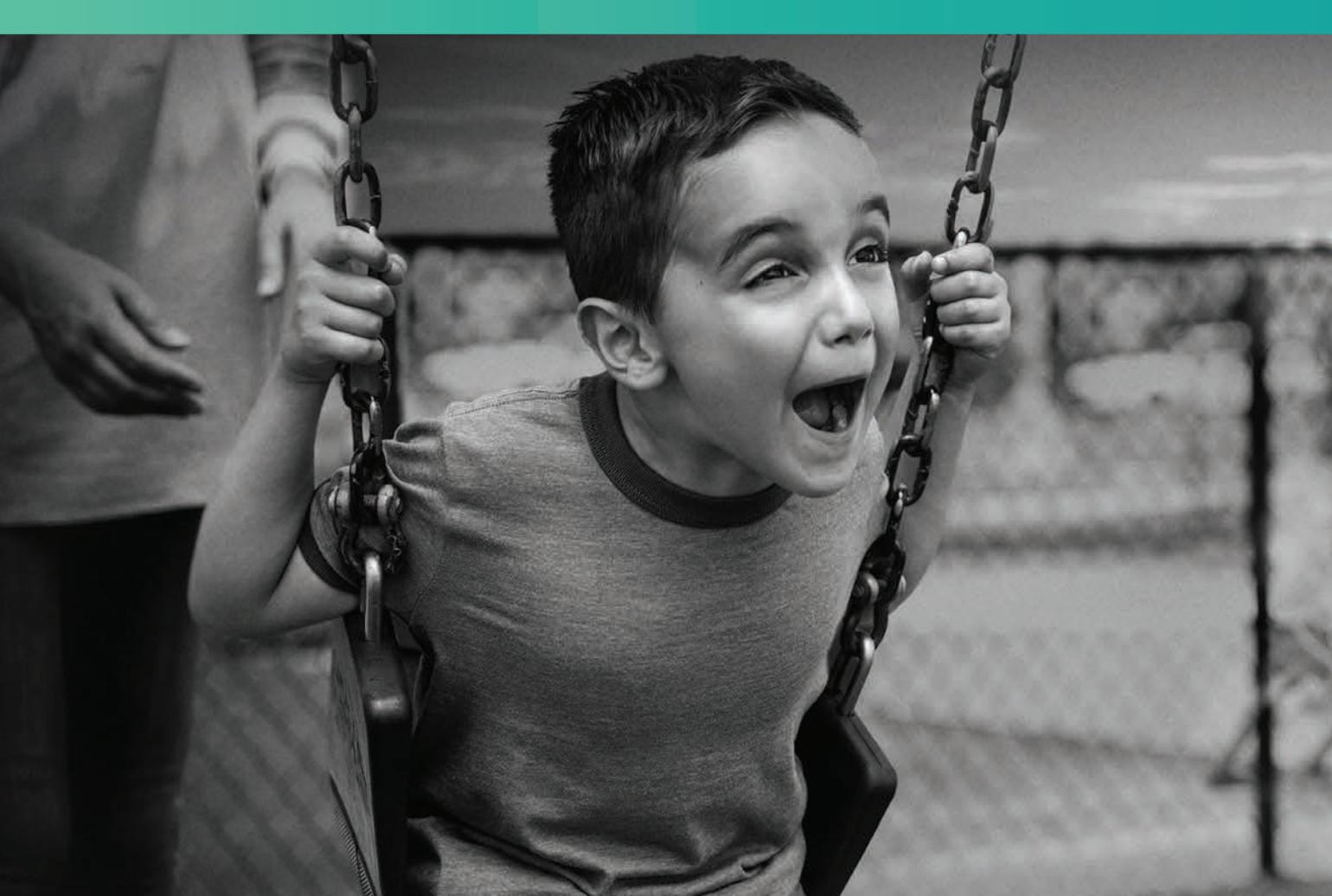


Figure 3A: Fundus photograph showing a leaking RAM and precipitation of exudates in a patient with a visual acuity of 20/60. **3B:** Fundus photograph after treatment with both focal laser and anti-VEGF agents, with resolution of hemorrhage and exudates and final visual acuity of 20/40.

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- Lewis RA, Norton EW, Gass JD. Acquired arterial macroaneurysms of the retina. *Br J Ophthalmol* 1976;60:1:21.
- Robertson DM. Macroaneurysms of the retinal arteries. *Trans Am Acad Ophthalmol Otolaryngol* 1973;77:OP55.
- Lavin MJ, Marsh RJ, Pearl S, Rehman A. Retinal arterial macroaneurysms: A retrospective study of 40 patients. *Br J Ophthalmol* 1987;71:11:817-25.
- Xu L, Wang Y, Jonas JB. Frequency of retinal macroaneurysms in adult Chinese: The Beijing eye study. *Br J Ophthalmol* 2007;91:6:840-41.
- Rabb MF, Galiano DA, Tske MP. Retinal arterial macroaneurysms. *Surv Ophthalmol* 1988;33:2:73-96.
- Bormann C, Heichel J, Hammer U, Habermann A, Hammer T. Intravitreal anti-vascular endothelial growth factor for macular edema due to complex retinal arterial macroaneurysms. *Case Rep Ophthalmol* 2017;8:1:137-143.
- Fichte C, Streeten BW, Friedman AH. A histopathologic study of retinal arterial aneurysms. *Am J Ophthalmol* 1978;85:4:509-18.
- McCabe CM, Flynn HW Jr, McLean WC et al. Nonsurgical management of macular hemorrhage secondary to retinal artery macroaneurysm. *Arch Ophthalmol* 2000;118:780-785.
- Meyer JC, Ahmad BU, Blinder KJ, Shah GK. Laser therapy versus observation for symptomatic retinal artery macroaneurysms. *Graefes Arch Clin Exp Ophthalmol* 2015;53:4:537-41.
- Chanana B, Azad RV. Intravitreal bevacizumab for macular edema secondary to retinal arterial macroaneurysm. *Eye (Lond)* 2009;23:2:493-4.
- Jonas JB, Schmidbauer M. Intravitreal bevacizumab for retinal macroaneurysm. *Acta Ophthalmol* 2010;88:7:e284.
- Jonas JB. Intravitreal bevacizumab for macular complications from RAM. *Am J Ophthalmol* 2013;155:4:774.
- Javey G, Moshfeghi AN, Moshfeghi AA. Management of ruptured retinal arterial macroaneurysm with intravitreal bevacizumab. *Ophthalmic Surg Lasers Imaging* 2010;41:4:1-5.
- Wenkstern AR, Petersen H. Intravitreal ranibizumab in retinal macroaneurysm. *Graefes Arch Clin Exp Ophthalmol* 2010;248:11:1667-70.
- Golan S, Golderberg D, Goldstein M. Long-term follow-up of intravitreal bevacizumab in retinal arterial macroaneurysm: A case report. *Case Rep Ophthalmol* 2011;2:3:387-91.
- Tsakpinis D, Nasr MB, Tranos P, Krassas N, Giannopoulos T, Symeonidis C, Dimitrakos SA, Konstantas AG. The use of bevacizumab in a multilevel retinal hemorrhage secondary to retinal macroaneurysm: A 39-month follow-up case report. *Clin Ophthalmol* 2011;5:1475-7.
- Zweifel SA, Tonz MS, Pfenninger L, Becker M, Michels S. Intravitreal anti-VEGF therapy for retinal macroaneurysm. *Klin Monbl Augenheilkd* 2013;230:4:392-5.
- Cho HJ, Rhee TK, Kim HS, Han JI, Lee DW, Cho SW, Kim JW. Intravitreal bevacizumab for symptomatic retinal arterial macroaneurysm. *Am J Ophthalmol* 2013;155:5:898-904.
- Pichi F, Morara M, Torrazza C, Manzi G, Alkabes M, Balducci N, Vitale L, Lembo A, Ciardella AP, Nucci P. Intravitreal bevacizumab for macular complications from retinal arterial macroaneurysms. *Am J Ophthalmol* 2013;155:2:287-294.
- Erol MK, Dogan B, Coban DT, Toslak D, Cengiz A, Ozel D. Intravitreal ranibizumab therapy for retinal arterial macroaneurysm. *Int J Clin Exp Med* 2015;8:7:11572-8.
- Leung EH, Reddy AK, Vedula AS, Flynn HW Jr. Serial bevacizumab injections and laser photocoagulation for macular edema associated with a retinal artery macroaneurysm. *Clin Ophthalmol* 2015;9:601-609.
- Bercoval MH, Lewis ML, Flynn HW Jr. Variations in the clinical course of submacular hemorrhage. *Am J Ophthalmol* 1996;122:486.
- Humayun M, Lewis H, Flynn HW Jr et al. Management of submacular hemorrhage associated with retinal arterial macroaneurysms. *Am J Ophthalmol* 1998;126:358-361.



