REVIEW® of Ophthalmology

July 2017

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REFRACTIVE SURGERY ISSUE

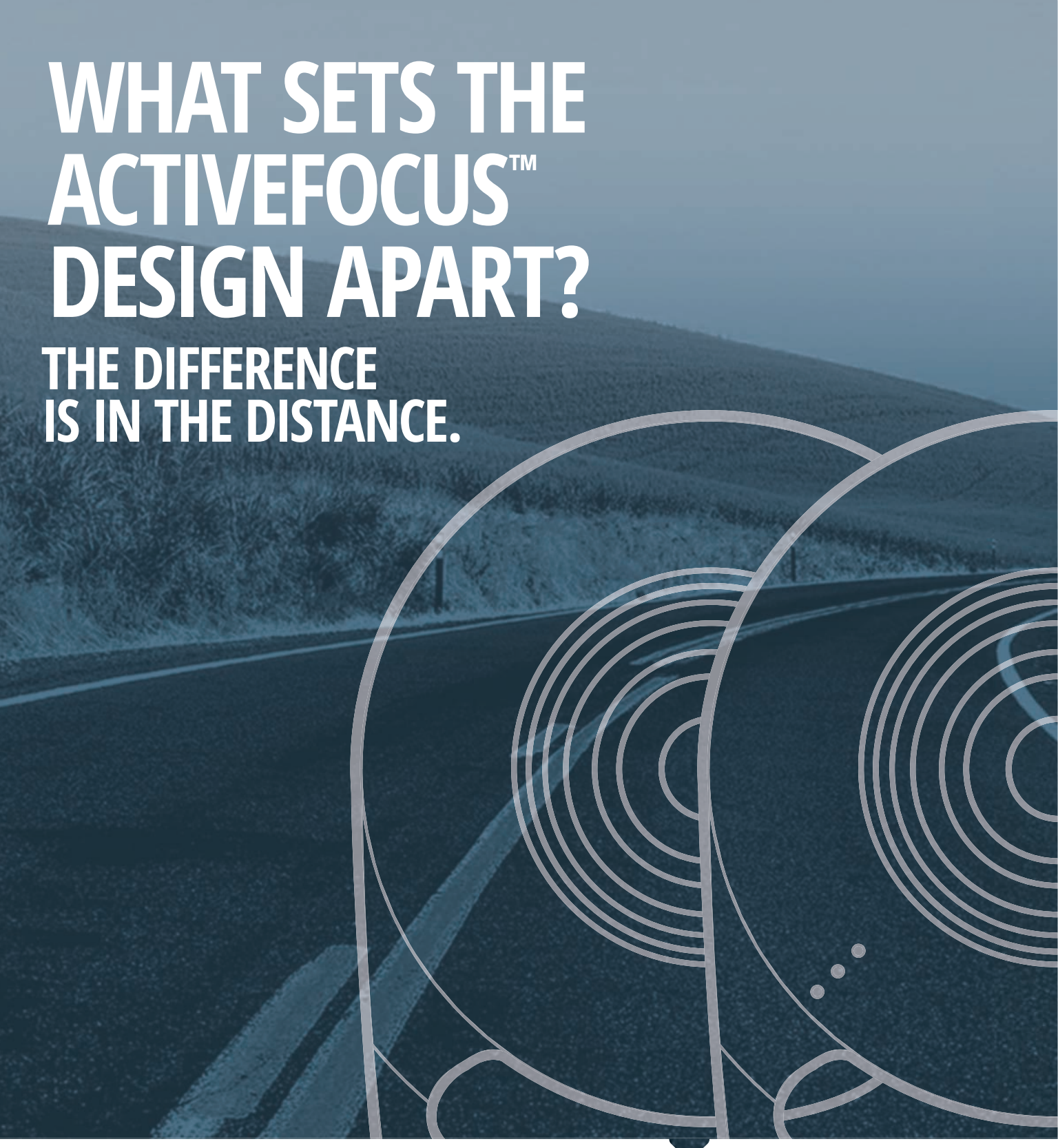
TOPO-GUIDED SURGERY FOR IRREGULAR ASTIGMATISM

Page 20

ALSO INSIDE:

WHAT SETS THE ACTIVEFOCUS™ DESIGN APART?

THE DIFFERENCE IS IN THE DISTANCE.



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See adjacent page for Important Product Information.

IMPORTANT PRODUCT INFORMATION FOR THE ACRYSOF® IQ RESTOR® FAMILY OF IOLs

CAUTION: Federal (USA) law restricts this device to the sale by or on the order of a physician.

INDICATIONS: The AcrySof® IQ ReSTOR® Posterior Chamber Intraocular Multifocal IOLs include AcrySof® IQ ReSTOR® and AcrySof® IQ ReSTOR® Toric and are intended for primary implantation for the visual correction of aphakia secondary to removal of a cataractous lens in adult patients with and without presbyopia, who desire near, intermediate and distance vision with increased spectacle independence. In addition, the AcrySof® IQ ReSTOR® Toric IOL is intended to correct pre-existing astigmatism. The lenses are intended to be placed in the capsular bag.

WARNINGS/PRECAUTIONS: Careful preoperative evaluation and sound clinical judgment should be used by the surgeon to decide the risk/benefit ratio before implanting a lens in a patient with any of the conditions described in the Directions for Use labeling for each IOL. Physicians should target emmetropia, and ensure that IOL centration is achieved. Care should be taken to remove viscoelastic from the eye at the close of surgery.

The ReSTOR Toric IOL should not be implanted if the posterior capsule is ruptured, if the zonules are damaged, or if a primary posterior capsulotomy is planned. Rotation can reduce astigmatic correction; if necessary lens repositioning should occur as early as possible prior to lens encapsulation.

Some patients may experience visual disturbances and/or discomfort due to multifocality, especially under dim light conditions. A reduction in contrast sensitivity may occur in low light conditions. Visual symptoms may be significant enough that the patient will request explant of the multifocal IOL. Spectacle independence rates vary; some patients may need glasses when reading small print or looking at small objects.

Posterior capsule opacification (PCO), when present, may develop earlier into clinically significant PCO with multifocal IOLs. Prior to surgery, physicians should provide prospective patients with a copy of the Patient Information Brochure available from Alcon informing them of possible risks and benefits associated with the AcrySof® IQ ReSTOR® IOLs.

Do not resterilize; do not store over 45° C; use only sterile irrigating solutions such as BSS® or BSS PLUS® Sterile Intraocular Irrigating Solutions.

ATTENTION: Reference the Directions for Use labeling for each IOL for a complete listing of indications, warnings and precautions.

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REVIEW NEWS Volume XXIV • No. 7 • July 2017

Avedro Takes Heat for Its Riboflavin Price Increase

Recently, Avedro, manufacturer of the KXL System for corneal cross-linking and the riboflavin formulas used in that procedure (Photrexa and Photrexa Viscous), stirred controversy by deciding to raise the price of the drug formulations from $595 to $2,850 as of July 1, 2017. At the same time, Avedro announced an initiative the company says is intended to make the procedure available to more patients in the United States by helping to secure commercial insurance coverage of the procedure, and supporting its reimbursement. That initiative includes the Avedro Reimbursement Customer Hub program, or ARCH, which is comprised of three parts: a reimbursement support service that will assist with appeals to commercial payers for both the drugs and the procedure; a patient-assistance program that will provide the formulations to financially eligible, uninsured patients at no charge; and a prescription-assistance program that will limit patients' out-of-pocket payments for the formulations to $595, if a commercial insurer denies the claim.

According to Reza Zadno, CEO of Avedro, the change in pricing is one part of an overall reimbursement effort and the result of a combination of factors: Insurance claims were already being submitted by patients and practices; the original pricing wasn't sustainable; the new price more accurately reflects the clinical and health economic value of the procedure; it helps support the ARCH program; it will allow the company to earn back some of the cost of getting the drugs approved; and it will support future research to improve the procedure.

A surgeon (who asked that his name be withheld) sympathizes with Avedro's situation. "I understand that's it's been a long, frustrating journey for Avedro to get this commercially available and viable," he says. "Nevertheless, clinicians are disappointed with the price increase. The last thing most of us want to do is haggle with multiple insurance carriers over a procedure that's done on a limited number of patients. These patients can require a lot of care and chair time, and the uncertainty of getting reimbursement can make it financially challenging, particularly for young, uninsured or underinsured patients, who might benefit the most from the procedure."

The surgeon notes that the increased drug cost will be added to other substantial costs. "If I spend $80,000 on a unit and amortize it over 20 patients per year for four years, that's $1,000 per procedure," he says. "In addition, I have to charge $800 to $1,000 to cover the cost of about eight office visits and performing the procedure, which can take an hour and a half for the surgeon and a technician. With the new drug price, the total cost is then approaching $5,000.

"I understand the rationale for the price increase, but it could be a real hardship for some of the patients that need it the most, and they've already been forced to wait years for the procedure to be approved while their vision deteriorated," he adds. "Meanwhile, no one is excited about having to convince multiple insurance companies to cover the procedure. This procedure could end up being done mostly as a labor of love by surgeons who are willing to do whatever is necessary to help these patients—which, of course, is the right thing to do."

Avedro's Mr. Zadno notes that keratoconus is an orphan indication for the procedure. "In the past year, approximately 8,000 procedures were performed," he says. "The initial price was set to allow immediate patient access while insurance coverage was limited, but it wasn't sustainable. It also didn't reflect the benefit of this procedure, which potentially eliminates the need for a corneal transplant—and some patients need more than one transplant. The average cost of a transplant is between $13,000 and $27,000. So even at $2,850, plus the physician-determined cost of performing the procedure, the total cost is well below that of a single corneal transplant. If you look at orphan drugs in general, the average price is much higher than $2,850, and there are other products used in ophthalmology that are not orphan drugs but cost much more. Furthermore, this is a one-time treatment; some expensive drugs have to be used monthly.

"Our company has invested close to $130 million in the development and approval of its cross-linking technology," he continues. "If 10,000 procedures were performed per year at the

$595 cost, that's only $5 or $6 million in revenue per year. More important, our goal is to pursue new applications for cross-linking and improve the procedure, which requires resources."

Mr. Zadno says that some doctors are concerned that raising the cost of the drugs will lower their reimbursement for the procedure. "The two reimbursements are not bundled," he says. "The cost of the drugs is billed separately from the payment to physicians for the procedure. The fee the physician charges is up to him or her."

What about the cost to the patient? "What the patient pays will depend on the practice and the insurance carrier," he explains. "When a patient has the procedure, the claim will be submitted to the patient's insurance company. Our prescription assistance program will come into play if the insurance company says, 'Sorry, we're not paying for that new technology at this early stage.' If that happens, $595 is the maximum the patient will pay for the drug. Meanwhile, our job is to work with the insurance companies to show the benefits of the procedure and convince them of its merits."

Mr. Zadno notes that the price increase could be an issue for practices that don't accept insurance. "In cornea, many procedures have been private pay," he says. "But I suspect that as insurance companies start covering this procedure, patients will go where their insurance is accepted."

Mr. Zadno says the company's ARCH initiative is intended to ensure that all parties involved will benefit. "After the product launch last September, we saw that many patients

Continued on pg. 53

Correction

In the June 2017 News section, Ben Casella was mistakely listed as an MD. Dr. Casella's correct title is Ben Casella, OD. *Review* regrets the error.

REVIEW® of Ophthalmology

REVIEW

Editor's Page

Walter C. Bethke, Editor in Chief

Pushing the Envelope

In the military, fighter pilots are taught the concept of their airplane's "envelope," or the combination of speed and stress that a plane can handle. This combination is often expressed as a graph of a line with a certain slope. As long as the pilot keeps the plane within the area demarcated by the line—the envelope—he's relatively safe. But if he goes beyond the limits of the line, such as when he's being pursued by an enemy plane intent on shooting him down, he's said to be "pushing the envelope," or entering a region of speed and stress that could bring him crashing to earth.

Certain corners of ophthalmology have always been known to push the envelope. Whether it's the black-box excimer lasers ophthalmologists invented in the '90s to enable them to perform refractive surgery on their own, or retina specialists compounding the anti-vascular endothelial growth factor drug Avastin for use in age-related macular degeneration, this discipline doesn't shy away from new frontiers. I was reminded of this as I read through the articles in this month's issue.

Irregular astigmatism, such as that induced by a decentered excimer laser ablation, has long been a tough nut to crack for corneal surgeons. As this month's cover story ("Topo-guided Ablation and Irregular Astigmatism," by Senior Editor Christopher Kent, p. 20) demonstrates, however the latest topography-guided excimer laser systems, though not approved for irregular astigmatism in the United States, are being used creatively by surgeons outside the country to treat these patients. These surgeons are helping these patients see better than they were ever able to before.

And speaking of giving people hope for better vision, what class of refractive surgery patient is more desperate for a solution than the presbyopes, whose progressively decreasing vision is a constant, frustrating reminder of the ravages of age? However, as the feature, "A Peek into the Presbyopia Pipeline," on pg. 36 points out, numerous new devices and drugs—envelope-pushers, all—are waiting in the wings for their chance to give presbyopes some relief.

And speaking of pushing the envelope, the grandaddy of all cutting-edge research meetings in ophthalmology, the Association for Research in Vision and Ophthalmology, receives the deluxe treatment in Therapeutic Topics on pg. 48. In it, a squadron of researchers and medical writers from Dr. Abelson's group Ora, who descended upon the meeting in Baltimore in May, give a detailed report on the highlights of the latest research in such heady disciplines as genetics and stem cell therapy for eye disease. If you weren't able to attend the meeting, their article will help make you feel as if you didn't miss a beat.

We hope these and the other articles in this month's issue help you push your own personal envelope in your daily practice. However, just be sure to watch your altitude.

—Walter Bethke, Editor in Chief

Discover Strength in efficacy

As demonstrated in phase 3 clinical trials in patients with Wet AMD, Macular Edema following RVO, DME, and DR in patients with DME

Choose EYLEA® (aflibercept) Injection from the start

Learn about EYLEA at EYLEA.us/ro

INDICATIONS AND IMPORTANT SAFETY INFORMATION

INDICATIONS

- EYLEA® (aflibercept) Injection is indicated for the treatment of patients with Neovascular (Wet) Age-related Macular Degeneration (AMD), Macular Edema following Retinal Vein Occlusion (RVO), Diabetic Macular Edema (DME), and Diabetic Retinopathy (DR) in Patients with DME.

CONTRAINDICATIONS

- EYLEA® (aflibercept) Injection is contraindicated in patients with ocular or periocular infections, active intraocular inflammation, or known hypersensitivity to aflibercept or to any of the excipients in EYLEA.

WARNINGS AND PRECAUTIONS

- Intravitreal injections, including those with EYLEA, have been associated with endophthalmitis and retinal detachments. Proper aseptic injection technique must always be used when administering EYLEA. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay and should be managed appropriately. Intraocular inflammation has been reported with the use of EYLEA.
- Acute increases in intraocular pressure have been seen within 60 minutes of intravitreal injection, including with EYLEA. Sustained increases in intraocular pressure have also been reported after repeated intravitreal dosing with VEGF inhibitors. Intraocular pressure and the perfusion of the optic nerve head should be monitored and managed appropriately.
- There is a potential risk of arterial thromboembolic events (ATEs) following intravitreal use of VEGF inhibitors, including EYLEA. ATEs are defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause). The incidence of reported thromboembolic events in wet AMD studies during the first year was 1.8% (32 out of 1824) in the combined group of patients treated with EYLEA. The incidence in the DME studies from baseline to week 52 was 3.3% (19 out of 578) in the combined group of patients treated with EYLEA compared with 2.8% (8 out of 287) in the control group; from baseline to week 100, the incidence was 6.4% (37 out of 578) in the combined group of patients treated with EYLEA compared with 4.2% (12 out of 287) in the control group. There were no reported thromboembolic events in the patients treated with EYLEA in the first six months of the RVO studies.

ADVERSE REACTIONS

- Serious adverse reactions related to the injection procedure have occurred in <0.1% of intravitreal injections with EYLEA including endophthalmitis and retinal detachment.
- The most common adverse reactions (≥5%) reported in patients receiving EYLEA were conjunctival hemorrhage, eye pain, cataract, vitreous floaters, intraocular pressure increased, and vitreous detachment.

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

EYLEA®
(aflibercept) Injection
For Intravitreal Injection

TARGETED SCIENCE

EYLEA is a registered trademark of Regeneron Pharmaceuticals, Inc.