IMPORTANT SAFETY INFORMATION

Warnings and Precautions

- **Endophthalmitis** may occur following any intraocular surgical procedure or injection. Use proper aseptic injection technique when administering LUXTURNA, and monitor for and advise patients to report any signs or symptoms of infection or inflammation to permit early treatment of any infection.
- **Permanent decline in visual acuity** may occur following subretinal injection of LUXTURNA. Monitor patients for visual disturbances.
- **Retinal abnormalities** may occur during or following the subretinal injection of LUXTURNA, including macular holes, foveal thinning, loss of foveal function, foveal dehiscence, and retinal hemorrhage. Monitor and manage these retinal abnormalities appropriately. Do not administer LUXTURNA in the immediate vicinity of the fovea. Retinal abnormalities may occur during or following vitrectomy, including retinal tears, epiretinal membrane, or retinal detachment. Monitor patients during and following the injection to permit early treatment of these retinal abnormalities. Advise patients to report any signs or symptoms of retinal tears and/or detachment without delay.
- **Increased intraocular pressure** may occur after subretinal injection of LUXTURNA. Monitor and manage intraocular pressure appropriately.
- **Expansion of intraocular air bubbles** Instruct patients to avoid air travel, travel to high elevations or scuba diving until the air bubble formed following administration of LUXTURNA has completely dissipated from the eye. It may take one week or more following injection for the air bubble to dissipate. A change in altitude while the air bubble is still present can result in irreversible vision loss. Verify the dissipation of the air bubble through ophthalmic examination.
- **Cataract** Subretinal injection of LUXTURNA, especially vitrectomy surgery, is associated with an increased incidence of cataract development and/or progression.

Adverse Reactions

- In clinical studies, ocular adverse reactions occurred in 66% of study participants (57% of injected eyes), and may have been related to LUXTURNA, the subretinal injection procedure, the concomitant use of corticosteroids, or a combination of these procedures and products.

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IMPORTANT SAFETY INFORMATION (CONT'D)

- The most common adverse reactions (incidence \geq 5% of study participants) were conjunctival hyperemia (22%), cataract (20%), increased intraocular pressure (15%), retinal tear (10%), dellen (thinning of the corneal stroma) (7%), macular hole (7%), subretinal deposits (7%), eye inflammation (5%), eye irritation (5%), eye pain (5%), and maculopathy (wrinkling on the surface of the macula) (5%).

Immunogenicity

Immune reactions and extra-ocular exposure to LUXTURNA in clinical studies were mild. No clinically significant cytotoxic T-cell response to either AAV2 or RPE65 has been observed. In clinical studies, the interval between the subretinal injections into the two eyes ranged from 7 to 14 days and 1.7 to 4.6 years. Study participants received systemic corticosteroids before and after subretinal injection of LUXTURNA to each eye, which may have decreased the potential immune reaction to either AAV2 or RPE65.

Pediatric Use

Treatment with LUXTURNA is not recommended for patients younger than 12 months of age, because the retinal cells are still undergoing cell proliferation, and LUXTURNA would potentially be diluted or lost during the cell proliferation. The safety and efficacy of LUXTURNA have been established in pediatric patients. There were no significant differences in safety between the different age subgroups.

Please see a brief summary of the US Full Prescribing Information on the following pages.

Reference: 1. LUXTURNA [package insert]. Philadelphia, PA: Spark Therapeutics, Inc; 2017.

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LUXTURNA (voretigene neparvovect-rzyl) is an adeno-associated virus vector-based gene therapy indicated for the treatment of patients with confirmed biallelic RPE65 mutation-associated retinal dystrophy. Patients must have viable retinal cells as determined by the treating physicians.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Endophthalmitis

Endophthalmitis may occur following any intraocular surgical procedure or injection. Proper aseptic injection technique should be used when administering LUXTURNA. Following the injection, patients should be monitored to permit early treatment of any infection. Advise patients to report any signs or symptoms of infection or inflammation without delay.

5.2 Permanent decline in visual acuity

Permanent decline in visual acuity may occur following subretinal injection of LUXTURNA. Monitor patients for visual disturbances.

5.3 Retinal abnormalities

Retinal abnormalities may occur during or following the subretinal injection of LUXTURNA, including macular holes, foveal thinning, loss of foveal function, foveal dehiscence, and retinal hemorrhage. Monitor and manage these retinal abnormalities appropriately. LUXTURNA must not be administered in the immediate vicinity of the fovea. [See Dosage and Administration (2.3) in full prescribing information]

Retinal abnormalities may occur during or following vitrectomy, including retinal tears, epiretinal membrane, or retinal detachment. Monitor patients during and following the injection to permit early treatment of these retinal abnormalities. Advise patients to report any signs or symptoms of retinal tears and/or detachment without delay.

5.4 Increased intraocular pressure

Increased intraocular pressure may occur after subretinal injection of LUXTURNA. Monitor and manage intraocular pressure appropriately.

5.5 Expansion of intraocular air bubbles

Instruct patients to avoid air travel, travel to high elevations, or scuba diving until the air bubble formed following administration of LUXTURNA has completely dissipated from the eye. It may take one week or more following injection for the air bubble to dissipate. A change in altitude while the air bubble is still present can result in irreversible vision loss. Verify the dissipation of the air bubble through ophthalmic examination.

5.6 Cataract

Subretinal injection of LUXTURNA, especially vitrectomy surgery, is associated with an increased incidence of cataract development and/or progression.

6 ADVERSE REACTIONS

The most common adverse reactions (incidence ≥5%) were conjunctival hyperemia, cataract, increased intraocular pressure, retinal tear, dellens (thinning of the corneal stroma), macular hole, subretinal deposits, eye inflammation, eye irritation, eye pain, and maculopathy (wrinkling on the surface of the macula).

6.1 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 other products and may not reflect the rates observed in practice.

The safety data described in this section reflect exposure to LUXTURNA in two clinical trials consisting of 41 subjects (81 eyes) with confirmed biallelic RPE65 mutation-associated retinal dystrophy. Forty of the 41 subjects received sequential subretinal injections of LUXTURNA to each eye. One subject received LUXTURNA in only one eye. Seventy-two of the 81 eyes were exposed to the recommended dose of LUXTURNA at 1.5 x 10¹¹ vg; 9 eyes were exposed to lower doses of LUXTURNA. Study 1 (n=12) was an open-label, dose-exploration safety study. Study 2 (n=29) was an open-label, randomized, controlled study for both efficacy and safety [see Clinical Studies (14) in full prescribing information]. The average age of the 41 subjects was 17 years, ranging from 4 to 44 years. Of the 41 subjects, 25 (61%) were pediatric subjects under 18 years of age, and 23 (56%) were females.

Twenty-seven (27/41, 66%) subjects had ocular adverse reactions that involved 46 injected eyes (46/81, 57%). Adverse reactions among all subjects in Studies 1 and 2 are described in Table 1. Adverse reactions may have been related to LUXTURNA, the subretinal injection procedure, the concomitant use of corticosteroids, or a combination of these procedures and products.

Table 1. Ocular Adverse Reactions Following Treatment with LUXTURNA (N=41)

Adverse Reactions	Subjects n=41	Treated Eyes n=81
Any ocular adverse reaction	27 (66%)	46 (57%)
Conjunctival hyperemia	9 (22%)	9 (11%)
Cataract	8 (20%)	15 (19%)
Increased intraocular pressure	6 (15%)	8 (10%)
Retinal tear	4 (10%)	4 (5%)
Dellens (thinning of the corneal stroma)	3 (7%)	3 (4%)
Macular hole	3 (7%)	3 (4%)
Subretinal deposits*	3 (7%)	3 (4%)
Eye inflammation	2 (5%)	4 (5%)
Eye irritation	2 (5%)	2 (2%)
Eye pain	2 (5%)	2 (2%)
Maculopathy (wrinkling on the surface of the macula)	2 (5%)	3 (4%)

Adverse Reactions	Subjects n=41	Treated Eyes n=81
Foveal thinning and loss of foveal function	1 (2%)	2 (2%)
Endophthalmitis	1 (2%)	1 (1%)
Foveal dehiscence (separation of the retinal layers in the center of the macula)	1 (2%)	1 (1%)
Retinal hemorrhage	1 (2%)	1 (1%)

*Transient appearance of asymptomatic subretinal precipitates inferior to the retinal injection site 1-6 days after injection.

Immunogenicity

At all doses of LUXTURNA evaluated in Studies 1 and 2, immune reactions and extra-ocular exposure were mild. In Study 1 (n=12), the interval between the subretinal injections into the two eyes ranged from 1.7 to 4.6 years. In Study 2, the interval between the subretinal injections into the two eyes ranged from 7 to 14 days. No subject had a clinically significant cytotoxic T-cell response to either AAV2 or RPE65.

Subjects received systemic corticosteroids before and after subretinal injection of LUXTURNA to each eye. The corticosteroids may have decreased the potential immune reaction to either vector capsid (adeno-associated virus serotype 2 [AAV2] vector) or transgene product (retinal pigment epithelial 65 kDa protein [RPE65]).

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary: Adequate and well-controlled studies with LUXTURNA have not been conducted in pregnant women. Animal reproductive studies have not been conducted with LUXTURNA. In the US general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

8.2 Lactation

Risk Summary: There is no information regarding the presence of LUXTURNA in human milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for LUXTURNA and any potential adverse effects on the breastfed infant from LUXTURNA.

8.3 Females and Males of Reproductive Potential

No nonclinical or clinical studies were performed to evaluate the effect of LUXTURNA on fertility.

8.4 Pediatric Use

Treatment with LUXTURNA is not recommended for patients younger than 12 months of age because the retinal cells are still undergoing cell proliferation, and LUXTURNA would potentially be diluted or lost during cell proliferation.

The safety and efficacy of LUXTURNA have been established in pediatric patients. Use of LUXTURNA is supported by Study 1 and Study 2 [see Clinical Studies (14) in full prescribing information] that included 25 pediatric patients with biallelic RPE65 mutation-associated retinal dystrophy in the following age groups: 21 children (age 4 years to less than 12 years) and 4 adolescents (age 12 years to less than 17 years). There were no significant differences in safety between the different age subgroups.

8.5 Geriatric Use

The safety and effectiveness of LUXTURNA have not been established in geriatric patients. Clinical studies of LUXTURNA for this indication did not include patients age 65 years and over.

17 PATIENT COUNSELING INFORMATION

Advise patients and/or their caregivers of the following risks:

Endophthalmitis and other eye infections: Serious infection can occur inside of the eye and may lead to blindness. In such cases, there is an urgent need for management without delay. Advise patients to call their healthcare provider if they experience new floaters, eye pain, or any change in vision.

Permanent decline in visual acuity: Permanent decline in visual acuity may occur following subretinal injection of LUXTURNA. Advise patients to contact their healthcare provider if they experience any change in vision.

Retinal abnormalities: Treatment with LUXTURNA may cause some defects in the retina such as a small tear or a hole in the area or vicinity of the injection. Treatment may cause thinning of the central retina or bleeding in the retina. Advise patients to follow up with their healthcare provider on a regular basis and report any symptoms, such as decreased vision, blurred vision, flashes of light, or floaters in their vision without delay.

Increased intraocular pressure: Treatment with LUXTURNA may cause transient or persistent increase in intraocular pressure. If untreated, such increases in intraocular pressure may cause blindness. Advise patients to follow up with their healthcare provider to detect and treat any increase in intraocular pressure.

Expansion of intraocular air bubbles: Advise patients to avoid air travel, travel to high elevations, or scuba diving until the air bubble formed following administration of LUXTURNA has completely dissipated from the eye. A change in altitude while the air bubble is still present may cause irreversible damage.

Cataract: Advise patients that following treatment with LUXTURNA, they may develop a new cataract, or any existing cataract may get worse.

Shedding of LUXTURNA: Transient and low-level shedding of LUXTURNA may occur in patient tears. Advise patients and/or their caregivers on proper handling of waste material generated from dressing, tears, and nasal secretion, which may include storage of waste material in sealed bags prior to disposal. These handling precautions should be followed for up to 7 days following LUXTURNA administration.

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A New Gene Therapy For Early-onset RP

Gene therapy may be the next innovation for improving vision in young patients with retinal degenerative disease.

Jonathan Barnett and Gennady Landa, MD, New York City

Retinitis pigmentosa most often strikes younger patients, including those in the pediatric age group, and the onset of Leber's congenital amaurosis, a disease associated with RP, can occur in infancy. For years, we could do nothing but chart the disease's damage to our patients' vision. With the Food and Drug Administration approval of Luxturna (voretigene neparvovec/AAV2-hRPE65v2; Spark Therapeutics, Philadelphia) late in 2017, however, we finally have a treatment for this disease.

This article will discuss the basic mechanism of gene therapy, the promising results of Luxturna's trial, and the challenges that gene therapies like Luxturna must surmount in the future.

Etiology of RP

Three million people across the globe are afflicted with retinitis pigmentosa, a hereditary disease that causes progressive degeneration of the retina's rod and cone cells that eventually leads to total or near-total blindness (See Figure 1). Unfortunately, given the disease's devastating

effects, there is often little that can be done to improve visual outcomes in these patients.