REGENERON

06/2016
US-LEA-1648(1)

EYLEA®
(aflibercept) Injection
For Intravitreal Injection

BRIEF SUMMARY OF FULL PRESCRIBING INFORMATION

FOR COMPLETE DETAILS, SEE FULL PRESCRIBING INFORMATION.

1 INDICATIONS AND USAGE

EYLEA® (aflibercept) Injection is indicated for the treatment of patients with Neovascular (Wet) Age-Related Macular Degeneration (AMD), Macular Edema following Retinal Vein Occlusion (RVO), Diabetic Macular Edema (DME), and Diabetic Retinopathy (DR) in Patients with DME.

2 DOSAGE AND ADMINISTRATION

2.1 Important Injection Instructions. For ophthalmic intravitreal injection. EYLEA must only be administered by a qualified physician.

2.2 Neovascular (Wet) Age-Related Macular Degeneration (AMD). The recommended dose for EYLEA is 2 mg (0.05 mL or 50 microliters) administered by intravitreal injection every 4 weeks (monthly) for the first 12 weeks (3 months), followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months). Although EYLEA may be dosed as frequently as 2 mg every 4 weeks (monthly), additional efficacy was not demonstrated in most patients when EYLEA was dosed every 4 weeks compared to every 8 weeks. Some patients may need every 4 week (monthly) dosing after the first 12 weeks (3 months).

2.3 Macular Edema Following Retinal Vein Occlusion (RVO). The recommended dose for EYLEA is (0.05 mL or 50 microliters) administered by intravitreal injection once every 4 weeks (monthly).

2.4 Diabetic Macular Edema (DME). The recommended dose for EYLEA is (0.05 mL or 50 microliters) administered by intravitreal injection every 4 weeks (monthly) for the first 5 injections followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months). Although EYLEA may be dosed as frequently as 2 mg every 4 weeks (monthly), additional efficacy was not demonstrated in most patients when EYLEA was dosed every 4 weeks compared to every 8 weeks. Some patients may need every 4 week (monthly) dosing after the first 20 weeks (5 months).

2.5 Diabetic Retinopathy (DR) in Patients with DME. The recommended dose for EYLEA is 2 mg (0.05 mL or 50 microliters) administered by intravitreal injection every 4 weeks (monthly) for the first 5 injections, followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months). Although EYLEA may be dosed as frequently as 2 mg every 4 weeks (monthly), additional efficacy was not demonstrated in most patients when EYLEA was dosed every 4 weeks compared to every 8 weeks. Some patients may need every 4 week (monthly) dosing after the first 20 weeks (5 months).

2.6 Preparation for Administration. EYLEA should be inspected visually prior to administration. If particulates, cloudiness, or discoloration are visible, the vial must not be used. Using aseptic technique, the intravitreal injection should be performed with a 30-gauge x ½-inch injection needle. For complete preparation for administration instructions, see full prescribing information.

2.7 Injection Procedure. The intravitreal injection procedure should be carried out under controlled aseptic conditions, which include surgical hand disinfection and the use of sterile gloves, a sterile drape, and a sterile eyelid speculum (or equivalent). Adequate anesthesia and a topical broad–spectrum microbicide should be given prior to the injection.

Immediately following the intravitreal injection, patients should be monitored for elevation in intraocular pressure. Appropriate monitoring may consist of a check for perfusion of the optic nerve head or tonometry. If required, a sterile paracentesis needle should be available.

Following intravitreal injection, patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment (e.g., eye pain, redness of the eye, photophobia, blurring of vision) without delay (*see Patient Counseling Information*).

Each vial should only be used for the treatment of a single eye. If the contralateral eye requires treatment, a new vial should be used and the sterile field, syringe, gloves, drapes, eyelid speculum, filter, and injection needles should be changed before EYLEA is administered to the other eye.

After injection, any unused product must be discarded.

3 DOSAGE FORMS AND STRENGTHS

Single-use, glass vial designed to provide 0.05 mL of 40 mg/mL solution (2 mg) for intravitreal injection.

4 CONTRAINDICATIONS

EYLEA is contraindicated in patients with

- Ocular or periocular infections
- Active intraocular inflammation
- Known hypersensitivity to aflibercept or any of the excipients in EYLEA.

Hypersensitivity reactions may manifest as severe intraocular inflammation.

5 WARNINGS AND PRECAUTIONS

5.1 Endophthalmitis and Retinal Detachments. Intravitreal injections, including those with EYLEA, have been associated with endophthalmitis and retinal detachments (*see Adverse Reactions*). Proper aseptic injection technique must always be used when administering EYLEA. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay and should be managed appropriately (*see Dosage and Administration and Patient Counseling Information*).

5.2 Increase in Intraocular Pressure. Acute increases in intraocular pressure have been seen within 60 minutes of intravitreal injection, including with EYLEA (*see Adverse Reactions*). Sustained increases in intraocular pressure have also been reported after repeated intravitreal dosing with vascular edothelial growth factor (VEGF) inhibitors. Intraocular pressure and the perfusion of the optic nerve head should be monitored and managed appropriately (*see Dosage and Administration*).

5.3 Thromboembolic Events. There is a potential risk of arterial thromboembolic events (ATEs) following intravitreal use of VEGF inhibitors, including EYLEA. ATEs are defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause). The incidence of reported thromboembolic events in wet AMD studies during the first year was 1.8% (32 out of 1824) in the combined group of patients treated with EYLEA. The incidence in the DME studies from baseline to week 52 was 3.3% (19 out of 578) in the combined group of patients treated with EYLEA compared with 2.8% (8 out of 287) in the control group; from baseline to week 100, the incidence was 6.4% (37 out of 578) in the combined group of patients treated with EYLEA compared with 4.2% (12 out of 287) in the control group. There were no reported thromboembolic events in the patients treated with EYLEA in the first six months of the RVO studies.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in the *Warnings and Precautions* section of the labeling:

- Endophthalmitis and retinal detachments
- Increased intraocular pressure
- Thromboembolic events

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 other clinical trials of the same or another drug and may not reflect the rates observed in practice. A total of 2711 patients treated with EYLEA constituted the safety population in seven phase 3 studies. Among those, 2110 patients were treated with the recommended dose of 2 mg. Serious adverse reactions related to the injection procedure have occurred in <0.1% of intravitreal injections with EYLEA including endophthalmitis and retinal detachment. The most common adverse reactions (≥5%) reported in patients receiving EYLEA were conjunctival hemorrhage, eye pain, cataract, vitreous floaters, intraocular pressure increased, and vitreous detachment.

Neovascular (Wet) Age-Related Macular Degeneration (AMD). The data described below reflect exposure to EYLEA in 1824 patients with wet AMD, including 1223 patients treated with the 2-mg dose, in 2 double-masked, active-controlled clinical studies (VIEW1 and VIEW2) for 12 months.

Table 1: Most Common Adverse Reactions (≥1%) in Wet AMD Studies

Adverse Reactions	EYLEA (N=1824)	Active Control (ranibizumab) (N=595)
Conjunctival hemorrhage	25%	28%
Eye pain	9%	9%
Cataract	7%	7%
Vitreous detachment	6%	6%
Vitreous floaters	6%	7%
Intraocular pressure increased	5%	7%
Ocular hyperemia	4%	8%
Corneal epithelium defect	4%	5%
Detachment of the retinal pigment epithelium	3%	3%
Injection site pain	3%	3%
Foreign body sensation in eyes	3%	4%
Lacrimation increased	3%	1%
Vision blurred	2%	2%
Intraocular inflammation	2%	3%
Retinal pigment epithelium tear	2%	1%
Injection site hemorrhage	1%	2%
Eyelid edema	1%	2%
Corneal edema	1%	1%

Less common serious adverse reactions reported in <1% of the patients treated with EYLEA were hypersensitivity, retinal detachment, retinal tear, and endophthalmitis.

Macular Edema Following Retinal Vein Occlusion (RVO). The data described below reflect 6 months exposure to EYLEA with a monthly 2 mg dose in 218 patients following CRVO in 2 clinical studies (COPERNICUS and GALILEO) and 91 patients following BRVO in one clinical study (VIBRANT).

Table 2: Most Common Adverse Reactions (≥1%) in RVO Studies

Adverse Reactions	CRVO		BRVO	
	EYLEA (N=218)	Control (N=142)	EYLEA (N=91)	Control (N=92)
Eye pain	13%	5%	4%	5%
Conjunctival hemorrhage	12%	11%	20%	4%
Intraocular pressure increased	8%	6%	2%	0%
Corneal epithelium defect	5%	4%	2%	0%
Vitreous floaters	5%	1%	1%	0%
Ocular hyperemia	5%	3%	2%	2%
Foreign body sensation in eyes	3%	5%	3%	0%
Vitreous detachment	3%	4%	2%	0%
Lacrimation increased	3%	4%	3%	0%
Injection site pain	3%	1%	1%	0%
Vision blurred	1%	<1%	1%	1%
Intraocular inflammation	1%	1%	0%	0%
Cataract	<1%	1%	5%	0%
Eyelid edema	<1%	1%	1%	0%

Less common adverse reactions reported in <1% of the patients treated with EYLEA in the CRVO studies were corneal edema, retinal tear, hypersensitivity, and endophthalmitis.

Diabetic Macular Edema (DME). The data described below reflect exposure to EYLEA in 578 patients with DME treated with the 2-mg dose in 2 double-masked, controlled clinical studies (VIVID and VISTA) from baseline to week 52 and from baseline to week 100.

Table 3: Most Common Adverse Reactions (≥1%) in DME Studies

Adverse Reactions	Baseline to Week 52		Baseline to Week 100	
	EYLEA (N=578)	Control (N=287)	EYLEA (N=578)	Control (N=287)
Conjunctival hemorrhage	28%	17%	31%	21%
Eye pain	9%	6%	11%	9%
Cataract	8%	9%	19%	17%
Vitreous floaters	6%	3%	8%	6%
Corneal epithelium defect	5%	3%	7%	5%
Intraocular pressure increased	5%	3%	9%	5%
Ocular hyperemia	5%	6%	5%	6%
Vitreous detachment	3%	3%	8%	6%
Foreign body sensation in eyes	3%	3%	3%	3%
Lacrimation increased	3%	2%	4%	2%
Vision blurred	2%	2%	3%	4%
Intraocular inflammation	2%	<1%	3%	1%
Injection site pain	2%	<1%	2%	<1%
Eyelid edema	<1%	1%	2%	1%

Less common adverse reactions reported in <1% of the patients treated with EYLEA were hypersensitivity, retinal detachment, retinal tear, corneal edema, and injection site hemorrhage.

6.2 Immunogenicity. As with all therapeutic proteins, there is a potential for an immune response in patients treated with EYLEA. The immunogenicity of EYLEA was evaluated in serum samples. The immunogenicity data reflect the percentage of patients whose test results were considered positive for antibodies to EYLEA in immunoassays. The detection of an immune response is highly dependent on the sensitivity and specificity of the assays used, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to EYLEA with the incidence of antibodies to other products may be misleading.

In the wet AMD, RVO, and DME studies, the pre-treatment incidence of immunoreactivity to EYLEA was approximately 1% to 3% across treatment groups. After dosing with EYLEA for 24-100 weeks, antibodies to EYLEA were detected in a similar percentage range of patients. There were no differences in efficacy or safety between patients with or without immunoreactivity.

6.3 Postmarketing Experience. The following adverse reactions have been identified during postapproval use of EYLEA. 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.

- Hypersensitivity including rash, pruritus, and urticaria as well as isolated cases of severe anaphylactic/anaphylactoid reactions.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy. Pregnancy Category C. Aflibercept produced embryo-fetal toxicity when administered every three days during organogenesis to pregnant rabbits at intravenous doses ≥3 mg per kg, or every six days at subcutaneous doses ≥0.1 mg per kg. Adverse embryo-fetal effects included increased incidences of postimplantation loss and fetal malformations, including anasarca, umbilical hernia, diaphragmatic hernia, gastroschisis, cleft palate, ectrodactyly, intestinal atresia, spina bifida, encephalomeningocele, heart and major vessel defects, and skeletal malformations (fused vertebrae, sternebrae, and ribs; supernumerary vertebral arches and ribs; and incomplete ossification). The maternal No Observed Adverse Effect Level (NOAEL) in these studies was 3 mg per kg. Aflibercept produced fetal malformations at all doses assessed in rabbits and the fetal NOAEL was less than 0.1 mg per kg. Administration of the lowest dose assessed in rabbits (0.1 mg per kg) resulted in systemic exposure (AUC) that was approximately 10 times the systemic exposure observed in humans after an intravitreal dose of 2 mg.

There are no adequate and well-controlled studies in pregnant women. EYLEA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Females of reproductive potential should use effective contraception prior to the initial dose, during treatment, and for at least 3 months after the last intravitreal injection of EYLEA.

8.3 Nursing Mothers. It is unknown whether aflibercept is excreted in human milk. Because many drugs are excreted in human milk, a risk to the breastfed child cannot be excluded. EYLEA is not recommended during breastfeeding. A decision must be made whether to discontinue nursing or to discontinue treatment with EYLEA, taking into account the importance of the drug to the mother.

8.4 Pediatric Use. The safety and effectiveness of EYLEA in pediatric patients have not been established.

8.5 Geriatric Use. In the clinical studies, approximately 76% (2049/2701) of patients randomized to treatment with EYLEA were ≥65 years of age and approximately 46% (1250/2701) were ≥75 years of age. No significant differences in efficacy or safety were seen with increasing age in these studies.

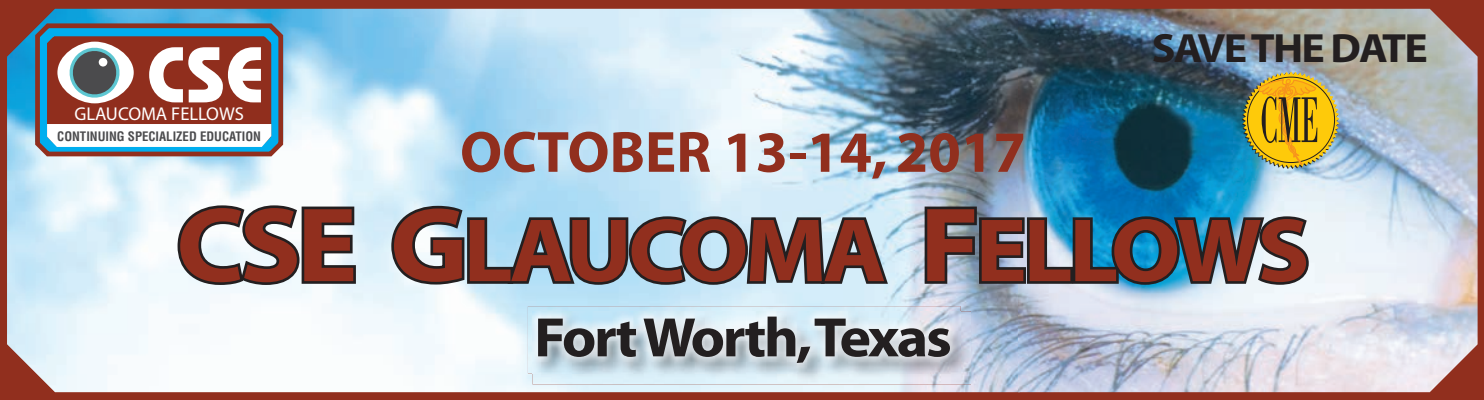
17 PATIENT COUNSELING INFORMATION

In the days following EYLEA administration, patients are at risk of developing endophthalmitis or retinal detachment. If the eye becomes red, sensitive to light, painful, or develops a change in vision, advise patients to seek immediate care from an ophthalmologist (*see Warnings and Precautions*). Patients may experience temporary visual disturbances after an intravitreal injection with EYLEA and the associated eye examinations (*see Adverse Reactions*). Advise patients not to drive or use machinery until visual function has recovered sufficiently.

REGENERON

Manufactured by:
Regeneron Pharmaceuticals, Inc.
777 Old Saw Mill River Road
Tarrytown, NY 10591-6707

Issue Date: June 2016
Initial U.S. Approval: 2011
June 2016



Dear Fellowship Program Director and Coordinator,

We would like to invite you to review the upcoming 2017 Glaucoma Fellowship Program and Wet Lab in Fort Worth at the Renaissance Worthington hotel. The program offers a unique educational opportunity for fellows by providing the chance to meet and exchange ideas with some of the most respected thought leaders in glaucoma. The Glaucoma Fellows Program and Wet Lab is designed to provide your fellows with a state-of-the-art didactic and wet lab experience. The program also serves as an opportunity for your fellows to network with fellows from other programs.