Part of the difficulty in treating RP is its complex and diverse genetic etiology: There are approximately 70 known genes and 3,000 genetic mutations associated with RP. Furthermore, RP is genetically associated with other retinal degenerative diseases, such as Leber's. While there are several different supportive treatments available, including supplementation with vitamin A and omega-3 fatty acids, or usage of neurotrophic factors and antioxidants, these therapies have often been shown to be ineffective, failing to address the root cause

of the disease. However, gene therapy—a technique by which wild-type cDNA is delivered to the host retina's genetically defective cells via a viral vector—has begun to show promising results for improving visual outcomes, as evidenced by new clinical trials like the one used to secure Luxturna's approval.^{1,2}

The RPE65 Gene Mutation

A variety of genetic mutations cause RP, but the sole target of Luxturna is the uncommon, autosomal recessive mutation of gene RPE65. Only about 5 to 20 percent of all forms of RP are autosomal recessive and, of those,

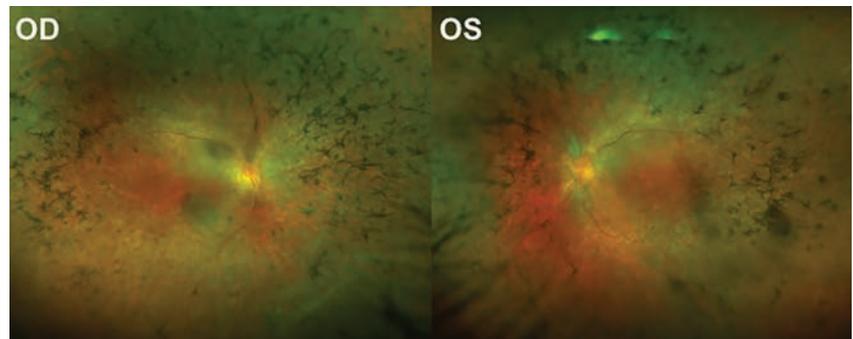


Figure 1. Fundus images of a patient with retinitis pigmentosa.

only about 2 to 5 percent of all recessive forms of RP involve the RPE65 mutation.³ The genetic codes for the RPE65 enzyme, also called retinoid isomerohydrolase, are found within the cells of the retinal pigment epithelium. RPE65 normally regenerates 11-cis-retinal, a molecule essential to the opsins (visual pigments) of the photoreceptors (See Figure 2). When both copies of the RPE65 gene are defective, the RPE65 enzyme isn't produced and visual pigment can't be regenerated, leading to photoreceptor dysfunction and death.¹

Patients with two copies of the autosomal recessive RPE65 mutation will develop complete blindness in both eyes at an early age. Depending on when the patient is diagnosed, the patient is deemed to have LCA or early onset RP. The effect of this mutation has been established through animal models, with studies of dog and mouse models with RPE65 knockout (RPE65^{-/-}) demonstrating a disease progression that mimics the pattern of disease found in LCA or early-onset RP in humans.^{4,5,6}

Early Trials of Gene Therapy

Gene therapy requires two main components: the non-mutated, wild-type version of the given DNA sequence encoding for a functional protein—in this case, RPE65 encoding for the functional RPE65 enzyme—and the delivery vector (See Figure 3). Previous investigations into retinal gene therapy have demonstrated that the adeno-associated virus (AAV) is among the safest and most experimentally malleable vectors for delivery to deep retinal cells.⁷ The vector needs to be injected subretinally to reach its target, the RPE layer. Research has shown RPE cell transduction success with many serotypes of the AAV vector.⁸⁻¹⁰ Studies in animal models demonstrated that subretinal injection of RPE65 cDNA via an AAV

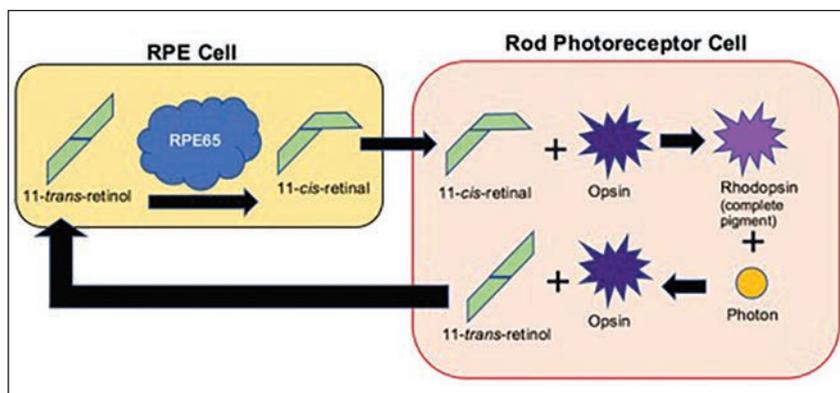


Figure 2. Simplified schematic showing the role of the RPE65 enzyme (retinoid isomerohydrolase) in visual pigment restoration. Note that RPE65 is among several of the enzymes (not shown) in the RPE cell that participate in regenerating visual pigment.

vector into the RPE65 sequence enhanced visual acuity and ERG readings.^{11,12}

Beginning in 2008, the first Phase I/II human clinical trials were performed using this model on 12 human patients with the autosomal recessive RPE65 mutation. However, the findings were mixed, with some patients showing only short-lived improvement in retinal function, and others showing no improvement or severe retinal decline.^{13,14} Other Phase I/II clinical trials were subsequently performed, but also didn't show significant visual improvement.^{11,15-17}

To address these outcomes, modifications to the RPE65 gene promoter and AAV2 vector apparatus were made in another Phase I/II clinical trial, sponsored by Spark Therapeutics. Twelve patients with the autosomal recessive RPE65 mutation were recruited for the trial. After two years of subretinal injections in one eye, all of the study patients demonstrated improvement in retinal function and visual acuity measurements in the injected eye without any major adverse incidents.^{18,19} A follow-up trial involving 11 of these 12 patients, in which the AAV2 vector was injected into each patient's other eye showed improvement in retinal function across all patients that lasted for about three years.²⁰

Luxturna is Born

The promising results of Spark Therapeutics' early trials led the research team in July 2017 to publish a randomized, open-label, Phase III clinical trial of Luxturna. A total of 29 patients with autosomal recessive RPE65 mutations participated in the study, with 20 individuals receiving the treatment and nine acting as controls. Luxturna was injected subretinally in both eyes of each patient in the intervention group. The efficacy of the intervention was determined via the Multi-Luminance Mobility Test score, measured at baseline prior to intervention and at follow-up one year later.

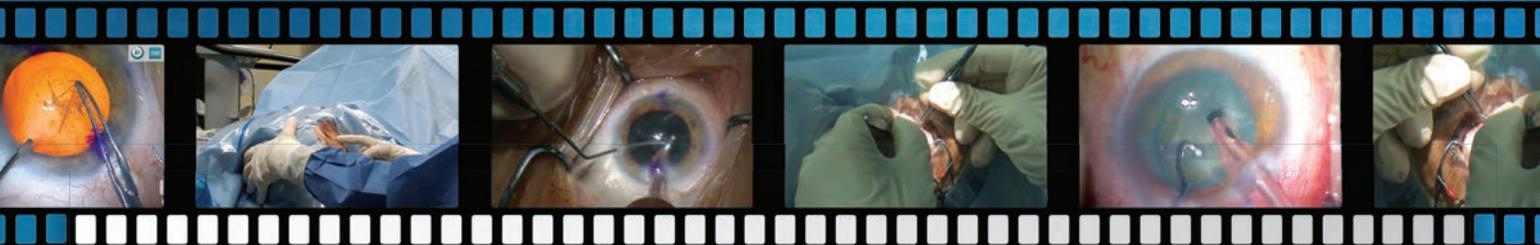
In the MLMT, patients are asked to navigate through an obstacle course at different environmental light levels. The MLMT assesses not only visual acuity, but also light perception, contrast sensitivity and visual field. At the one-year follow-up, the MLMT score in the intervention group improved by 1.8 (SD 1.1), whereas the MLMT score in the control group improved by only 0.2 (SD 1.0)—a statistically significant difference ($p=0.0013$). Furthermore, a large percentage of the intervention group (65 percent) navigated the MLMT successfully at the minimum luminance setting of 1 lux, compared to none of the control-



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Episode 35: “Dense Nucleus, Lax Zonule and Capsular Tension Ring Insertion”

Surgical Video by:
Richard J. Mackool, MD

Video Overview:

Continuing with complicated cases, this month I demonstrate removal of a dense cataract in an eye with zonular laxity and a possible preexisting posterior capsule defect. Techniques employed include hydrodelineation, insertion of capsule retractors, and insertion of a capsular tension ring.

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Richard J. Mackool, MD

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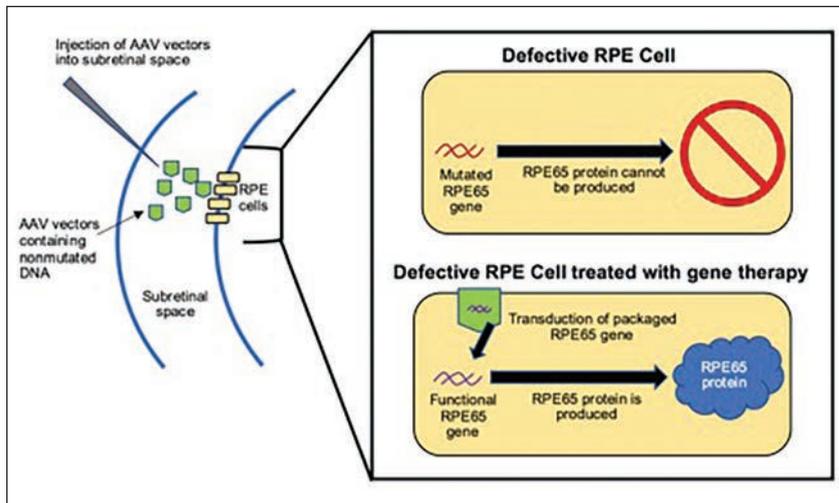


Figure 3. Simplified schematic of the mechanism behind RPE65-targeted gene therapy.

group patients. There were no immunological reactions or other major adverse events.² Spark Therapeutics' Phase III trial thus demonstrated that the treatment is both safe and effective and, in December 2017, the FDA approved the use of Luxturna for individuals afflicted with retinal degenerative disease due to RPE65 mutation.²¹

Triumphs and Challenges

Luxturna casts a positive light on the outlook for the success of gene therapy to completely restore vision and vastly improve the quality of life of those with severe visual impairment from RP, LCA and other retinal degenerative diseases. In contrast to other treatment approaches, Luxturna's mechanism specifically, and gene therapy in general, offer several key advantages.

First, injections into the retina will rarely elicit an immune response, due to the blood-retina barrier and the eye's naturally immunosuppressive environment. Thus, gene therapy is a relatively safe means of treatment, and is likely to become even safer as the technology for vector delivery advances.⁷ Another advantage of

gene therapy is that it addresses the fundamental etiology of the disease: the defective genes. Unlike artificial retinal implants—which are inserted only in the late stages of disease when most of the photoreceptor layer is already destroyed—gene therapy can be implemented in the earlier stages. Gene therapy therefore has potential to save the photoreceptors from an otherwise doomed genetic fate.¹⁹

However, there are still several important challenges for gene therapies like Luxturna. One major disadvantage of Luxturna is its severely limited therapeutic target, since it is effective only for the 1,000 to 2,000 patients in the United States with the recessive RPE65 mutation. Many more thousands of patients suffering from hereditary retinal degenerative disease do not yet have a viable gene therapy. Unfortunately, gene therapy tends to work best only for recessive and X-linked mutations, which result in complete failure of production of a functional, essential protein. In this situation, the nonmutated versions of the genes can be delivered to the necessary cells, replacing the mutated genes and allowing for normal production of the essential protein. Gene therapy doesn't work as well for domi-

nant mutations, which are the cause of 15 to 25 percent of RP cases, due to the "dominant negative" phenomenon.¹ Dominant mutations result in the overproduction of a dysfunctional protein, negating the effect of any functional protein present. Therefore even if the gene for functional proteins were delivered to the cells, it's unlikely that enough functional protein could be made to overcome the mass quantities of dysfunctional protein made by the patient's own native genes.²²⁻²⁴

Another drawback of Luxturna is the need to inject the delivery vector into the subretinal space. Surgical invasion into the subretinal space necessitates inducing a temporary retinal detachment and increases the chance for necrosis and inflammation in the area. A potential solution to this problem is to deliver the vector into the vitreous humor, which avoids direct contact with the retina, and would also make the therapy more accessible for ophthalmologists who haven't undergone vitreoretinal surgical training. Yet, previous trials with gene therapy delivered through intravitreal injection have shown diminished visual outcomes and higher chances of an immune response; for adequate vector-cell transduction to occur, the vectors need to be placed in close proximity to the deeper layers of the retina (the subretinal space). Future research in gene therapy should therefore focus upon ways to optimize vector delivery to render intravitreal injections more feasible.^{18,25,26}

One last disadvantage of Luxturna is its current exorbitant cost of \$425,000 per eye. Even though the product has just entered the market as a promising innovation, critics argue that it's difficult to justify the price given that the long-term efficacy of the treatment is still unknown.²⁷

Gene therapy is a new and developing field. We hope that as advance-

ments in gene therapy are made and the field becomes more mainstream, treatment will become more affordable, accessible and effective. With every innovation like Luxturna that comes into the foreground, we move one step closer to curing retinal degenerative disease. **REVIEW**

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1. Dias M, Joo K, Kemp J, et al. Molecular genetics and emerging therapies for retinitis pigmentosa: Basic research and clinical perspectives. *Progress in retinal and eye research* 2017;63:107-131
2. Russell S, Bennett J, Wellman JA, et al. Efficacy and safety of voretigene neparvovec (AAV2-hRPE65v2) in patients with RPE65-mediated inherited retinal dystrophy: a randomized, controlled, open-label, phase 3 trial. *The Lancet* 2017;390:849-60.

3. Ferrari, S, Di Iorio E, et al. Retinitis pigmentosa: Genes and disease mechanisms. *Curr Genomics* 2011;12:238-249.
4. Cideciyan AV. Leber congenital amaurosis due to RPE65 mutations and its treatment with gene therapy. *Prog Retin Eye Res* 2010;29:398-427.
5. Nilsson SE, Wrigstad A, Narfstrom K. Changes in the DC electroretinogram in Briard dogs with hereditary congenital night blindness and partial day blindness. *Exp Eye Res* 1992;54:291-296.
6. Rohrer B, Goletz P, et al. Correlation of regenerable opsin with rod ERG signal in Rpe65^{-/-} mice during development and aging. *Invest Ophthalmol Vis Sci* 2003;44:310-315.
7. Dalkara D, Gourreau O, et al. Let there be light: Gene and cell therapy for blindness. *Hum Gene Ther* 2016;27:134-147.
8. Auricchio A, Kobinger G, et al. Exchange of surface proteins impacts on viral vector cellular specificity and transduction characteristics: The retina as a model. *Hum Mol Genet* 2001;10:3075-3081.
9. Dinulescu A, Glushakova L, et al. Adeno-associated virus-vectored gene therapy for retinal disease. *Hum Gene Ther* 2005;16:649-663.
10. Weber M, Rabinowitz J, et al. Recombinant adeno-associated virus serotype 4 mediates unique and exclusive long-term transduction of retinal pigmented epithelium in rat, dog, and nonhuman primate after subretinal delivery. *Mol Ther* 2003;7:774-781.
11. Jacobson SG, Acland GM, et al. Safety of recombinant adeno-associated virus type 2-RPE65 vector delivered by ocular subretinal injection. *Mol Ther* 2006;13:1074-1084.
12. Bencicelli J, Wright JF, et al. Reversal of blindness in animal models of leber congenital amaurosis using optimized AAV2-mediated gene transfer. *Mol Ther* 2008;16:458-465.
13. Bainbridge JW, Smith, AJ, et al. Effect of gene therapy on visual function in Leber's congenital amaurosis. *N Engl J Med* 2008;358:2231-2239.
14. Bainbridge, JW, Mehat MS, et al. Long-term effect of gene therapy on Leber's congenital amaurosis. *N. Engl. J. Med* 2015;372:1887-1897.
15. Hauswirth, WW, Aleman TS, et al. Treatment of leber congenital amaurosis due to RPE65 mutations by ocular subretinal injection of adeno-associated virus gene vector: Short-term results of a