After reviewing the material, it is our hope that you will select and encourage your fellows to attend this educational activity which is CME accredited to ensure fair balance.

Sincerely,
Postgraduate Healthcare Education

Course Director:

Kuldev Singh, MD
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Wet Lab Directors:

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The PROLENSA® Effect

POWERED FOR PENETRATION

Advanced Formulation to Facilitate Corneal Penetration[1-3]

PROLENSA® delivers potency and corneal penetration with QD dosing at a low concentration[1-3]

INDICATIONS AND USAGE

PROLENSA® (bromfenac ophthalmic solution) 0.07% is a nonsteroidal anti-inflammatory drug (NSAID) indicated for the treatment of postoperative inflammation and reduction of ocular pain in patients who have undergone cataract surgery.

IMPORTANT SAFETY INFORMATION ABOUT PROLENSA®

- PROLENSA® contains sodium sulfite, a sulfite that may cause allergic type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than in non-asthmatic people.
- All topical nonsteroidal anti-inflammatory drugs (NSAIDs), including bromfenac, may slow or delay healing. Concomitant use of topical NSAIDs and topical steroids may increase the potential for healing problems.
- There is the potential for cross-sensitivity to acetylsalicylic acid, phenylacetic acid derivatives, and other NSAIDs, including bromfenac. Use with caution in patients who have previously exhibited sensitivities to these drugs.
- There have been reports that ocularly applied NSAIDs may cause increased bleeding of ocular tissues (including hyphemas) in conjunction with ocular surgery. Use with caution in patients with known bleeding tendencies or who are receiving other medications which may prolong bleeding time.
- Use of topical NSAIDs may result in keratitis. Patients with evidence of corneal epithelial breakdown should immediately discontinue use of topical NSAIDs, including bromfenac, and should be closely monitored for corneal health. Patients with complicated ocular surgeries, corneal denervation, corneal epithelial defects, diabetes mellitus, ocular surface diseases (e.g., dry eye syndrome), rheumatoid arthritis, or repeat ocular surgeries within a short period of time may be at increased risk for corneal adverse events which may become sight threatening. Topical NSAIDs should be used with caution in these patients. Post-marketing experience with topical NSAIDs suggests that use more than 24 hours prior to surgery or use beyond 14 days post-surgery may increase patient risk for the occurrence and severity of corneal adverse events.
- PROLENSA® should not be instilled while wearing contact lenses. The preservative in PROLENSA®, benzalkonium chloride, may be absorbed by soft contact lenses. Lenses may be reinserted after 10 minutes following administration of PROLENSA®.
- The most commonly reported adverse reactions in 3%-8% of patients were anterior chamber inflammation, foreign body sensation, eye pain, photophobia, and blurred vision.

Please see brief summary of full Prescribing Information for PROLENSA® on adjacent page.

References: 1. PROLENSA Prescribing Information, April 2013. **2.** Data on file, Bausch & Lomb Incorporated. **3.** Baklayan GA, Patterson HM, Song CK, Gow JA, McNamara TR. 24-hour evaluation of the ocular distribution of (14)C-labeled bromfenac following topical instillation into the eyes of New Zealand white rabbits. *J Ocul Pharmacol Ther.* 2008;24(4):392-398.

BAUSCH + LOMB

PROLENSA®
(bromfenac ophthalmic solution) 0.07%

BRIEF SUMMARY OF PRESCRIBING INFORMATION

This Brief Summary does not include all the information needed to prescribe Prolensa safely and effectively. See full prescribing information for Prolensa.

PROLENSA (bromfenac opthalmic solution) 0.07%

Rx only
Initial Rx Approval: 1997

INDICATIONS AND USAGE

PROLENSA® (bromfenac ophthalmic solution) 0.07% is indicated for the treatment of postoperative inflammation and reduction of pain in patients who have undergone cataract surgery.

DOSAGE AND ADMINISTRATION

Recommended Dosing

One drop of PROLENSA ophthalmic solution should be applied to the affected eye once daily beginning 1 day prior to cataract surgery, continued on the day of surgery, and through the first 14 days of the postoperative period.

Use with Other Topical Ophthalmic Medications

PROLENSA ophthalmic solution may be administered in conjunction with other topical ophthalmic medications such as alpha-agonists, beta-blockers, carbonic anhydrase inhibitors, cycloplegics, and mydriatics. Drops should be administered at least 5 minutes apart.

CONTRAINDICATIONS

None

WARNINGS AND PRECAUTIONS

Sulfite Allergic Reactions

Contains sodium sulfite, a sulfite that may cause allergic-type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than in non-asthmatic people.

Slow or Delayed Healing

All topical nonsteroidal anti-inflammatory drugs (NSAIDs), including bromfenac, may slow or delay healing. Topical corticosteroids are also known to slow or delay healing. Concomitant use of topical NSAIDs and topical steroids may increase the potential for healing problems.

Potential for Cross-Sensitivity

There is the potential for cross-sensitivity to acetylsalicylic acid, phenylacetic acid derivatives, and other NSAIDs, including bromfenac. Therefore, caution should be used when treating individuals who have previously exhibited sensitivities to these drugs.

Increased Bleeding Time

With some NSAIDs, including bromfenac, there exists the potential for increased bleeding time due to interference with platelet aggregation. There have been reports that ocularly applied NSAIDs may cause increased bleeding of ocular tissues (including hyphemas) in conjunction with ocular surgery.

It is recommended that PROLENSA ophthalmic solution be used with caution in patients with known bleeding tendencies or who are receiving other medications which may prolong bleeding time.

Keratitis and Corneal Reactions

Use of topical NSAIDs may result in keratitis. In some susceptible patients, continued use of topical NSAIDs may result in epithelial breakdown, corneal thinning, corneal erosion, corneal ulceration, or corneal perforation. These events may be sight threatening. Patients with evidence of corneal epithelial breakdown should immediately discontinue use of topical NSAIDs, including bromfenac, and should be closely monitored for corneal health.

Post-marketing experience with topical NSAIDs suggests that patients with complicated ocular surgeries, corneal denervation, corneal epithelial defects, diabetes mellitus, ocular surface diseases (e.g., dry eye syndrome), rheumatoid arthritis, or repeat ocular surgeries within a short period of time may be at increased risk for corneal adverse events which may become sight threatening. Topical NSAIDs should be used with caution in these patients.

Post-marketing experience with topical NSAIDs also suggests that use more than 24 hours prior to surgery or use beyond 14 days post-surgery may increase patient risk for the occurrence and severity of corneal adverse events.

Contact Lens Wear

PROLENSA should not be instilled while wearing contact lenses. Remove contact lenses prior to instillation of PROLENSA. The preservative in PROLENSA, benzalkonium chloride may be absorbed by soft contact lenses. Lenses may be reinserted after 10 minutes following administration of PROLENSA.

ADVERSE REACTIONS

Clinical Trial Experience

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

The most commonly reported adverse reactions following use of PROLENSA ophthalmic solution following cataract surgery include: anterior chamber inflammation, foreign body sensation, eye pain, photophobia and vision blurred. These reactions were reported in 3 to 8% of patients.

USE IN SPECIFIC POPULATIONS

Pregnancy

Treatment of rats at oral doses up to 0.9 mg/kg/day (systemic exposure 90 times the systemic exposure predicted from the recommended human ophthalmic dose [RHOD] assuming the human systemic concentration is at the limit of quantification) and rabbits at oral doses up to 7.5 mg/kg/day (150 times the predicted human systemic exposure) produced no treatment-related malformations in reproduction studies. However, embryo-fetal lethality and maternal toxicity were produced in rats and rabbits at 0.9 mg/kg/day and 7.5 mg/kg/day, respectively. In rats, bromfenac treatment caused delayed parturition at 0.3 mg/kg/day (30 times the predicted human exposure), and caused dystocia, increased neonatal mortality, and reduced postnatal growth at 0.9 mg/kg/day.

There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Because of the known effects of prostaglandin biosynthesis-inhibiting drugs on the fetal cardiovascular system (closure of ductus arteriosus), the use of PROLENSA ophthalmic solution during late pregnancy should be avoided.

Nursing Mothers

Caution should be exercised when PROLENSA is administered to a nursing woman.

Pediatric Use

Safety and efficacy in pediatric patients below the age of 18 have not been established.

Geriatric Use

There is no evidence that the efficacy or safety profiles for PROLENSA differ in patients 70 years of age and older compared to younger adult patients.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis and Impairment of Fertility

Long-term carcinogenicity studies in rats and mice given oral doses of bromfenac up to 0.6 mg/kg/day (systemic exposure 30 times the systemic exposure predicted from the recommended human ophthalmic dose [RHOD] assuming the human systemic concentration is at the limit of quantification) and 5 mg/kg/day (340 times the predicted human systemic exposure), respectively, revealed no significant increases in tumor incidence.

Bromfenac did not show mutagenic potential in various mutagenicity studies, including the reverse mutation, chromosomal aberration, and micronucleus tests. Bromfenac did not impair fertility when administered orally to male and female rats at doses up to 0.9 mg/kg/day and 0.3 mg/kg/day, respectively (systemic exposure 90 and 30 times the predicted human exposure, respectively).

PATIENT COUNSELING INFORMATION

Slowed or Delayed Healing

Advise patients of the possibility that slow or delayed healing may occur while using NSAIDs.

Sterility of Dropper Tip

Advise patients to replace bottle cap after using and to not touch dropper tip to any surface, as this may contaminate the contents. Advise patients that a single bottle of PROLENSA be used to treat only one eye.

Concomitant Use of Contact Lenses

Advise patients to remove contact lenses prior to instillation of PROLENSA. The preservative in PROLENSA, benzalkonium chloride, may be absorbed by soft contact lenses. Lenses may be reinserted after 10 minutes following administration of PROLENSA.

Concomitant Topical Ocular Therapy

If more than one topical ophthalmic medication is being used, the medicines should be administered at least 5 minutes apart.

Rx Only

Manufactured by:
Bausch + Lomb, a division of Valeant Pharmaceuticals
North America LLC, Bridgewater, NJ 08807 USA

Product under license from:
Senju Pharmaceutical Co., Ltd., Osaka, Japan 541-0046

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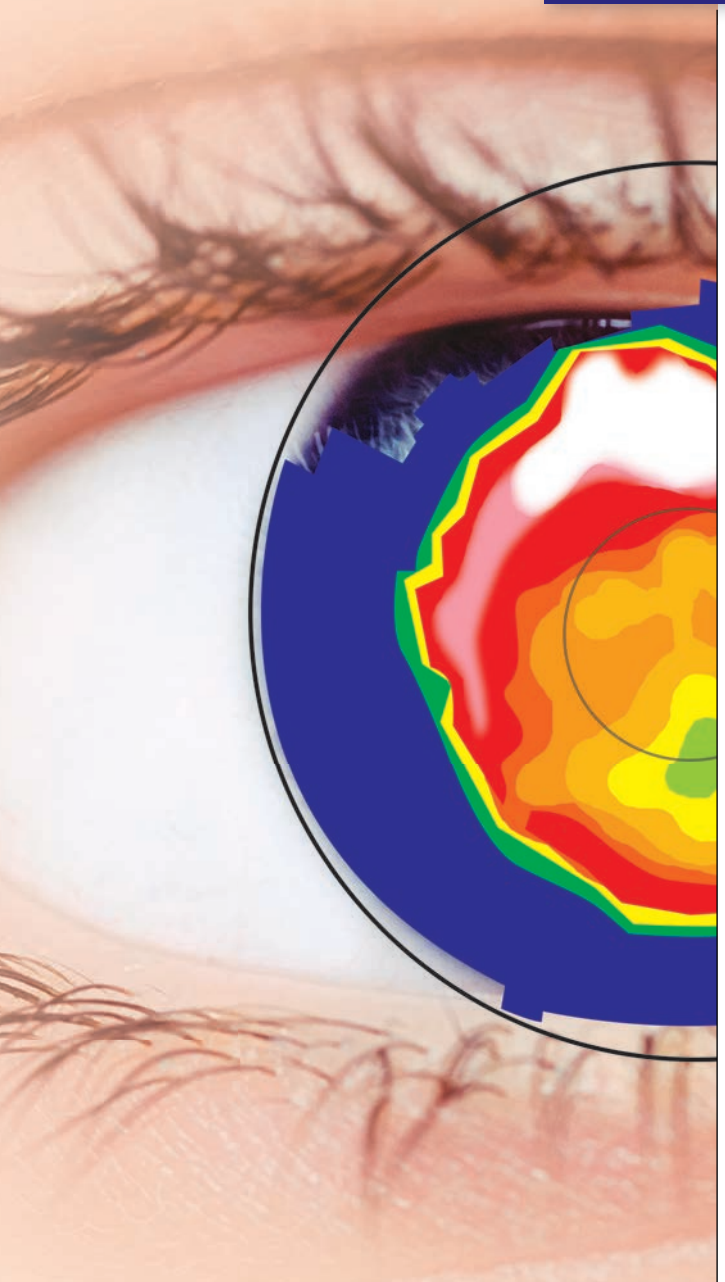

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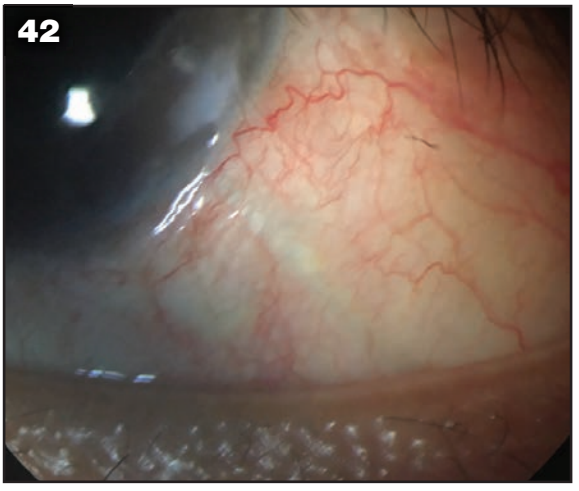

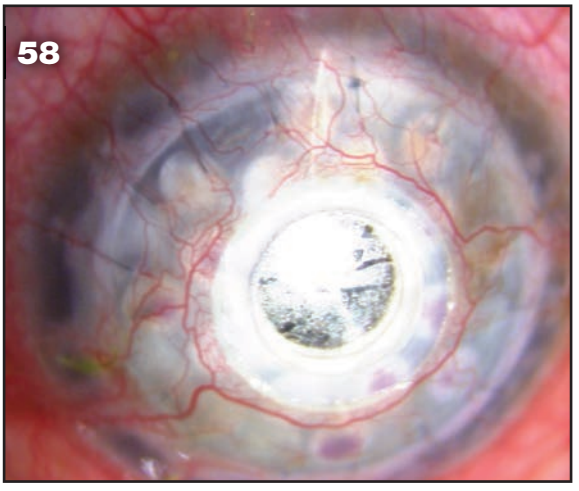

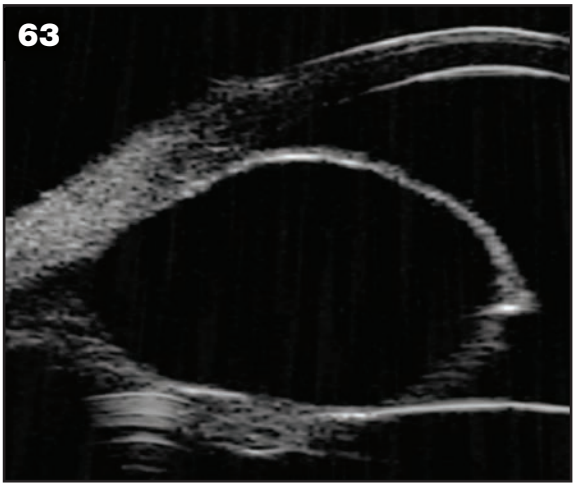

THE POWER OF PREEMPTION

OMIDRIA® is the first and only FDA-approved drug that provides continuous intracameral delivery of NSAID and mydriatic/anti-miotic therapy during cataract surgery[1]

CHOOSE OMIDRIA FOR YOUR NEXT CATARACT SURGERY PATIENT

- **Preempt miosis and inhibit postoperative pain[1]**
- **Block the surgically induced inflammatory cascade with the first and only NSAID FDA-approved for intracameral use[1]**
- **Eliminate the risks and liabilities of compounded products by using FDA-approved, GMP-manufactured OMIDRIA**
- **Avoid reimbursement difficulties by using broadly covered OMIDRIA and the OMIDRIAssure® services (OMIDRIAssure.com)***

IMPORTANT SAFETY INFORMATION

OMIDRIA (phenylephrine and ketorolac injection) 1% / 0.3% must be added to irrigation solution prior to intraocular use.