- phase I trial. *Hum Gene Ther* 2008;19:979-990.
16. Cideciyan AV, Hauswirth WW, et al. Human RPE65 gene therapy for Leber congenital amaurosis: Persistence of early visual improvements and safety at 1 year. *Hum Gene Ther* 2009;20:999-1004.
17. Jacobson SG, Cideciyan AV, et al. Improvement and decline in vision with gene therapy in childhood blindness. *N Engl J Med* 2015;372:1920-1926.
18. Maguire AM, Simonelli F, et al. Safety and efficacy of gene transfer for Leber's congenital amaurosis. *N Engl J Med* 2008;358:2240-2248.
19. Maguire AM, High KA, et al. Age-dependent effects of RPE65 gene therapy for Leber's congenital amaurosis: A phase 1 dose-escalation trial. *Lancet* 2009;374:1597-1605.
20. Bennett J, Wellman J, et al. Safety and durability of effect of contralateral-eye administration of AAV2 gene therapy in patients with childhood-onset blindness caused by RPE65 mutations: A follow-on phase 1 trial. *Lancet* 2016;388:661-672.
21. FDA approves novel gene therapy to treat patients with a rare form of inherited vision loss. U.S. Food and Drug Administration 2017 [cited March 2018]. Available from: <https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm589467.htm>.
22. Dalkara D, Sahel JA. Gene therapy for inherited retinal degenerations. *C R Biol* 2014;337:185-192.
23. Chadderton N, Millington-Ward S, et al. Improved retinal function in a mouse model of dominant retinitis pigmentosa following AAV-delivered gene therapy. *Mol Ther* 2009;17:593-599.
24. Petrs-Silva H, Linden R. Advances in gene therapy technologies to treat retinitis pigmentosa. *Clin Ophthalmol* 2014;8:127-136.
25. Dalkara D, Kolstad KD, et al. Inner limiting membrane barriers to AAV-mediated retinal transduction from the vitreous. *Mol Ther* 2009;17:2096-2102.
26. Dalkara D, Byrne LC, et al. In vivo-directed evolution of a new adeno-associated virus for therapeutic outer retinal gene delivery from the vitreous. *Sci Transl Med* 2013;5:189.
27. Berkrot, B. Spark's price for Luxturna blindness gene therapy too high: ICER. Reuters 2018 [cited March 2018]. Available from: <https://www.reuters.com/article/us-spark-icer/sparks-price-for-luxturna-blindness-gene-therapy-too-high-icer-idUSKBN1F1298>.

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A 56-year-old woman presents to the Wills Eye Oncology Service with progressive vision loss in one eye.

Erin E. Nichols, MD, Lucas Bonafede, MD, and Carol L. Shields, MD

Presentation

A 56-year-old woman presented with progressive decreased vision in the right eye over the preceding few months. She denied additional ocular complaints such as pain or discomfort. Of note, complete ophthalmic examination in the past year demonstrated unremarkable findings, with the exception of a stable conjunctival nevus.

Medical History

Medical history revealed arthritis, asthma, a benign thyroid nodule, a benign adrenal gland nodule of undetermined histopathology, basal cell carcinoma, chondrosarcoma, a pituitary microadenoma and an auricular glomus jugulare tumor status post proton irradiation. Past ophthalmic history included anatomically narrow angles, which were monitored conservatively, and refractive error. The patient was a non-smoker. Family history revealed age-related macular degeneration, leukemia and multiple sclerosis. Current medications included Allegra, and calcium and vitamin D supplementation.

Examination

On examination, visual acuity with correction was 20/25 OU. Both pupils were equal, round and reactive to light without relative afferent pupillary defect. Intraocular pressure was 15 mmHg OD and 14 mmHg OS. Confrontation visual fields and extraocular motility were full OU. Anterior segment examination was unremarkable aside from a stable conjunctival nevus OS.

On posterior examination, the right eye was noted to have a normal optic nerve appearance and minimal parafoveal drusen. However, the inferior retinal vessels were dilated and slightly tortuous with asymmetric inferior “boxcarring” of the retinal veins (*Figure 1A*). The far periphery revealed the vessels led to a retinal vascular mass surrounded by exudation (*Figure 1B*). The posterior evaluation of the left eye revealed mild macular drusen. These features were consistent with the diagnosis of unilateral retinal hemangioblastoma, requiring investigation into whether she had von Hippel Lindau (VHL) disease. Genetic testing for VHL was negative for the mutation.



Figure 1. A: Fundus photo of the right eye reveals tortuous, dilated retinal vessels with asymmetric inferior “boxcarring” of the retinal veins. B: A vascular lesion with feeder vessels and surrounding hard exudates was found in the peripheral retina inferiorly.

What is your diagnosis? What further workup would you pursue? The diagnosis appears on p. 64.

Workup, Diagnosis and Treatment

At the time of diagnosis, optical coherence tomography of the macula was normal bilaterally without evidence of cystoid macula edema or epiretinal membrane. B-scan ultrasonography OD revealed a highly

reflective retinal mass 2.5 mm in thickness. Fluorescein angiography disclosed a dilated and tortuous artery and vein as well as staining and leakage of the mass.

Therapeutic options were dis-

cussed, including observation (given the absence of macular involvement), anti-VEGF intravitreal injection, photodynamic therapy, and laser photocoagulation to the hemangioblastoma. The patient elected PDT,

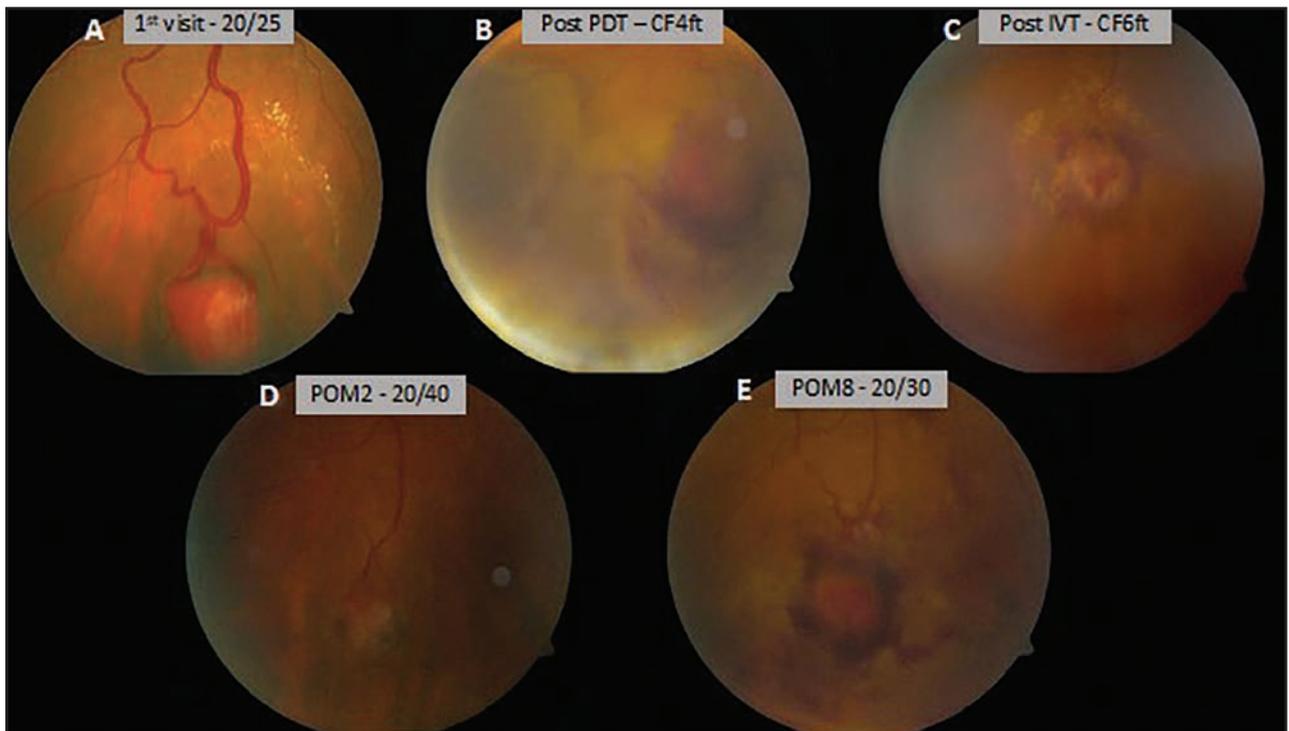


Figure 2. Peripheral fundus photographs of the right eye, documenting the retinal hemangioblastoma at the time of diagnosis (A), after initial photodynamic therapy (B), following intravitreal preservative-free triamcinolone acetamide (C), and at postoperative months two (D) and eight (E).



Figure 3. OCT of the macula documenting the grossly normal macular contour at time of diagnosis (A), as well as the presence of cystoid macular edema after initial photodynamic therapy (B). Following intravitreal injection of preservative-free triamcinolone acetamide (C), and at postoperative month eight (D), hard exudates remained in the outer and inner nuclear layers, in addition to subretinal debris and shallow subfoveal fluid.

which proceeded using standard settings (50 J/cm² with a 689-nm laser for 83 seconds). Following PDT, the patient noted gradually reduced vision to CF at 4 feet and was found to have an exudative retinal detach-

ment adjacent to the tumor and cystoid macular edema. She was treated with intravitreal preservative-free triamcinolone acetonide 4 mg/0.1 cc. Slowly, the tumor resolved over several months after PDT, with the

subretinal fluid and cystoid macular edema also resolving. Visual acuity returned to 20/30 in the affected eye. Figures 2 and 3 document the initial presentation and the course of the disease over time in this case.

Discussion

Retinal hemangioblastoma (RH, also known as retinal capillary hemangioma) is classically described as a red-orange, well-defined retinal mass with prominent dilated feeding vessels. These tumors are typically classified by their location (peripheral vs. juxtapapillary), morphology (endophytic vs. exophytic vs. sessile), local effects on the retina (exudation or vitreoretinal traction), and the presence or absence of the VHL mutation. Most RH are found in the peripheral retina with a proclivity for the superotemporal and inferotemporal quadrants. The natural history of RH is variable, with the potential for progression, regression or clinical stability.¹

RH pathology is notable for vascular channels lined by foamy stromal cells, which are postulated to be neoplastic in light of their loss of heterozygosity of the VHL gene and upregulation of VEGF.¹ Researchers at the National Institutes of Health conducted a prospective consecutive case series documenting 335 patients with RH in the context of VHL. Fifty-eight percent of patients had bilateral RH, and 85 percent of RH masses were located in the peripheral retina.² A 2001 retrospective consecutive case series of 68 patients diagnosed with RH at the Ocular Oncology Service at Wills Eye Hospital revealed that the median age of diagnosis with associated VHL was 18 years younger than for patients with sporadic RH.³ In the study, sporadic

RH tended to affect middle-aged individuals (approximately 36 to 48 years old) with unilateral, solitary tumors.¹ Approximately 46 percent of solitary RH are associated with VHL.⁴

VHL is an inherited autosomal dominant cancer predisposition syndrome carried on chromosome 3 (3p25-26).¹ This condition is caused by a germline mutation in the VHL tumor suppressor gene and affects approximately 1 in 40,000 births; approximately 20 percent are *de novo* mutations.¹ Mounting evidence supports the classical “two-hit” hypothesis in which patients have an initial germline mutation resulting in the loss of a tumor suppressor such as VHL in all cells, followed by local loss of the second (and sole functioning) allele, which results in complete loss of tumor suppression.³

Common manifestations of VHL include RH, CNS hemangioblastoma, pheochromocytoma, renal cell carcinoma (RCC), and cysts of the kidneys and pancreas.^{1,5} RH is often the presenting feature, but rarer ophthalmic findings associated with VHL have been reported, including twin vessels (paired retinal arteriole and venule, separated by less than one venule diameter) and vision loss secondary to CNS hemangiomas.^{1,6} Average life expectancy of patients with VHL is between 40 and 52 years of life, with the most common causes of death being RCC and CNS heman-

gioblastoma.

A diagnosis of VHL reflects both clinical and genetic findings. In patients without a known family history of VHL, a diagnosis may be made based on the presence of two of more of the following: two or more hemangioblastomas affecting the retina, spine or brain; a single other visceral hemangioma; RCC; pheochromocytoma; or, more rarely, endolymphatic sac tumors; papillary cystadenomas; or pancreatic neuroendocrine tumors. Alternatively, patients with a known family history only need one of more of the following features: retinal angioma; CNS hemangioblastoma; pheochromocytoma; RCC; or multiple cysts of the kidney or pancreas.⁷ VHL genetic testing is positive in more than 95 percent of patients who meet the clinical diagnostic criteria for VHL.⁸

VHL can be classified based on the absence or presence of CNS hemangioblastoma, pheochromocytoma and RCC. Type 1A is characterized by CNS hemangioblastoma and RCC. Type 1B is marked by CNS hemangioblastoma in the absence of RCC. Type 2 is characterized by the presence of pheochromocytoma and further subclassified based on the presence of CNS hemangioblastoma (Type 2A), CNS hemangioblastoma and RCC (Type 2B) or pheochromocytoma only (Type 2C).⁹

Upon diagnosis, patients are rigorously screened for manifestations

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of the VHL syndrome, including CNS hemangioblastomas, pheochromocytomas and RCC.¹⁰ Of note, an annual ophthalmic exam is recommended for VHL patients of all ages.¹¹ The Wills Eye Hospital Ocular Oncology Service takes a multidisciplinary approach to monitoring patients with VHL. All patients undergo systemic evaluation and genetic testing at the University of Pennsylvania's VHL clinic and undergo ophthalmic screening annually at Wills.

Treatment options for RH include close observation, laser photocoagulation surrounding the tumor, PDT, cryotherapy or plaque radiotherapy directed at the tumor. The preferred treatment is determined by the size of the RH. Small RH (<3 mm) respond well to laser photocoagulation or cryotherapy, while cryotherapy or PDT is more appropriate for medium (3 to 6 mm) RH. In our experience, larger RH (>6 mm) require PDT, plaque radiotherapy or internal resection.

Our patient elected to undergo photodynamic therapy and declined anti-VEGF. Initial treatment with PDT was complicated by an adjacent exudative retinal detachment and reduction of vision from 20/25 to counting fingers. In retrospect, this patient might have benefited from additional anti-VEGF at the time of the initial PDT administration. She was subsequently treated with intravitreal preservative-free triamcinolone acetonide to address macular edema and the exudative retinal detachment, both of which successfully responded over several months with return of vision.