OMIDRIA is contraindicated in patients with a known hypersensitivity to any of its ingredients.

Systemic exposure of phenylephrine may cause elevations in blood pressure.

Use OMIDRIA with caution in individuals who have previously exhibited sensitivities to acetylsalicylic acid, phenylacetic acid derivatives, and other nonsteroidal anti-inflammatory drugs (NSAIDs), or have a past medical history of asthma.

The most commonly reported adverse reactions at 2-24% are eye irritation, posterior capsule opacification, increased intraocular pressure, and anterior chamber inflammation.

Use of OMIDRIA in children has not been established.

INDICATIONS AND USAGE

OMIDRIA is added to ophthalmic irrigation solution used during cataract surgery or intraocular lens replacement and is indicated for maintaining pupil size by preventing intraoperative miosis and reducing postoperative ocular pain.

Reference: 1. OMIDRIA [package insert]. Seattle, WA: Omeros Corporation; 2016.

Please see the Full Prescribing Information at www.omidria.com/prescribinginformation.

*Individual insurance coverage and policies may vary, and Omeros does not guarantee insurance coverage or payment. Omeros offers payments under the OMIDRIAssure "We Pay the Difference" program on behalf of qualifying patients. OMIDRIAssure is subject to change without notice.

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OMEROS

OMIDRIA®
(phenylephrine and ketorolac injection) 1% / 0.3%


Low-Vision Devices: Trusted Tech, New Twists

A look at recent releases that take magnification and screen- and text-reading capabilities to new levels.

Kristine Brennan, Senior Associate Editor

In 2014, the World Health Organization estimated that globally, 246 million people were visually impaired, and another 39 million were blind.[1] Although the causes vary geographically and economically, with most of these estimated to be people aged 50 and up, these numbers suggest that a good number of Americans of all ages have visual deficits severe enough to affect their educations, activities of daily living and work. The use of carefully selected assistive devices that help maximize remaining vision or capitalize on hearing and/or touch can enhance the independent pursuit of work, school and hobbies.

iZoom 6 USB

The iZoom 6 USB (Issist Assistive Technologies; Georgetown, Ontario, Canada) is a plug-and-play flash drive that users can take to the office, their school's computer lab, the library or anywhere else that life or work takes them to make any desktop or laptop computer's display low-vision friendly without software installation or licensing hassles. The software permits magnification of text by up to 40 times its regular size with default text smoothing, which the user can disable if desired. It also has text-reading capabilities that let users hear the text of web pages, emails or documents.

Enhanced Vision

The Jordy is a head-worn HD autofocus camera with a portable battery pack.

The iZoom 6 software works with the Windows XP, Vista 7, 8 or 8.1 operating systems to make any computer with 500MB of free disk space accessible to users with visual impairment. Since it works with MS Office 2013, users can catch up on school, personal or work tasks anywhere they go.

The Eye Care Edition includes a short setup assistant that walks users through choosing magnification and viewing options that suit them best among a menu of popular choices. The iZoom 6 package also offers a menu of preset color schemes, as well as the option to customize one for optimal contrast between text, images and background. The iZoom also includes the ability to customize the size of the mouse pointer and to add an optional locator box to the pointer, as well as caret tracking to highlight the progress of the cursor. The software will accommodate a second monitor, either for additional magnification of single images or to facilitate working with dual screens.

The narration options users can select include echo keys, which speak every keystroke, in addition to the narration of web pages, Notepad or Word documents. The SmartAlign feature rapidly reformats web pages for easier browsing.

Jordy

The Jordy (Enhanced Vision; Hun-

This article has no commercial sponsorship.

The *FIRST* and *ONLY* NSAID indicated to prevent ocular pain in cataract surgery patients[1]

A DROP OF PREVENTION

FOR YOUR CATARACT SURGERY PATIENTS

Defend against ocular pain and combat postoperative inflammation with the penetrating power of BromSite® formulated with DuraSite®[1]

- DuraSite® increases ocular surface retention time, resulting in increased bromfenac absorption[2-5]
- Provides 24-hour coverage with BID dosing[1]
- Available in 5 mL bottle

Visit bromsite.com to find out more.

BromSite®
(bromfenac ophthalmic solution) 0.075%
Formulated with DURASITE® DELIVERY SYSTEM

Indications and Usage

BromSite® (bromfenac ophthalmic solution) 0.075% is a nonsteroidal anti-inflammatory drug (NSAID) indicated for the treatment of postoperative inflammation and prevention of ocular pain in patients undergoing cataract surgery.

Recommended Dosing

One drop of BromSite® should be applied to the affected eye twice daily (morning and evening) 1 day prior to surgery, the day of surgery, and 14 days postsurgery.

Important Safety Information

- **Slow or Delayed Healing:** All topical nonsteroidal anti-inflammatory drugs (NSAIDs), including BromSite®, may slow or delay healing. Topical corticosteroids are also known to slow or delay healing. Concomitant use of topical NSAIDs and topical steroids may increase the potential for healing problems.
- **Potential for Cross-Sensitivity:** There is the potential for cross-sensitivity to acetylsalicylic acid, phenylacetic acid derivatives, and other NSAIDs, including BromSite®. Therefore, caution should be used when treating individuals who have previously exhibited sensitivities to these drugs.
- **Increased Bleeding Time of Ocular Tissue:** With some NSAIDs, including BromSite®, there exists the potential for increased bleeding time due to interference with platelet aggregation. There have been reports that ocularly applied NSAIDs may cause increased bleeding of ocular tissues (including hyphemas) in conjunction with ocular surgery. It is recommended that BromSite® be used with caution in patients with known bleeding tendencies or who are receiving other medications which may prolong bleeding time.
- **Keratitis and Corneal Effects:** Use of topical NSAIDs may result in keratitis. In some susceptible patients, continued use of topical NSAIDs may result in epithelial breakdown, corneal thinning, corneal erosion, corneal ulceration or corneal perforation. Patients with evidence of corneal epithelial breakdown should immediately discontinue use of topical NSAIDs, including BromSite®, and should be closely monitored for corneal health. Patients with complicated ocular surgeries, corneal denervation, corneal epithelial defects, diabetes mellitus, ocular surface diseases (e.g., dry eye syndrome), rheumatoid arthritis, or repeat ocular surgeries within a short period of time may be at increased risk for corneal adverse events which may become sight threatening. Topical NSAIDs should be used with caution in these patients. Post-marketing experience with topical NSAIDs also suggests that use more than 24 hours prior to surgery or use beyond 14 days postsurgery may increase patient risk for the occurrence and severity of corneal adverse events.
- **Contact Lens Wear:** BromSite® should not be administered while wearing contact lenses. The preservative in BromSite®, benzalkonium chloride, may be absorbed by soft contact lenses.
- **Adverse Reactions:** The most commonly reported adverse reactions in 1% to 8% of patients were anterior chamber inflammation, headache, vitreous floaters, iritis, eye pain, and ocular hypertension.

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

NSAID=nonsteroidal anti-inflammatory drug.

References: 1. BromSite® [package insert]. Cranbury, NJ: Sun Pharmaceutical Industries, Inc.; 2016. **2.** Hosseini K, Hutcheson J, Bowman L. Aqueous humor concentration of bromfenac 0.09% (Bromday™) compared with bromfenac in DuraSite® 0.075% (BromSite™) in cataract patients undergoing phacoemulsification after 3 days dosing. Poster presented at: ARVO Annual Meeting; May 5-9, 2013; Seattle, Washington. **3.** ClinicalTrials.gov. Aqueous humor concentration of InSite Vision (ISV) 303 (bromfenac in DuraSite) to Bromday once daily (QD) prior to cataract surgery. https://clinicaltrials.gov/ct2/show/results/NCT01387464?sect=X70156&term=insite+vision&rank=1. Accessed March 2, 2017. **4.** Si EC, Bowman LM, Hosseini K. Pharmacokinetic comparisons of bromfenac in DuraSite and Xibrom. *J Ocul Pharmacol Ther.* 2011;27(1):61-66. **5.** Bowman LM, Si E, Pang J, et al. Development of a topical polymeric mucoadhesive ocular delivery system for azithromycin. *J Ocul Pharmacol Ther.* 2009;25(2):133-139.

SUN OPHTHALMICS

BromSite® (bromfenac ophthalmic solution) 0.075%
Brief Summary

INDICATIONS AND USAGE
BromSite® (bromfenac ophthalmic solution) 0.075% is indicated for the treatment of postoperative inflammation and prevention of ocular pain in patients undergoing cataract surgery.

CONTRAINDICATIONS
None

WARNINGS AND PRECAUTIONS
Slow or Delayed Healing
All topical nonsteroidal anti-inflammatory drugs (NSAIDs), including BromSite® (bromfenac ophthalmic solution) 0.075%, may slow or delay healing. Topical corticosteroids are also known to slow or delay healing. Concomitant use of topical NSAIDs and topical steroids may increase the potential for healing problems.

Potential for Cross-Sensitivity
There is the potential for cross-sensitivity to acetylsalicylic acid, phenylacetic acid derivatives, and other NSAIDs, including BromSite® (bromfenac ophthalmic solution) 0.075%. Therefore, caution should be used when treating individuals who have previously exhibited sensitivities to these drugs.

Increased Bleeding Time of Ocular Tissue
With some NSAIDs, including BromSite® (bromfenac ophthalmic solution) 0.075%, there exists the potential for increased bleeding time due to interference with platelet aggregation. There have been reports that ocularly applied NSAIDs may cause increased bleeding of ocular tissues (including hyphemas) in conjunction with ocular surgery.

It is recommended that BromSite® be used with caution in patients with known bleeding tendencies or who are receiving other medications which may prolong bleeding time.

Keratitis and Corneal Reactions
Use of topical NSAIDs may result in keratitis. In some susceptible patients, continued use of topical NSAIDs may result in epithelial breakdown, corneal thinning, corneal erosion, corneal ulceration or corneal perforation. These events may be sight threatening. Patients with evidence of corneal epithelial breakdown should immediately discontinue use of topical NSAIDs, including BromSite® (bromfenac ophthalmic solution) 0.075%, and should be closely monitored for corneal health.

Post-marketing experience with topical NSAIDs suggests that patients with complicated ocular surgeries, corneal denervation, corneal epithelial defects, diabetes mellitus, ocular surface diseases (e.g., dry eye syndrome), rheumatoid arthritis, or repeat ocular surgeries within a short period of time may be at increased risk for corneal adverse events which may become sight threatening. Topical NSAIDs should be used with caution in these patients.

Post-marketing experience with topical NSAIDs also suggests that use more than 24 hours prior to surgery or use beyond 14 days postsurgery may increase patient risk for the occurrence and severity of corneal adverse events.

Contact Lens Wear
BromSite® should not be administered while wearing contact lenses. The preservative in BromSite®, benzalkonium chloride, may be absorbed by soft contact lenses.

ADVERSE REACTIONS
The following serious adverse reactions are described elsewhere in the Brief Summary:
- Slow or Delayed Healing
- Potential for Cross-Sensitivity
- Increased Bleeding Time of Ocular Tissue
- Keratitis and Corneal Reactions
- Contact Lens Wear

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

The most commonly reported adverse reactions in 1–8% of patients were: anterior chamber inflammation, headache, vitreous floaters, iritis, eye pain and ocular hypertension.

USE IN SPECIFIC POPULATIONS
Pregnancy
Risk Summary
There are no adequate and well-controlled studies in pregnant women to inform any drug associated risks. Treatment of pregnant rats and rabbits with oral bromfenac did not produce teratogenic effects at clinically relevant doses.

Clinical Considerations
Because of the known effects of prostaglandin biosynthesis-inhibiting drugs on the fetal cardiovascular system (closure of ductus arteriosus), the use of BromSite® during late pregnancy should be avoided.

Data
Animal Data
Treatment of rats with bromfenac at oral doses up to 0.9 mg/kg/day (195 times a unilateral daily human ophthalmic dose on a mg/m^2 basis, assuming 100% absorbed) and rabbits at oral doses up to 7.5 mg/kg/day (3243 times a unilateral daily dose on a mg/m^2 basis) produced no structural teratogenicity in reproduction studies. However, embryo-fetal lethality, neonatal mortality and reduced postnatal growth were produced in rats at 0.9 mg/kg/day, and embryo-fetal lethality was produced in rabbits at 7.5 mg/kg/day. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Lactation
There are no data on the presence of bromfenac in human milk, the effects on the breastfed infant, or the effects on milk production; however, systemic exposure to bromfenac from ocular administration is low. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for bromfenac and any potential adverse effects on the breast-fed child from bromfenac or from the underlying maternal condition.

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

Geriatric Use
There is no evidence that the efficacy or safety profiles for BromSite® differ in patients 65 years of age and older compared to younger adult patients.

NONCLINICAL TOXICOLOGY
Carcinogenesis, Mutagenesis and Impairment of Fertility
Long-term carcinogenicity studies in rats and mice given oral doses of bromfenac up to 0.6 mg/kg/day (129 times a unilateral daily dose assuming 100% absorbed, on a mg/m^2 basis) and 5 mg/kg/day (540 times a unilateral daily dose on a mg/m^2 basis), respectively revealed no significant increases in tumor incidence.

Bromfenac did not show mutagenic potential in various mutagenicity studies, including the bacterial reverse mutation, chromosomal aberration, and micronucleus tests.

Bromfenac did not impair fertility when administered orally to male and female rats at doses up to 0.9 mg/kg/day and 0.3 mg/kg/day, respectively (195 and 65 times a unilateral daily dose, respectively, on a mg/m^2 basis).

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SUN-OPH-BRO-017-1 03/2017

SUN OPHTHALMICS

tington Beach, Calif.) is a head-worn HD autofocus camera that fits over the eyes with a comfort-fit nosepiece and a head strap. It features a wide field of view, adjustable magnification, brightness control, color select, locator, freeze and focus-lock modes. The headpiece weighs in at eight ounces and connects to a portable battery pack.

The device will become available starting in July 2017 after a long absence from the market. "The Jordy was originally introduced in 1999, but we phased it out in 2010," says Jeri Scanlon of Enhanced Vision. "The new Jordy features all the latest new technology, including an HD autofocus camera, extended eight-hour battery life, and optical and digital zoom for distance, intermediate and near viewing."

The newest version of the Jordy can help users with low vision enhance their level of independent functioning and enjoyment at school, work or home. Students can wear the Jordy to read textbooks, complete assignments and to see the board and their classmates. The device has the potential to allow users to enjoy hobbies they may have believed were lost to them, like painting or crossword puzzles, as well as watching TV and movies. Since it facilitates close work like writing or reading a recipe, the Jordy may increase users' independence in activities such as bill paying and meal preparation.

When it's not being worn, docking the Jordy into an optional stand allows it to assist in other ways. "The Jordy will convert into a fully functioning desktop CCTV with our patented optional docking stand," says Ms. Scanlon. The docking stand incorporates a 24-inch high-resolution HD monitor and built-in LED lighting.

Ruby 7 HD Video Magnifier

Video magnifiers use a camera to project a magnified image onto a self-contained video screen or monitor, depending upon the size of the device. The Ruby 7 HD (Freedom Scientific; St. Petersburg, Fla.) is a handheld that combines a generous 7-inch screen with a total weight of just 18 ounces, so that a wide field of view for reading is possible without compromising portability; that portability can make some personal errands and hobbies just as easy as reading documents, books, newspapers and magazines.

Freedom Scientific

The Ruby 7 HD is a portable video magnifier for reading, hobbies and everyday activities.

The battery-operated magnifier can run for three hours on a single charge. The enlarged screen in the newest Ruby, which became available in the spring of 2017, bests the 5-inch screen of the prior model, the Ruby XL. The Ruby HD also has greater magnifying capabilities, according to the manufacturer, as well as new features that include a full-sized HDMI port to connect the device to a television, allowing users to view text or images on an even larger screen. For transfer of saved images to a computer, the Ruby 7 HD has a USB port.

The hardware includes a spring-loaded, integrated reading stand that enables the unit to automatically open up with the screen tilted toward the user in reading mode. There's also a foldaway handle, so that the user can grip the Ruby 7 HD like a magnifying glass and use it to view price tags, grocery labels, receipts and tickets while on the go.

The Ruby 7 HD's proprietary PivotCam rotating camera features spotting, writing, mirror and distance-viewing modes in addition to reading mode.

ZoomText Fusion 11

This software program combines the best of ZoomText, a magnifier, and JAWS, a screen and text reader, to make independent reading and computer work possible for users with any degree of visual impairment. ZoomText Fusion 11 (Ai Squared; St. Petersburg, Fla.) is essentially three products in one: the magnification and screen-reading program ZoomText 11; the speech capabilities of JAWS 18; and the ZoomText Fusion 11 program itself, which is the synthesis of the former two.

The combination of the two popular accessibility programs means that with one install and one license (licenses are available for a Professional or a Home Edition) users can run either of the two component programs or the Fusion to get the optimum level of magnification, contrast and speech narration for their particular level of visual impairment.

For users who desire or need more speech narration, Fusion 11 features the Eloquence text-to-speech synthesizer and Vocalizer Expressive for clear and natural-sounding speech narration. The manufacturer says that all three software programs comprising ZoomText Fusion 11 allow Braille output. Ai Squared has also updated ZoomText's toolbar and simplified keyboard commands to facilitate quicker navigation.

Ai Squared says that ZoomText Fusion 11 is a good choice for schools and workplaces because it can adjust to meet the individual needs of visually impaired users on software platforms that many already know and use successfully. REVIEW

1. World Health Organization (2014). Visual impairment and blindness: Fact sheet N°282. http://www.who.int/mediacentre/factsheets/fs282/en/. Accessed 6/19/2017.

Topo-guided Ablation & Irregular Astigmatism

Christopher Kent, Senior Editor

Finally able to offer topography-guided treatments, American surgeons look forward to the next frontier: abnormal corneas.

The recent U.S. Food and Drug Administration approval of limited topography-guided ablation was based on clinical trial results that involved treating corneas considered "normal," and the limited approval reflects that. But despite the excellent outcomes achieved in normal eyes during those trials, surgeons outside the United States primarily use this technology to address corneas with abnormalities such as keratoconus and ectasia, or those left aberrated by previous refractive surgery.

Many surgeons in the United States are already looking forward to being able to offer this to patients who find themselves in similar straits. With that in mind, three surgeons with extensive experience treating these more-aberrated eyes share some of their experience, to help prevent missteps as American surgeons start to move in this direction.

Working Within Limits

Karl G. Stonecipher, MD, medical director for TLC Laser Eye Centers in Greensboro, N.C., and clinical associate professor of ophthalmology at the University of North Carolina, uses Alcon's Contoura Vision to perform topography-guided ablation. "The FDA approval allows the use of topography-guided ablation to reduce or eliminate up to -9 D of spherical-equivalent myopia, with up to -8 D of spherical component and up to -3 D of astigmatic component at the spectacle plane," he notes. "For comparison, standard wavefront-optimized platforms treat 0 to -14 D of myopia, 0 to -6 D of myopia with astigmatism, and 0 to +6 D of hyperopia, with or without astigmatism. Other limitations for the use of topography-guided treatment include only treating patients age 18 and over who have a stable manifest refraction—meaning a preoperative spherical equivalent shift of 0.5 D or less over a period of one year prior to surgery—and eyes without previous refractive surgery, keratoconus, forme fruste keratoconus or any other topographic abnormality."

Dr. Stonecipher explains that the Contoura Vision system creates an ablation pattern by generating a hypothetical reference shape based on the eye's topography and figuring out how it can ablate tissue to most closely approximate that shape. "The reference shape is calculated based on the peaks and valleys of that eye," he says. "The maps you see show the actual height data compared to the hypothetical reference shape. Any area taller than that hypothetical surface shows up as red; anything below that level is blue.

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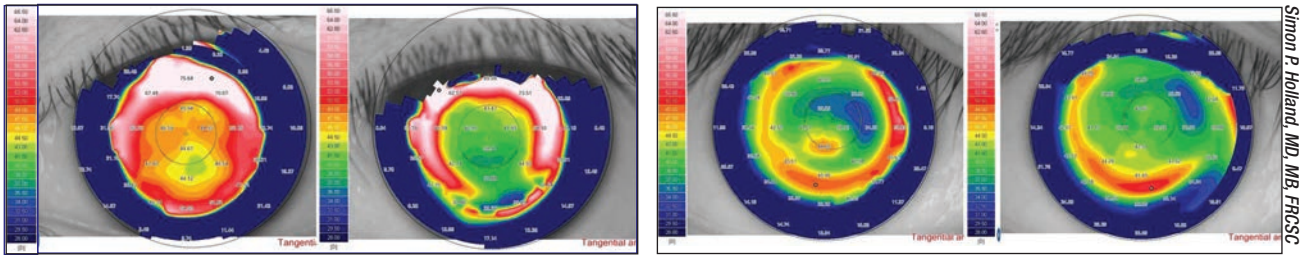


Simon P. Holland, MD, MB, FRCSC

Before and after scans show dramatic improvement in the central cornea following topography-guided treatment in these eyes.

Think of the warmer colors as a volcanic mountaintop and the cooler colors as the deep blue sea. When the ablation is based on this, it normalizes the corneal shape, reducing aberrations, smoothing the topography and making your optical system better. It also incorporates the principles used in wavefront-optimized systems, aiming to reduce spherical aberration."

Dr. Stonecipher says that for most patients who fall outside the FDA limits, he resorts to wavefront-optimized treatment with the Allegretto system. "Nevertheless, I measure every person," he says. "If the patient is a candidate and I can get good measurements, I'll do Contoura Vision. In my experience, Contoura vision gives me better-than-normal outcomes more frequently. In fact, Arthur Cummings and colleagues just reported that in the *Journal of Refractive Surgery*.[1]

Dr. Stonecipher points out, however, that there's more than one level of astigmatism. "If the cornea is considered abnormal, treating it with this technology is not an on-label option," he says. "But if I have someone with a cornea that's normal according to the FDA criteria but has a little asymmetry, this technology will allow me to treat that cornea's unique topographical features. So it's important to make a distinction between an abnormal cornea with irregular astigmatism, like keratoconus, and one that's regular with asymmetry within treatable LASIK guidelines. You can treat those topographical variations."

Dr. Stonecipher says the results they're achieving are exceptional. "Our topography-guided treatments are leaving patients with the sharpest uncorrected vision we've ever seen," he says. "We have patients routinely report that they see better after Contoura treatments than they saw before surgery in their glasses or contact lenses. When we participated in the clinical trial with Contoura Vision, we operated on normal corneas and got a third of patients seeing 20/12 and two-thirds seeing 20/16, some of the best data ever seen in an FDA trial. In our practice, many patients are seeing 20/15 and 20/10. I've had two patients measure 20/8 after the procedure, which I've never seen before.

"As a result, we can tell patients that we're likely to make their vision better, even if it was pretty good to start with," he says. "If it was 20/25 or 20/30, we might get you to 20/20, and in 33 percent of cases patients see one line better than they did before surgery. In the FDA trial, 19 percent of participants had one line or more of improvement; 8.3 percent had two lines or more. About a third of the patients saw better by at least one line. For nine out of 10 patients, uncorrected postop acuity without enhancement was equal to their best corrected visual acuity preoperatively.[2] That was unprecedented. For the first time we could say, 'We can reduce your light sensitivity, your difficulty driving at night, your reading difficulty and your complaints about glare.' In the trial this was all statistically significant compared to baseline at 12 months."

Outside the U.S.

Simon P. Holland, MD, MB, FRCSC, who practices at Pacific Laser Eye Centre and is clinical professor of ophthalmology at the University of British Columbia in Vancouver, British Columbia, Canada, works with topography-guided technology pioneer David T.C. Lin, MD, FRCSC. Dr. Holland says they currently use the Schwind Amaris 1050, although they previously used the Allegretto Wavelight T-CAT laser. They used it primarily for abnormal corneas, rather than the normal ones currently approved by the FDA.

"We treated irregular astigmatism, keratoconus and ectasia—combining the laser treatment with cross-linking for those corneas—and refractive surgery complications such as decentered ablations," he says. "We switched to the Schwind Amaris 1050 more than three years ago because of advantages such as high speed and an iris-based multidirectional tracker that includes torsion control. This technology lets us selectively treat the abnormal areas of a cornea and restore more normal topography, which has been shown to alleviate symptoms such as glare, halos and difficulty driving at night. It may also add lines of best-corrected distance visual acuity."

Dr. Holland says they use transepithelial PRK for the vast majority of their cases. "That approach spares tis-

sue," he points out. "In post-LASIK cases we treat on the flap, not on the interface where the patient had the previous surgery. The flap tissue isn't contributing much to the strength of the cornea, so we can do a relatively high degree of treatment on a patient who has, for example, post-LASIK ectasia. Then we cross-link the patient. We haven't seen a need for going deeper into the cornea by lifting—or making—flaps and then treating the bed. With a transepithelial technique we get our best results."

Wavefront- vs. Topography-guided

Many surgeons with access to both wavefront and topography-guided lasers resort to wavefront-guided or wavefront-optimized treatment when topography-guided treatment isn't an option. "In most cases if you compare a topography-guided map and a wavefront map of a virgin eye, once you subtract out the sphere and cylinder from the wavefront map, they look very similar," says Dr. Stonecipher. "However, the treatments do have some noteworthy differences. For one thing, topography-guided treatment is centered on the line of sight and the vertex of the cornea, while wavefront-optimized treatment is centered on the geometric center of the pupil. The difference between the two, called angle kappa, can be significant.

"Another difference is that with topography-guided treatments we're just treating the topographic abnormalities on the surface where they occur," he continues. "Because of that, these treatments are not dependent on pupil size, and the lens and vitreous don't matter. You aren't making changes to the cornea that may affect the optical system down the road when the individual undergoes refractive cataract surgery. Topography-guided ablation treats the source of the vast majority of the optical problems—the cornea—rather than the aberrations of the whole optical system, which can be moving targets. To put it another way, we make the lens of the camera better. In fact, our studies have found that 93 percent of patients don't need wavefront-guided treatment."[3]

"Topography-guided and wavefront-optimized systems both work well in appropriate patients," says Raymond Stein, MD, FRCSC, Fellow of the Royal College of Surgeons in Canada, medical director of the Bochner Eye Institute and associate professor of ophthalmology at the University of Toronto. "However, for patients with irregular corneas, topography-guided is definitely the way to go. The Oculyzer and Pentacam measure more than 20,000 data points on the cornea; this information gets introduced into the laser. Most wavefront units only measure 1,000 or 1,200 data points, so there's a significant difference in data quantity. In addition, wavefront imaging often has a difficult time with irregular corneas. So most surgeons around

the world who are treating irregular corneas use topography-guided systems."

Spherical Changes

One potential problem with topography-guided treatment is that smoothing the cornea can produce a refractive change. There are two main ways to deal with this possibility: Plan to perform a second procedure later to correct the altered spherical component; or estimate the likely change that your procedure will cause and compensate for it during the procedure. Each option has pros and cons.

Dr. Holland says it's probably best to go for an improvement in best corrected visual acuity, if the patient accepts that, rather than trying to leave the patient plano at distance. "Any topographic change can cause a power change, so many surgeons still do two treatments—one to regularize the cornea and then a second refractive correction once the eye is stable," he says.

"My partner David Lin developed and published a topographical neutralization technique designed to compensate for the potential refractive shift caused by topography-based treatment," he continues. "Compensating for the shape change is key if you want to achieve a good outcome in a single treatment when dealing with a very aberrated cornea. It can be challenging, however, because patients with ectatic conditions may have insufficient thickness to do a complete refractive treatment, and there's always a degree of unpredictability. On the other hand, improving the topography will lessen or eliminate problematic visual symptoms, regardless of the spherical outcome. You can always correct the power with glasses or contacts, if the patient will tolerate that.

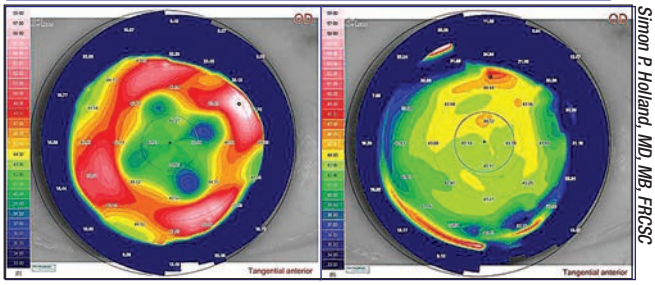
"Of course, the patient needs to know about this ahead of time," he adds. "On our informed consent, we explain that this procedure is not likely to leave the patient free of glasses, but will almost certainly leave the individual with much better vision when wearing glasses or contact lenses."

Dr. Holland notes that one group of patients who may not be receptive to this tradeoff is those who've had refractive surgery. "They almost always want to be corrected for distance vision," he says. "They usually say, 'I wouldn't have had the laser surgery if I didn't want to be free of glasses and contacts.' Patients with pathologies such as keratoconus or scarred corneas tend to be more tolerant."

Dr. Stein agrees. "For these patients, just being able to wear a soft contact lens is a major improvement," he says. "Of course, we can go back later to correct the spherical component, but we generally don't use an excimer laser because of their thin corneas. We like to limit the laser ablation to 50 µm."

Dr. Stein acknowledges that it's possible to try to compensate for the spherical change during the surgery. "If the prescription is low, we can try to correct a little bit," he says. "The question is, how much tissue can we safely remove? In patients with ectasia we want to err on the side of caution by not removing too much. On the other hand, in cases such as a decentered ablation or small optical zone, in which cross-linking isn't necessary, we'll do the spherical correction. Afterwards, if there's any residual sphere we can always go back and do a little bit more. The initial treatment would be topography-guided, while the follow-up would be a standard ablation. Corneal thinness isn't an issue in many of those patients."

Topography-guided PRK to Address Prior RK



Simon P. Holland, MD, MB, FRCSC

Treatment normalizes a cornea that had previous radial keratotomy.

Patient Selection

As with any laser ablation, selecting appropriate patients is a key to getting outstanding results:

• ***Make sure your patient will be happy if there's a trade-off.*** Dr. Stein points out that some patients, despite having irregular astigmatism, are not good candidates for topography-guided treatment. "I wouldn't do a topography-guided treatment on patients with an uncorrected visual acuity of 20/30, because although these patients could benefit from an improvement in their best corrected visual acuity, the procedure could induce some nearsightedness or farsightedness," he says. "The bottom line is that you want a satisfied patient."

• ***Warn patients they may need a second procedure.*** "Be sure to advise patients when you start that it's probably going to take two treatments," says Dr. Holland, referring to the possibility that correcting the corneal surface may alter its spherical power. "They may need a touch-up."

• ***Remember that some patients may benefit more than others.*** Dr. Holland says the patients most likely to appreciate the value of this treatment are those with the most aberrated eyes. "The best patients are those who will gain the most," he says. "Those are the ones with severely aberrated corneas, such as post-refractive surgery complications, keratoconus, post-LASIK ectasia or central islands. These patients are highly symptomatic."

Dr. Holland also notes that in most cases, the more central the abnormal-

ity, the better the results he gets. "That's because there's less tissue to remove, particularly in the ectatic patients," he says. "For example, pellucid marginal degeneration cases can be difficult because you have to treat a wider area of thinning and elevation and use more tissue. But eyes with a more central problem, such as those needing optical zone expansion, do very well with topography-guided treatment."

• ***Avoid treating corneas with steepening outside of the pupillary zone.*** "The fact that topography-guided ablation aims to smooth the cornea can be a problem in some cases," notes Dr. Stein. "It flattens steep areas and steepens flat areas. If a cornea has steepening outside of the pupillary zone, the flat area would be over the pupil and the laser would work to steepen that. As a result, it could make the patient significantly more nearsighted."

• ***Beware of misleading epithelial abnormalities.*** Although topography-guided treatment is excellent at eliminating corneal abnormalities, it's important to correctly identify the type of abnormality you're seeing. "You can't just look at the topography to make a diagnosis of keratoconus," notes Dr. Stein. "You have to do a proper slit-lamp examination to make sure there isn't any epithelial abnormality, because there are a variety of what we call pseudokeratoconus conditions.

"These conditions include a small focal scar, punctate keratopathy and amiodarone-induced vortex keratopathy," he notes. "Amiodarone is a lifesaving cardiac medication that can cause topography abnormalities. That's a challenge to treat, even if we identify the correct problem, because we can't ask the patient to stop a lifesaving medication. Another misleading condition is epithelial basement membrane dystrophy. That can cause big problems because it's a transient condition that doesn't need topography-guided PRK; it just needs a debridement of the epithelium.