In summary, our patient had a solitary peripheral retinal hemangioblastoma and negative genetic testing for VHL. She responded well to PDT with slow tumor involution over eight months. **REVIEW**

1. Singh AD, Shields CL, Shields JA. von Hippel-Lindau disease. *Surv Ophthalmol* 2001;46:117-42.
2. Wong WT, Agron E, Coleman HR, et al. Clinical characterization of retinal capillary hemangioblastomas in a large population of patients with von Hippel-Lindau disease. *Ophthalmology* 2008;115:181-8.
3. Singh AD, Nouri M, Shields CL, et al. Retinal capillary hemangioma: A comparison of sporadic cases and cases associated with von Hippel-Lindau disease. *Ophthalmology* 2001;108:1907-11.
4. Singh A, Shields J, Shields C. Solitary retinal capillary hemangioma: Hereditary (von Hippel-Lindau disease) or nonhereditary? *Arch Ophthalmol* 2001;119:232-4.
5. Glasker S, Neumann HPH, Koch CA, et al. Von Hippel-Lindau Disease. In: De Groot LJ, Chrousos G, Dungan K, et al., eds. *Endotext* (online text). South Dartmouth, Mass.:2000.
6. Maher ER, Yates JR, Harries R, et al. Clinical features and natural history of von Hippel-Lindau disease. *Q J Med* 1990;77:1151-63.
7. van Leeuwen RS, Ahmad S, Links TP, et al. von Hippel-Lindau Syndrome. In: Adam MP, Ardinger HH, Pagon RA, et al., eds. *GeneReviews* (online text). Seattle:1993.
8. Binderup MLM, Stendell AS, Galanakis M, et al. Retinal hemangioblastoma: Prevalence, incidence and frequency of underlying von Hippel-Lindau disease. *Br J Ophthalmol* 2018;102:942-7.
9. Maher ER, Neumann HP, Richard S. von Hippel-Lindau disease: A clinical and scientific review. *Eur J Hum Genet* 2011;19:617-23.
10. Shields C, Shields J. Retinal tumors: Understanding clinical features, OCT morphology, and therapy. *J Vitreoretinal Dis* 2017;1:10-23.
11. Varshney N, Kebede AA, Owusu-Dapaah H, et al. A review of von Hippel-Lindau syndrome. *J Kidney Cancer VHL* 2017;4:20-9.



BRIEF SUMMARY:

Consult the Full Prescribing Information for complete product information.

INDICATIONS AND USAGE

Xiidra® (lifitegrast ophthalmic solution) 5% is indicated for the treatment of the signs and symptoms of dry eye disease (DED).

DOSAGE AND ADMINISTRATION

Instill one drop of Xiidra twice daily (approximately 12 hours apart) into each eye using a single-use container. Discard the single-use container immediately after using in each eye. Contact lenses should be removed prior to the administration of Xiidra and may be reinserted 15 minutes following administration.

CONTRAINDICATIONS

Xiidra is contraindicated in patients with known hypersensitivity to lifitegrast or to any of the other ingredients in the formulation.

ADVERSE REACTIONS

Clinical Trials Experience

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in clinical studies 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 five clinical studies of dry eye disease conducted with lifitegrast ophthalmic solution, 1401 patients received at least 1 dose of lifitegrast (1287 of which received lifitegrast 5%). The majority of patients (84%) had ≤ 3 months of treatment exposure. 170 patients were exposed to lifitegrast for approximately 12 months. The majority of the treated patients were female (77%). The most common adverse reactions reported in 5-25 % of patients were instillation site irritation, dysgeusia and reduced visual acuity. Other adverse reactions reported in 1% to 5% of the patients were blurred vision, conjunctival hyperemia, eye irritation, headache, increased lacrimation, eye discharge, eye discomfort, eye pruritus and sinusitis.

Postmarketing Experience

The following adverse reactions have been identified during postapproval use of Xiidra. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Rare cases of hypersensitivity, including anaphylactic reaction, bronchospasm, respiratory distress, pharyngeal edema, swollen tongue, and urticaria have been reported. Eye swelling and rash have been reported.

USE IN SPECIFIC POPULATIONS

Pregnancy

There are no available data on Xiidra use in pregnant women to inform any drug associated risks. Intravenous (IV) administration of lifitegrast to pregnant rats, from pre-mating through gestation day 17, did not produce teratogenicity at clinically relevant systemic exposures. Intravenous administration of lifitegrast to pregnant rabbits during organogenesis produced an increased incidence of omphalocele at the lowest dose

tested, 3 mg/kg/day (400-fold the human plasma exposure at the recommended human ophthalmic dose [RHOD], based on the area under the curve [AUC] level). Since human systemic exposure to lifitegrast following ocular administration of Xiidra at the RHOD is low, the applicability of animal findings to the risk of Xiidra use in humans during pregnancy is unclear.

Animal Data

Lifitegrast administered daily by intravenous (IV) injection to rats, from pre-mating through gestation day 17, caused an increase in mean preimplantation loss and an increased incidence of several minor skeletal anomalies at 30 mg /kg /day, representing 5,400-fold the human plasma exposure at the RHOD of Xiidra, based on AUC. No teratogenicity was observed in the rat at 10 mg /kg /day (460-fold the human plasma exposure at the RHOD, based on AUC). In the rabbit, an increased incidence of omphalocele was observed at the lowest dose tested, 3 mg /kg /day (400-fold the human plasma exposure at the RHOD, based on AUC), when administered by IV injection daily from gestation days 7 through 19. A fetal No Observed Adverse Effect Level (NOAEL) was not identified in the rabbit.

Lactation

There are no data on the presence of lifitegrast in human milk, the effects on the breastfed infant, or the effects on milk production. However, systemic exposure to lifitegrast from ocular administration is low. The developmental and health benefits of breastfeeding should be considered, along with the mother's clinical need for Xiidra and any potential adverse effects on the breastfed child from Xiidra.

Pediatric Use

Safety and efficacy in pediatric patients below the age of 17 years have not been established.

Geriatric Use

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

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis: Animal studies have not been conducted to determine the carcinogenic potential of lifitegrast.

Mutagenesis: Lifitegrast was not mutagenic in the *in vitro* Ames assay. Lifitegrast was not clastogenic in the *in vivo* mouse micronucleus assay. In an *in vitro* chromosomal aberration assay using mammalian cells (Chinese hamster ovary cells), lifitegrast was positive at the highest concentration tested, without metabolic activation.

Impairment of fertility: Lifitegrast administered at intravenous (IV) doses of up to 30 mg/kg/day (5400-fold the human plasma exposure at the recommended human ophthalmic dose (RHOD) of lifitegrast ophthalmic solution, 5%) had no effect on fertility and reproductive performance in male and female treated rats.



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Xiidra is the only lymphocyte function-associated antigen-1 (LFA-1) antagonist treatment for Dry Eye Disease^{1,2}

Xiidra, the first in a class of LFA-1 antagonists for Dry Eye Disease, is a prescription eye drop FDA-approved to treat both signs and symptoms of the disease.^{1,3}

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References:

1. Xiidra [Prescribing Information]. Lexington, MA: Shire US.
2. TFOS DEWS II Research Subcommittee. Report of the Research Subcommittee of the Tear Film & Ocular Surface Society Dry Eye WorkShop II (2017). *Ocul Surf.* 2017;15(3):269-649.
3. FDA approves new medication for dry eye disease. FDA News Release. July 2016. <http://www.fda.gov/newsevents/newsroom/pressannouncements/ucm510720.htm>. Accessed July 12, 2016.
4. Food and Drug Administration. Electronic Orange Book. <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/UCM071436.pdf>. Accessed June 26, 2018.

Indication

Xiidra® (lifitegrast ophthalmic solution) 5% is indicated for the treatment of signs and symptoms of dry eye disease (DED).

Important Safety Information

Xiidra is contraindicated in patients with known hypersensitivity to lifitegrast or to any of the other ingredients.

In clinical trials, the most common adverse reactions reported in 5-25% of patients were instillation site irritation, dysgeusia and reduced visual acuity. Other adverse reactions reported in 1% to 5% of the patients were blurred vision, conjunctival hyperemia, eye irritation, headache, increased lacrimation, eye discharge, eye discomfort, eye pruritus and sinusitis.

To avoid the potential for eye injury or contamination of the solution, patients should not touch the tip of the single-use container to their eye or to any surface.

Contact lenses should be removed prior to the administration of Xiidra and may be reinserted 15 minutes following administration.

Safety and efficacy in pediatric patients below the age of 17 years have not been established.

For additional safety information, see accompanying Brief Summary of Safety Information on the adjacent page and Full Prescribing Information on Xiidra-ECP.com.