"If you mistakenly use topography-guided laser to treat those conditions, you can induce irregular astigmatism in the stroma that may be difficult to correct," he continues. "In those conditions the stroma was normal all along; what's abnormal is just the very superficial layer, which can change over time.

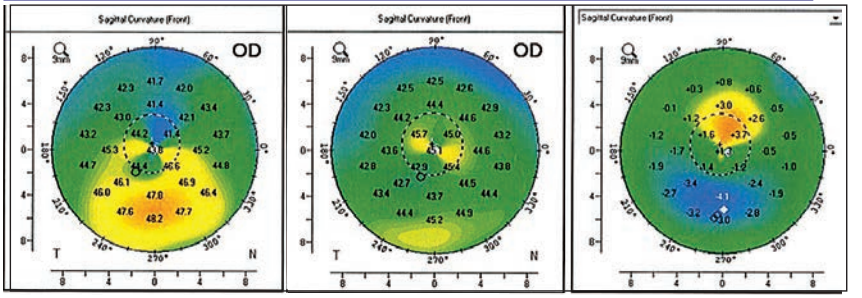
"This is one reason you can't just rely on the corneal measurements made by the topography-guided system," he adds. "That information is helpful in making a diagnosis, but in addition to that, a proper slit lamp exam is important to rule out pseudokeratoconus conditions."

Surgical tips

• ***Don't try to treat complex corneas until you're well acquainted with the technology and the way it works in your hands.*** Dr. Stonecipher says his best advice

for surgeons just starting to explore this technology is to walk before you run. "You don't want to begin by taking all of your highly aberrated postoperative LASIK, PRK and cataract patients and trying to fix them," he says. "You need to understand the technology. You want to do primary, normal eyes first, get your nomograms established and build your comfort level with the technology. Spend time with a surgeon who has a lot of experience with it, and consider taking one of the excellent courses on this topic taught by John Kanellopoulos, MD, at most of the major ophthalmology meetings. And when you do start treating more complex cases, contact one of those more-experienced surgeons and share the details of any challenging case you're working on; most of them will be happy to help you."

Topo-guided PRK Plus Cross-linking to Treat Keratoconus



Preop map (left) shows evidence of keratoconus with inferior steepening. Postop map (middle) shows significant reduction in the irregular astigmatism. The difference map (right) shows flattening of the inferior cornea and steepening of the superior cornea. This patient's best corrected visual acuity improved from 20/100 to 20/25 by six months.

• ***Treat every patient as a unique case.*** Dr. Holland notes that one factor making topography-guided treatment challenging is that every case is different. "It's really hard to apply the lessons you learned from one eye to another eye when you're normalizing aberrations," he says.

• ***Know when cross-linking is essential.*** "In our practice we see a lot of patients with keratoconus and pellucid marginal degeneration and post-LASIK ectasia," says Dr. Stein. "Once keratoconus or PMD reach a certain level, the cornea develops irregular astigmatism. Topography-guided ablation is a great treatment because it gives patients the best chance at improving their best-corrected spectacle vision. But if you're going to treat these conditions, it's very important to cross-link at the same time. If you remove tissue from these weakened corneas, you can further weaken the eye just by doing laser ablation. You have to cross-link to strengthen the tissue."

Dr. Stein notes, however, that not all topography-guided treatments have to be combined with cross-linking. "There are a number of indications for topography-guided treatment that aren't related to keratoconus or PMD," he says. "It's a great treatment for prior PRK or LASIK patients who ended up with a decentered ablation. It's also helpful for laser vision correction patients who have a small optical zone that's causing glare and halos. Those are cases that don't need cross-linking. They're irregularly shaped corneas, but not weakened corneas."

• ***Make sure the input data is good***. Dr. Stonecipher notes that you can see the system's analysis of the data quality onscreen, but sometimes just looking at the image will reveal a problem. "There are three onscreen markers whose color—green or red—tells you whether the data is acceptable," he says. "If all three of these are green, I know that my technician took a good picture and I can rely on this diagnostic picture for treatment. But sometimes the image on the screen will make it obvious that data is being blocked by the patient's nose, prominent brow or long eyelashes. That's a measurement I wouldn't want to use for treatment."

• ***Treat any problems on the ocular surface before measuring the cornea.*** "Treat any dry eye, allergy or ocular surface disease before you measure the topography," says Dr. Stonecipher. "If you have a bad ocular surface, whether before or during surgery, you'll get bad data."

• ***If you use a femto laser to make the flap and get an opaque bubble layer, wait for the bubbles to clear before measuring the cornea.*** Dr. Stonecipher notes that it may take 10 or 15 minutes for the bubbles to clear when this occurs, but a study conducted by his daughter Megan Stonecipher and him[4] found that trying to measure the cornea in the presence of an opaque bubble layer is the number-one source of requiring an enhancement when performing laser ablations.

• ***Always work toward creating a personal nomogram.*** Because altering the surface of the cornea may alter the spherical refraction, Dr. Stonecipher points out that surgeons should always be tracking their results to help create a personal nomogram that can minimize any unwanted shift. "We're using internet-based refractive analysis, IBRA for short, and Datalink, just as we do with our wavefront-guided and wavefront-optimized outcomes," he says. "Those will help you compensate for induced sphere, based on the characteristics of the cornea you're treating and the treatment you're performing.

"The nice thing about Datalink and IBRA," he adds, "is that they're based on data from thousands of eyes, so even if you're just starting out you'll have a nomogram to work with."

Not Easy, but Worth It

Dr. Stein believes that most practices that plan to offer patients cross-linking should also offer topography-guided treatment. "If you're a corneal specialist and you're going to offer cross-linking and hope to have a successful, busy practice, I think you need to offer a topography-guided laser option," he says. "On the other hand, if you're just going to do occasional cross-linking, I wouldn't offer topography-guided. This is not a simple technology. You have to spend time working with it and gain experience if you want to do it well."

Dr. Stonecipher notes that he's found topography-guided treatment to be a great practice-builder, for several reasons. "These patients are seeing as clearly as they previously saw with their glasses and contact lenses," he notes. "My current enhancement rate is 0.5 percent. So people are coming back happy, not needing a touchup. That's significant, because when I have to do a touch-up, patients think the procedure failed. If I can nail it first time out of the box, they're pretty happy. If I can give them good quality of vision with no halos, starburst, etc., they're even happier. In fact, I know some surgeons are charging a premium for performing it, so it definitely can provide added value to your practice."

Dr. Holland agrees. "If you're going to use topography-guided treatment off-label, you'll find there are great rewards for both the patient and the surgeon," he says. "However, you have to be prepared for a few bumps in the road to get there. There's no out-of-the-box technique that will work for all of the abnormalities you'll find in corneas."

Nevertheless, Dr. Stonecipher says that he'd recommend that surgeons add this to their armamentarium. "Topography-guided is allowing us to attain remarkable outcomes and much lower enhancement rates, much better than we were achieving with previous technologies," he says. "The proof is in the pudding. It's improving our better-than-20/20 rate; it's improving our best-corrected vs. uncorrected visual acuity; and it's allowing us to offer patients even better optical acuity than they were born with. It's good stuff." REVIEW

Dr. Stonecipher is a consultant for Abbott, Alcon, Allergan, Bausch + Lomb, Ellex and Nidek. Drs. Stein and Holland have no financial ties to any product mentioned.

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Risk Management for Corneal Inlays

By Kristine Brennan, Senior Associate Editor

Early data suggests there's little to fear. But there are some complications you can prevent or mitigate.

Middle age is often heralded by thinning hair, expanding waistlines—and waning near vision. Whether a stiffening of the crystalline lens, compromised functioning of the ciliary muscles or multiple factors contribute to presbyopia, the hunt for safe and effective glasses-free treatment has spanned decades. (*For more about emerging presbyopia treatments, see the article about presbyobia treatments in the pipeline, page 36.*) The relatively recent FDA approval of two corneal inlays, plus a third in Phase III FDA clinical trials, presents promising options for the right patients. Here, surgeons experienced with corneal inlays discuss what can potentially go off course, and what they do to help make things right for their patients.

The KAMRA (AcuFocus), the Raindrop (ReVision Optics), and the Presbia Flexivue Microlens (Presbia) each treat presbyopia via different mechanisms. The KAMRA is a donut-shaped inlay made of dark polyvinylidene fluoride, 3.8 mm in diameter with a 1.6-mm aperture and 8,400 microperforations that permit nutrients and oxygen to reach the cornea. The KAMRA relies on the pinhole effect to enhance near vision, allowing only central rays of light onto the cornea to enhance depth of focus. Approved by the FDA in 2015, the KAMRA is meant for monocular implantation in the non-dominant eye, into a femto-created stromal pocket at a minimum depth of 200 µm. Wayne Crewe-Brown, MD, of Crewe-Brown Vision Centers in London and Manchester, U.K., has approximately 1,000 KAMRA cases and some 350 cases with the Presbia Flexivue Microlens to his credit.

The Raindrop, FDA approved in 2016, is a biocompatible hydrogel inlay that measures 2 mm in diameter and 32 µm thick at the center, tapering to 10 µm thick at the periphery. Consisting of 77 percent water and devoid of inherent refractive power, the Raindrop steepens the central cornea when implanted in the non-dominant eye under a femto-made flap at the manufacturer-recommended depth of at least 150 µm and 30 percent of central corneal thickness. Jeffrey Whitman, MD, chief surgeon and founder of Key Whitman Eye Centers, based in Dallas, has more than 200 Raindrop procedures to his credit, and was an investigator in the FDA clinical trials.

For more about the Flexivue Microlens, see the sidebar on p. 31,

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Four randomized, double-masked, 12-week trials evaluated the efficacy and safety of Xiidra versus vehicle as assessed by improvement in the signs (measured by Inferior Corneal Staining Score) and symptoms (measured by Eye Dryness Score) of Dry Eye Disease (N=2133).

Indication

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

Important Safety Information

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 and Full Prescribing Information on Xiidra-ECP.com.

Shire

xiidra® (lifitegrast ophthalmic solution)5%

Rx Only

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.

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.

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.

Shire

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For more information, go to www.Xiidra.com or call 1-800-828-2088.

US Patents: 8367701; 9353088; 7314938; 7745460; 7790743; 7928122; 9216174; 8168655; 8084047; 8592450; 9085553; 8927574; 9447077; 9353088 and pending patent applications.
Last Modified: 12/2016 S26218

body inside the eye. In a small number of patients, the body's protective inflammatory response goes into overdrive, creating haze and fibrosis local to the inlay. In the early stages of KAMRA's development, it was implanted under a flap until this wound-healing response was noted. "I spent very little time doing that with KAMRA before switching to a pocket, and I probably would not have carried on with the KAMRA if we hadn't developed a pocket technique," says Dr. Crewe-Brown, adding that he also considered the flap technique to be associated with unacceptable dry-eye risk.

Dr. Crewe-Brown says that switching to a stromal pocket has helped to greatly reduce the number of KAMRA patients requiring explantation due to overly aggressive wound-healing responses. "It's not a big deal anymore, but it's something we still see from time to time," he says. On those occasions that a strong wound-healing response still occurs, Dr. Crewe-Brown chooses his words carefully when discussing it with patients. "We call it 'wound healing,' because if you use the word 'inflammation'—which it is, as well—the patient immediately thinks it's an infection," he says. "It's much less common now in the pocket than when they were under a thick flap.

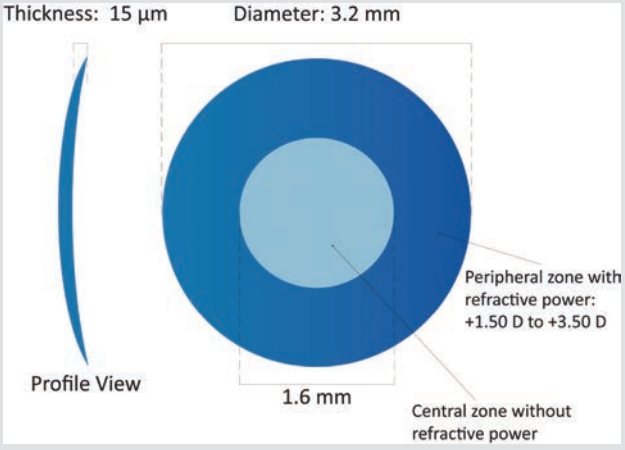
"You can reverse it with steroid drops," he continues "But I'm not one for using steroid drops indefinitely. So I will allow patients two series of treatments with steroid drops, for no more than about three months per series. After that, if they have a third episode of hyperopic shift, or aggressive wound response or inflammation—whatever we want to call it—the inlay is out. I do not believe in treating people who come to you to get rid of their reading glasses, to end up giving them steroid drops for months and years, and then suddenly they've got a rise in intraocular pressure or steroid-induced cataracts," he says.

Dr. Whitman also notes fibrosis as a rare complication in Raindrop procedures. "Some patients are going to have a reaction to having something under a flap, and we don't have a way of knowing beforehand who's at risk," he says. Although he empha-

The Flexivue Microlens

The Flexivue Microlens (Presbia) CE-certified since 2009, is in Phase III trials for FDA approval (NCT02110472). Wayne Crewe-Brown, MD, of Crewe-Brown Vision in London and Manchester, U.K., says he has implanted about 350 of these clear, UV-blocking hydrophilic copolymer inlays with good results. The Flexivue Microlens measures 3 mm in diameter with a 0.15-mm hole in the center to facilitate corneal metabolism. The remainder of the central zone is plano for distance vision. The outer zone of the inlay has a refractive add power ranging from +1.25 D to +3.5 D in 0.25-D increments. The inlay can be 15 to 20 µm thick, depending on the add.

Like the KAMRA, the Flexivue Microlens is intended for deeper implantation into a femto-created stromal pocket (280-300 µm). As the only inlay discussed here with refractive power, the Flexivue Microlens requires meticulous positioning for good visual results. "The centration is particularly critical with the Presbia," says Dr. Crewe-Brown. "In spite of that, even if the inlay is perfectly centered, you can get glare and halos anyway, and this is more of a problem with the Presbia than the KAMRA."

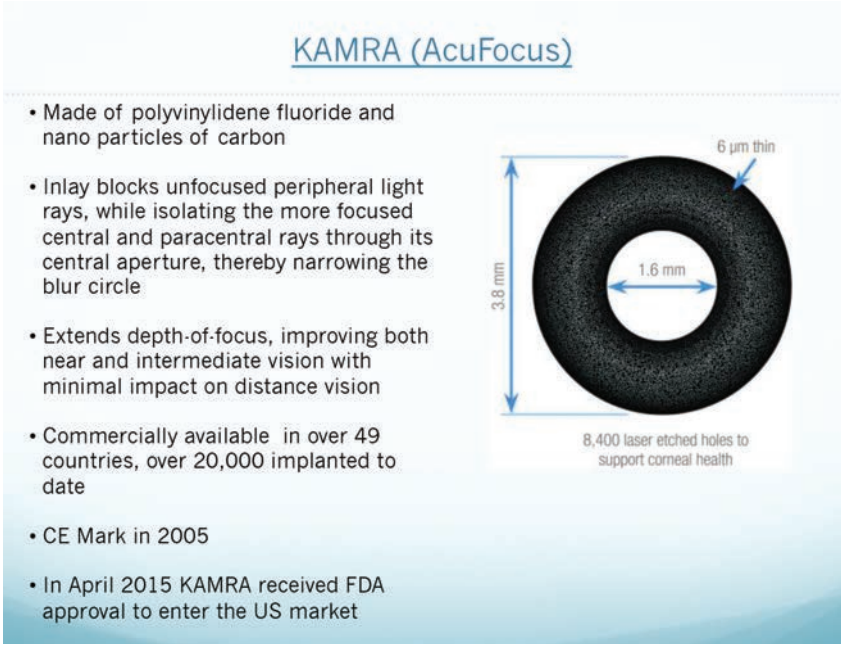


Dr. Crewe-Brown notes that the Flexivue's hydrophilic copolymer material is very biocompatible, which reduces the risk of inflammation. He can closely approximate vision with the Flexivue Microlens preop via a multifocal contact lens trial for his patients. "It's a very good simulation," he says.

"The U.S. has no Presbia follow-up data other than what's happening in the trials, and that's not public knowledge yet," he notes. One Greek study[8] of 47 emmetropic presbyopes implanted monocularly with the Flexivue Microlens in the non-dominant eye measured visual outcomes and safety at 12 months. At 12 months, UNVA was 20/32 or better in 75 percent of the surgical eyes; their mean UDVA was significantly lowered from 20/20 preoperatively to 20/50. However, binocular UDVA did not change much. Although higher-order aberrations increased and contrast sensitivity decreased in the operated eyes, no intraoperative or post-surgical complications occurred, and 81.25 percent of subjects reported that their UNVA was excellent in the operated eye.

Compared to the other inlays, Dr. Crewe-Brown acknowledges, "Generally, the Flexivue Microlens gives you better near vision, but worse distance vision," adding that many of his patients who read copiously have been happy with the Flexivue Microlens. "One of my first Presbia patients was a barrister—a specialist attorney—who spends his life reading documents. He is one of my happiest patients," he says.

—K.B.



The latest KAMRA model is 6 µm thick and designed for implantation into a stromal pocket at least 200 µm deep, potentially avoiding side effects that might accompany shallower placement under a flap.

sizes that fibrosis is rare, Dr. Whitman cautions that any sudden and dramatic postoperative improvement in near vision is actually an ominous sign. "One of the things that I warn other surgeons about is that when patients get fibrosis, they tend to get better reading vision because they get further steepening of the cornea," he explains. "I'll tell them that's a bad sign, and that they have to tell their patients it's a bad sign. If they see their near vision getting better and their distance vision getting worse, it may be that they're developing some fibrosis, and they need to come in and get it treated. If we treat it early, we can usually get rid of it with steroids.

"What may eventually happen is that there will be so much haze that their vision will go bad," Dr. Whitman continues. "If things get hazed up far enough, it's a foreign-body reaction so severe that they could get a melt in the cornea," he warns. In the FDA trial, Dr. Whitman did observe some fibrosis, but none in his private practice with Raindrop to date. The trial followed 373 patients with Raindrop in the non-dominant eye for a year. Of the 340 eyes evaluated at one year, 14 percent experienced haze, which responded to steroids in all but one case. Eleven eyes were explanted for causes including haze, surgical complications and patient dissatisfaction.[1]

Dr. Whitman believes that his intraoperative use of mitomycin-C has prevented fibrosis in his patients to date. He credits Julian Theng, FRCOphth, M.Med, FRCSEd, with adding mitomycin-C to the Raindrop procedure. Dr. Theng presented a paper on combining LASIK, mitomycin-C and Raindrop implantation at the American Society of Cataract and Refractive Surgeons 2017 Symposium and Congress in Los Angeles. "We do a flap, LASIK, and mitomycin-C off label, and then put the inlay in," says Dr. Whitman. "We see nice clear flaps and, so far, very nice, clear inlays using that regimen." Dr. Whitman is currently participating in a three-center clinical trial of mitomycin-C in Raindrop procedures (ClinicalTrials.gov Identifier: NCT03101501).

Infection

"As far as I know there's never been an infection reported, even in the FDA trial," says Dr. Whitman of the Raindrop. "But if you think about the number of infections that occur with LASIK, they're almost nonexistent in this day and age. Never say never, but it would be very, very rare."

Dr. Whitman and Dr. Crewe-Brown both say inlay patients don't have any greater risk of infection than those who undergo LASIK or PRK, but it can happen. "The first thing you do is remove the inlay immediately, urgently," says Dr. Crewe-Brown. "If there's infection in the pocket, and there's a foreign body there—which the KAMRA is—it makes treating infection all the more difficult," he cautions, adding that he warns all preoperative patients about this possibility.

In a case series of five eyes in Ireland (three implanted with KAMRA; two with the Flexivue Microlens) with suspected infectious keratitis from six days to four months postop (one case confirmed by culture; all responded favorably to antibiotics), two of the KAMRAs were explanted, but all eyes had residual visual acuity decreases due to stromal scarring.[2]

Epithelial Ingrowth

Although Dr. Crewe-Brown has not seen epithelial cell ingrowth affecting the stromal pockets for either KAMRA or Presbia Microlens, he takes preventative measures to discourage it. "We train surgeons that when they put the inlay in the pocket, they have to lift up the edge of the pocket with a flap lifter or

"If you think about the number of infections that occur with LASIK, they're almost nonexistent in this day and age. Never say never, but it would be very, very rare."
— Jeffrey Whitman, MD

something to make sure they don't catch any cells while pushing the inlay into the pocket," he explains. "You've got to be aware of it, but in my thousand cases of KAMRA and 350 with Presbia, I've never had pocket epithelial ingrowth." He says that besides lifting the pocket edge, another basic tenet of his surgical technique likely prevents ingrowth. "I use a fair amount of fluid, so I think I wash out a fair number of cells that might otherwise wind up in the pocket," he says. A five-year study of 32 eyes implanted with an older model of the KAMRA (ACI7000, which was thicker and had fewer perforations) under a flap showed one case of epithelial ingrowth.[3] In U.S. clinical trials of the latest version (ACI7000PDT) of the KAMRA, the incidence of epithelial ingrowth was 0.6 percent.[4]

Dr. Whitman didn't see epithelial ingrowth in his clinical trial patients, although it was reported in 11/373 eyes at 36 months,[1] and he hasn't encountered it in his commercial patients. "There's no higher risk to this than doing a LASIK flap, but it can happen," he acknowledges. "I really think that since we've gone to femtosecond lasers the incidence of epithelial ingrowth has come way down. With microkeratomes, it used to be more common because the seal wasn't as good. Now, because we can conform the geometry better for a better seal when we put the flap back down, epithelial ingrowth is thankfully very rare."

Visual Issues

Possible causes of postoperative vision problems include inlay decentration, dryness and poor neuroadaptation. Decentration of the Raindrop in clinical trials occurred in 18/373 eyes, which required replacement of the inlay.[1] With experience, Dr. Whitman has found a way to improve the efficacy of repositioning the Raindrop when it becomes necessary. "We've had two that slipped inferiorly in the first week," he says. "We took them out for about three weeks, then we put them back in." This technique differs from the protocol during FDA investigations, where the investigators moved decentered inlays back into place in a single procedure. "I found that if you just moved them back into place and put the flap back down, the very next day, they kind of followed the indentation or track of where they had decentered to in the first place. The inlay would go right back to the same place. Now, I take it out and put it back in later; now it's not a problem," he explains.

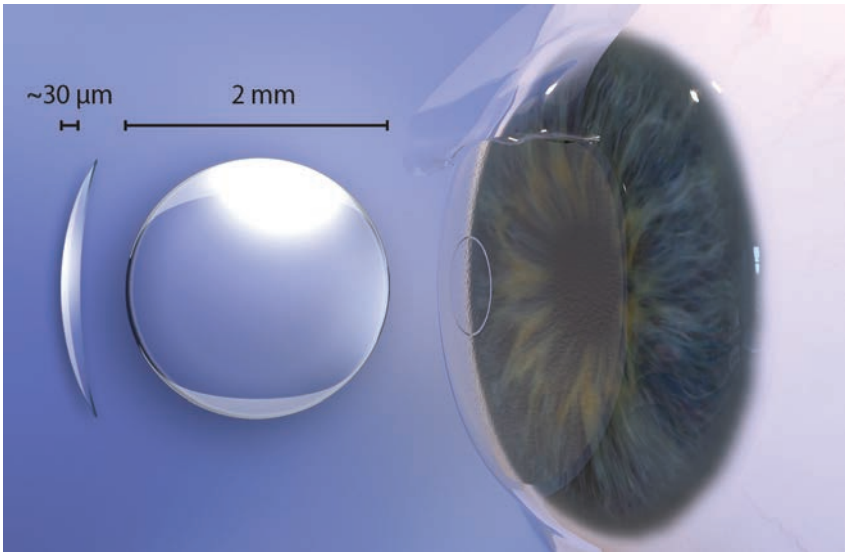
Recentration of a malpositioned KAMRA was associated with improved UNVA in a small study conducted right after FDA approval.[5] The same study found that stromal pockets ≤ 250 µm deep were associated with better UNVA. "You've got to be very careful about centration," Dr. Crewe-Brown says. "You must also be very careful that you don't explant an inlay because of glare and halos that could've been fixed

by re-centering it. I've certainly, in my time, re-centered a fair number of both of the inlays [KAMRA and Presbia]. But as I get better and better at centering them during the primary surgery, that doesn't happen much."

A more common factor in poor visual outcomes with inlays is dry eye. Of Raindrop patients in the clinical trial, 93 percent achieved UNVA of 20/25 or better, and 95 percent of them reported no or mild dry eye.[1] In the KAMRA trial, 5.8 percent complained of severe dry eye at 12 months, dropping to 5.5 percent at 36 months.[6] "Dry eye is the enemy of vision with inlays," says Dr. Whitman. "Anytime you change the curvature of the eye to give more than one level of vision, dryness is the enemy." He recommends standard dry-eye treatments like punctal plugs and drops, adding that postop dry eye usually improves after severed nerves into the surface of the cornea grow back into the flap.

"Doctors don't like failure; neither do patients," says Dr. Whitman, who nonetheless prepares his Raindrop candidates for the possibility that they may be among the few patients unable to tolerate a non-dominant eye programmed to see differently than their fellow eye. 'Most patients tend to neuroadapt over three months," he says. "If they aren't doing better by three or four months and are unhappy, we'll lift the flap and remove it. Anytime patients are unhappy I'll say, 'Some people take three months before things kick in, but if you're unhappy, we'll have to consider that maybe this is not for you.' But thankfully, that's very rare." He reports that only one of his patients to date has requested removal because he couldn't tolerate the visual discrepancy between his eyes.

"Every patient is told up front that about 2 percent of patients will need the inlay to be explanted," says Dr. Crewe-Brown. "That's not the doctor's fault; it's not the patient's fault. It's just the problem certain patients have coming to terms with having different vision in each eye. That's where there is an overlap with monovision. A lot of cynical doctors say that inlays are nothing more than monovision. That's not correct, because inlays do give better distance vision in the reading eye than monovision. But your brain still has to get used to the fact that through one eye, your vision is slightly different than the other," he says.



The Raindrop's manufacturer says that this tiny, clear hydrogel inlay is made of highly biocompatible materials similar to those used to make soft contacts. Implanted under a stromal flap at 30 percent central corneal thickness, it enhances near vision by creating a hyperprolate cornea.

Dr. Whitman says that preop contact lens trials were done for Raindrop patients in the FDA trials to help eliminate patients who might not respond well to planned anisemetropia. "We required patients to try a multifocal contact lens in a two- to three-day test," he says. The screening had limitations, however, because the visual result that non-dominant eyes got with a temporary multifocal contact differed in some respects from what they could expect with the Raindrop inlay. Since offering the Raindrop to his own patients, Dr. Whitman has stopped doing the contact-lens test. "I've seen one patient who had a removal because they just couldn't tolerate it," he says. "They had good near vision, but the difference between their eyes bothered them. You might say I could've ruled that out with a contact-lens trial, but we had so many patients judge the fit of the contact lens—and not the vision—that we thought it would be simpler to eliminate the contact lens trial. All in all, it's not been a big issue."

All of Dr. Crewe-Brown's Flexivue Microlens patients get a multifocal contact lens trial, since that inlay has refractive power and patients will get a closer approximation of the postop discrepancy between their eyes. However, he currently doesn't have access to an appropriate trial contact lens for KAMRA. "But there's talk of a Chinese company producing a pinhole contact lens, which I'm looking forward to, because I'm hoping to be able to use that as a simulator," he says.

Easily Reversible

Both surgeons find corneal inlays' additive nature and ease of revers-

ibility reassuring in the event that things don't go to plan. "One of the beauties of this versus almost every other technology I use is that it's easy to undo," observes Dr. Whitman. "I can give inlay patients back their original vision."

Dr. Crewe-Brown will explant a KAMRA or Presbia under certain circumstances. "I tell all patients to allow six months for their adaptation process. Unless there is an infection or the patient is violently unhappy, I will not remove the inlay before six months. It's a big adaptation, and patients need to be given time," he says. If a patient ultimately needs an inlay removed, he says the procedure is not nearly as problematic as an IOL removal and exchange can be. "Remove a multifocal IOL, and you've got a difficult operation to get it out without causing damage, and then you've got to put a monofocal intraocular lens into the eye, and the patient's going to end up with only distance vision—which is not why they came to you in the first place," he says. "But I can give an inlay patient back their cornea pretty much as it was before the inlay. That, to me, is one of the big distinctions between the two ways of treating presbyopia."

A 2015 review of published studies on KAMRA, Raindrop, and Flexivue inlays said of reported complications: "None of the published studies on these corneal inlays published data on serious or sight-threatening complications. Only a few cases of epithelial ingrowth and complaints of glare, halo, dry eye, or night vision problems were named. Ingrowth was either resolved in all cases and/or did not affect the visual axis. The complaints were described by patients as being mostly mild to moderate, and they happened to be the same complications as those encountered after LASIK."[7]

The general sense of inlays as low-risk may shift as more long-term follow-up becomes available. But right now, in some patients at least, the available and emerging corneal inlays may represent the new standard of care for corneal-based surgical presbyopia correction, ostensibly offering improved near vision without sacrificing distance vision—or ocular health. "We all like to feel better, different or younger for some reason. There's a good feeling about waking up in the morning and being able to see the alarm clock or read the back of the shampoo bottle," Dr. Whitman observes. "We've jumped through a lot of hoops to get inlays to a point where they are very good," says Dr. Crewe-Brown. "But who's to say they're not going to get better? That's why I hang in there. That's why I do them. That's why we have patients who want them." REVIEW

Dr. Crewe-Browne is a member of the medical advisory boards of AcuFocus and Presbia. Not a paid consultant, he is awarded travel expenses by both companies. Dr. Whitman is consultant to ReVision Optics.

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A Peek into the Presbyopia Pipeline

Review Staff

Researchers and clinicians alike continue to pursue The Grail as vigorously as ever.

Though the fires of LASIK and PRK refractive surgery may have cooled since their heyday early in the 21st century, the desire to find a magic bullet for presbyopia burns brighter than ever, with no fewer than a dozen devices and drugs trundling down the pipeline to your practice. In this article, we'll give you an overview of these would-be presbyopia-tamers.

Trifocal IOLs

In an effort to improve intermediate vision, trifocal IOLs rely on multiple foci to achieve this range of vision. With bifocal IOLs focusing mainly on near and distance visual acuity, trifocal IOLs, in use outside of the United States, also target intermediate vision. Trifocal IOLs have two repeating steps (intermediate and near), spread over the surface of the lens. This pattern allows for a flat area between steps to redirect light for distance.

The three mainstream trifocals are the Alcon PanOptix, FineVision PhysIOL and the Zeiss AT-LISA. These lenses differ in a few ways, including how they distribute light: The Zeiss and PhysIOL use 33 percent distance, 33 percent intermediate and 33 percent near. The PanOptix distributes 50 percent of the light for distance and 25 percent each for intermediate and near vision. The lenses also differ in the location of their focal points. Zeiss and PhysIOL have an intermediate vision target of 80 cm, while PanOptix's target is 60 cm.

They also differ in design. The Zeiss lens is trifocal in the center and bifocal in the periphery. The FineVision lens is apodized over the entire surface, so there is less light transferred to the intermediate points at the periphery. This allows enhancement of far vision the wider the pupil becomes. Although these lenses are only available overseas, a new wave of studies and their results might soon push these lenses into the U.S. market.

Florian Kretz, MD

The Zeiss AT-LISA trifocal intraocular lens has an intermediate visual distance target of 80 cm. The lens is trifocal in the center and bifocal in the periphery.

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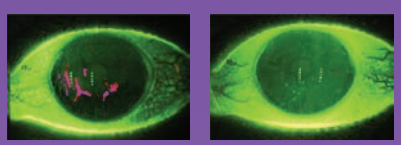

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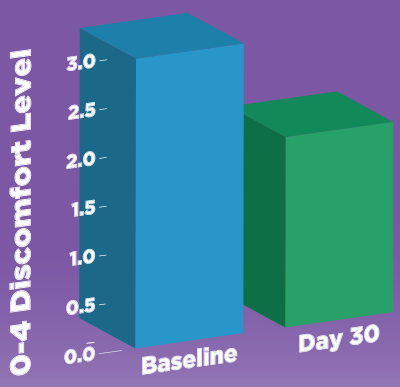


LensGen IOL

This clinical-stage lens uses the eye's natural accommodative mechanisms to change the IOL's curvature and the eye's range of vision from distance to near.

The design starts with a fixed lens, similar to a standard IOL. There is also a fluid lens, which sits inside the fixed lens to accommodate at different distances based on the lens's curvature. When the ciliary muscle contracts, zonules stretch, putting pressure on the capsule, which results in the change of shape. For this process of accommodation, with the lens implanted, the lens transfers the force to the fluid lens, letting it change shape in a way similar to the crystalline lens. Because it mimics the natural lens, the company says there's a seamless range of vision from far to near.

Another benefit of this IOL is that it can be implanted during cataract surgery in two steps, which involve first inserting the fixed lens and then injecting the fluid lens. Ostensibly, this two-part implantation system would solve the challenge of implanting a large lens through a small incision.

The lens conforms to the natural shape and volume of the capsule, in the hope of preserving the integrity, function and stability of the lens so that it's comparable in function to the natural lens. LensGen also claims that the lens is a complete vision-correction platform: The fixed lens treats myopia, hyperopia and astigmatism, while the fluid lens treats presbyopia by providing dynamic range of vision.

Uday Devgan, MD, discusses the timetable for this clinical stage lens. "It's promising enough that we just got $21 million of funding," he says. "A lot of these ophthalmic companies are showing interest in it based on our initial results. This funding will hopefully speed up our journey to market, which, in the U.S., I'd say is somewhere in the five- to 10-year range. It's hard to nail down, but that's what we're looking at now."

AcuFocus IC-8

AcuFocus' IC-8 is a small-aperture IOL that extends depth of focus by combining the KAMRA corneal inlay's small-aperture technology with a monofocal lens. Using the same small-aperture optics as the KAMRA, IC-8 incorporates a non-diffractive 2.23-mm diameter opaque mask with a 1.36-mm central aperture embedded within a 6-mm, one-piece, hydrophobic acrylic lens. This mask then creates a pinhole effect, delivering nearly 3 D of extended depth of focus by blocking unfocused peripheral light and isolating more central and focused paracentral rays through the aperture. The lens can be inserted through an incision of 3.2 to 3.5 mm.

In a post-market clinical study in Europe, at the six-month follow-up, the average binocular visual acuities were 20/16 at distance, 20/20 at intermediate and 20/25 at near. AcuFocus says that visual outcomes can be further optimized by achieving refractive targets of -0.75 D in the IC-8 eye and plano in the monofocal eye. The IC-8 has received approval in select European markets but is not approved for use in the U.S.

Light-adjustable Lens

The Light-adjustable Lens from RxSight (formerly Calhoun Vision) is an intriguing technology that's been in the pipeline for several years. It allows the surgeon to change the lens's refractive power after implantation using a non-invasive, postoperative irradiation procedure. The LAL is a three-piece silicone lens with a diameter of 6 mm.

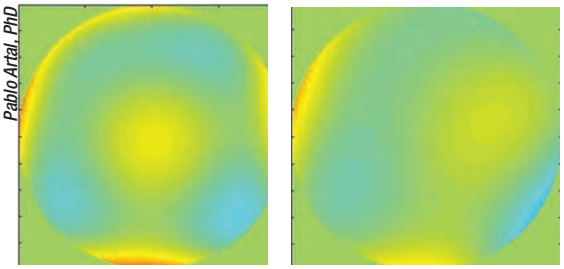
Once the lens is implanted, an adjustment to the lens's structure is made by irradiating the IOL's special silicone material with ultraviolet light, which changes the lens's shape and therefore its power. The same light is then used to lock in the shape change when the refraction is optimal. In terms of treating presbyopia, when the ultraviolet wavelength strikes the lens in a specific pattern, it changes the distribution of the lens's silicone macromers, resulting in an altered refractive power of the lens that yields multifocality.

The company says that trials have been positive, with the largest sample (122 eyes) showing 97 percent of patients within 0.25 D of attempted spherical equivalent and 100 percent uncorrected vision 20/25 or better.[1]

In February 2017, when Calhoun Vision became RxSight, the lens became known as the RxLAL. As of now, RxSight's RxLAL is still an investigational device, not yet approved by the FDA.

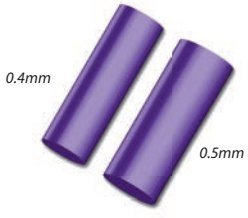
FluidVision IOL

Louis D. "Skip" Nichamin, MD, a private ophthalmic surgeon and consultant in Avon, Colo., and medical advisor for FluidVision's maker, PowerVision (Belmont, Calif.), describes this lens as the first true shape-changing lens designed to mimic the natural physiologic mechanism of accommodation. "The FluidVision technology consists of a proprietary fluid-driven system," he explains. "Small amounts of fluid—about a drop—move in response to the natural muscle forces in the eye, changing the shape of the lens. This achieves


Pablo Artal, PhD

Applied UV light can change the LAL's spherical aberration, shown here pre- (left) and post- (right) irradiation.

41% of refractive or cataract surgery patients have ocular surface dysfunction levels requiring some treatment beyond artificial tears![1]



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[1]ASCRS Clinical Survey 2015. Global Trends in Ophthalmology and the American Society of Cataract and Refractive Surgery.

accommodation the same way the crystalline lens does, for seamless vision from near to distance."

According to the company, the lens was designed to be placed inside the capsular bag to protect the lens and allow conventional implantation techniques.

Dr. Nichamin says studies presented at the 2016 meeting of the European Society of Cataract and Refractive Surgeons showed excellent, stable visual outcomes, with proven accommodative function out to 36 months. "The company recently launched its new second-generation foldable lens design, the FluidVision 20/20, into the clinic," he says. "Early results from 28 successful surgeries to date are promising, and excellent objective accommodation has been observed."

Dr. Nichamin notes that successful implantation requires an intact capsular bag and capsulorhexis, adequate zonular integrity and essentially uncomplicated surgery. "There's been no sign of drop-off in accommodative function over time in the patients implanted thus far," he says. "The company is currently conducting clinical trials, with the goal of having the lens available on the market within the next few years."

Lumina IOL

The Lumina (Akkolens International, The Netherlands) is a dual-optic, hydrophilic acrylic lens that's placed in the sulcus. Movement of the ciliary muscles causes one of the optics to slide over the other, progressively changing the refractive power of the lens and providing its accommodative effect.

"We've just submitted an article for publication in which we compared subjective and objective accommodation—subjective with the defocus curve, and objective with the WAM 5500 device," says Jorge L. Alio, MD, PhD, a professor and chairman of the department of ophthalmology at Miguel Hernandez University in Alicante, Spain. "The outcomes demonstrate that two-thirds of the near vision effect is due to an increase in the power of the eye, which means real accommodation. This rules out any pseudo-accommodation induced by other mechanisms the lens might trigger, such as pupil size." In his studies, Dr. Alio says the accommodation has ranged from 1.5 to 6 D (mean: 2.5 D). There currently is no timetable for the lens's approval in the United States.

LiquidVision Drops

"LiquidVision [Presbyopia Therapies; Coronado, Calif.] is an eye drop with a proprietary mixture of components that produce improved near vision without sacrificing distance vision," explains Terry Kim, MD, professor of ophthalmology at the Duke University Eye Center. "It works via the pinhole effect, but unlike some competing products, it contains no pilocarpine. Pilocarpine causes some accommodation, undercutting distance vision. In contrast, anterior segment OCT studies have shown that with LiquidVision the anterior chamber depth stays exactly the same. In some cases LiquidVision even improves distance vision so, unlike pilocarpine, it can be used binocularly."

Dr. Kim says the drop works within about 30 minutes of application and lasts five to six hours. "It's reversible, and you can repeat it," he notes. "It can be used every day or as needed, and it can be complimentary to whatever else you're doing to enhance vision, such as contact lenses or glasses. It's totally within the patient's control, in terms of when they get the effect."

Dr. Kim points out that this drop could also be therapeutic for patients with corneal scars or refractive surgery complications, especially if the patient isn't a candidate for a surgical cure. "The only negative effect so far is a dimming effect, due to pupil constriction," he says. "However, the studies have found that this effect fades with time."

Dr. Kim says preclinical studies produced excellent results. "The product is in Phase II-B trials now," he says. "Preliminary results should be available in time for the meeting of the American Academy of Ophthalmology this fall. We hope the drop will be available in about two years."

Presbia Flexivue Microlens

The 3-mm diameter Microlens is placed in a femtosecond-created corneal pocket in a patient's non-dominant eye. The procedure usually takes less than 10 minutes and results in an improved range of vision, Presbia says. The Microlens offers powers ranging from +1.5 D to +3.5 D in 0.25-D increments. The peripheral zone of the lens contains the power to refract light from near objects onto the retina, while the central zone has no power.

Presbia PLC reports that, in one study of the inlay, subjects gained an average of five lines of uncorrected near vision in treated eyes. Approximately 82 percent of subjects achieved 20/40 or better UCDVA vision in treated eyes, and there was little to no change in binocular UCDVA vision vs. preop. Ninety-eight percent of subjects achieved 20/40 or better best-corrected distance vision in the treated eyes and there was little to no change in binocular best-corrected distance vision from preoperative values.[2]

With regard to approval, the company tempers expectations, saying it can't say for sure the timetable for FDA marketing authorization.

VisAbility Micro-Inserts

VisAbility Micro-Inserts (ReFocus Group; Dallas, Texas) are premised on the Schachar theory of presbyopia, which holds that continual growth of the lens crowds the cilary body until

the muscles can no longer contract effectively. This scleral expansion system props up the lens via implants designed to give the ciliary muscles more room.

A docking system fixated to the sclera guides the positioning and orientation of 400-µm scleral tunnels at each quadrant of the sclera. A scleratome makes the incisions, and an interlocking two-piece PMMA implant smaller than a grain of rice goes into each tunnel.

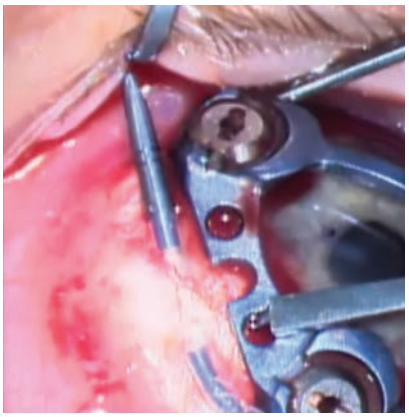
VisAbility Micro-Inserts are commercially available in in Europe. In the United States, surgeries are complete on 360 patients enrolled in a multicenter Phase III clinical trial. Early data (ClinicalTrials.gov Identifier: NCT02374671) shows that 95 percent achieved distance-corrected visual acuity of 20/40 or better in their dominant eye at six months, gaining an average of 3.2 lines of reading ability.[3]

Westerville, Ohio, surgeon Kenneth Beckman participated in the trial. "Patients ideally should be within approximately +0.50 or -0.50 of plano. While we excluded post-refractive surgery patients in the trial, they would likely be great candidates once the procedure is approved," he says.

Although the scleral implants don't affect the cornea and visual axis, the VisAbility procedure is not risk-free. "On the day of surgery, the main risk has to do with the location of the implants," says Dr. Beckman. "We try to place the four segments in between the four rectus muscles. This is to make sure that the implants do not compromise the anterior segment circulation, which travels in the line of the rectus muscles. If the implants are not placed in the proper location, anterior segment circulation may be compromised. Scleral thinning and erosion over the implants are also remote possibilities.

"Long term, the main risks are dry eye and prolonged redness," he adds. "Each of these adverse events is generally mild and treatable."

Kenneth Beckman, MD



VisAbility Micro-Inserts being passed through a shuttle device for insertion into scleral tunnels.

EV06

EV06 is a prodrug (specifically, a lipoic acid choline ester, 1.5%), which penetrates the cornea and metabolizes into choline and lipoic acid. The main aim of EV06 is to soften the stiffened crystalline lens, which the company says is a major cause of presbyopia.

A Phase I/II randomized, double-masked, multicenter study examined the safety and efficacy of EV06 compared to placebo for the treatment of presbyopia. Seventy-five subjects between the ages of 45 and 55 were randomized 2:1 to receive one drop of EV06 (n=50) or placebo (n=25) b.i.d. over 90 days.

The study met both primary safety and efficacy outcomes. A significant improvement of DCNVA from baseline was observed in the EV06 group compared to placebo, with onset of DCNVA improvement beginning at day 15 (p=0.017) and continuing throughout the 90-day study period (p=0.005). EV06 outperformed placebo in objective and subjective measures throughout the study duration.[4]

Further steps for EV06 include a Phase IIB dose-ranging study in Q1 of 2017, followed by a Phase III pivotal study in Q2 of 2018 to closely study the long-term safety of the drug and the effects of a longer duration of treatment.

FOV Tears

Luis Felipe Vejerano, MD, Fundación Oftalmológica Vejarano, Popayan, Colombia, has developed a topical eye drop that seems to improve near vision, without compromising distance vision, for hours at a time. The formula is a combination of FDA-approved agents that he selected to provide controlled miosis without inducing ciliary muscle spasm or causing irritation to the ocular surface.

In a pilot study of 14 emmetropic presbyopes, Dr. Vejerano and colleagues administered one drop binocularly to each patient.[5] Their UNVA improved by 2 to 3 Jeager lines (J 3.5 to J 1.5) without compromising UDVA. Myopic shift peaked at 0.5 D but resolved by hour four. Patients expressed satisfaction with the drops, with some saying that near visual acuity started to regress noticeably at eight hours; measurable improvement had dropped to 1 to 2 Jaeger lines at 10 hours.

Dr. Vejerano owns the patent to the drops, commercially known as FOV Tears. "The idea is to register them worldwide, including the U.S.," says Dr. Alio, one of the study's authors. "The best candidates for the drops have initial or intermediate presbyopia (up to 1.5 D) who wish to achieve spectacle independence for near." REVIEW

Dr. Alio is a consultant for FOV Tears. Dr. Kim is a consultant to Presbyopia Therapies. Dr. Devgan consults for LensGen. Dr. Beckman is an investigator for the ReFocus Group.

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Glaucoma Surgery: When The Conjunctiva Isn't Ideal

Damaged or unhealthy conjunctiva can significantly affect the course of glaucoma surgery. Here's help.

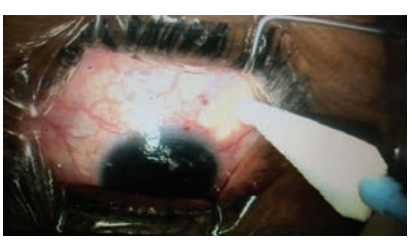
Jody R. Piltz-Seymour, MD, Huntingdon Valley, Pa.

Incisional glaucoma surgery is all about the conjunctiva. We love it when it's unscarred and mobile. But what do you do when you encounter a patient with compromised, scarred conjunctiva?

In an ideal world, we'd have unscarred conjunctiva to work with every time we perform filtration surgery. Unfortunately, many of us deal with patients who have had prior surgery or, in some cases, have inflammatory issues that have compromised the conjunctival tissue. As a result, in order to perform glaucoma surgery successfully, we have to know how to deal with less-than-virgin, and sometimes frankly scarred, conjunctiva.

How often is a glaucoma surgeon likely to encounter this problem? The answer depends partly on the type of glaucoma surgeon you are. Some surgeons only do first-round glaucoma surgery and refer the more advanced cases to other surgeons. Those specialists won't encounter this problem as often. But some surgeons accept many tertiary referrals, including patients who've already had incisional glaucoma surgery. In that situation this may be a very common problem.

The good news is that, thanks to changes in the way cataract surgery is performed, we don't encounter this nearly as often as in the past. Years ago, cataract surgery was done extracapsularly with a large corneoscleral incision, or phacoemulsification was done through a scleral tunnel, causing a great deal of conjunctival scarring. Moving cataract surgery to clear cornea has made life much easier for glaucoma surgeons. Today, most of the conjunctival scarring we encounter is the result of glaucoma surgery, although that's not the only thing that can cause this. Any surgery that manipulates the conjunctiva can lead to scarring. Sometimes conjunctiva can be very scarred without any prior surgery as a result of using topical medications or underlying inflammatory conditions.



Assessing conjunctival mobility using a surgical spear during the preop exam.

When we encounter scarred conjunctiva, any glaucoma surgery we need to perform becomes more challenging and less likely to succeed. To ensure the best possible outcome, we need to do several things:

- First, we need to carefully assess the situation before surgery.
- Second, we need to come up with a plan to work around any obstacles created by the less-than-ideal conjunctiva.
- Third, we need to be prepared to do very meticulous tissue dissection.
- Finally, we need to have several tricks up our sleeve to help us if we find ourselves backed into a corner: We have to know how to make a creative conjunctival flap; we need to be aware of all of the options for working around the problem; and we need to be prepared to use autologous or exogenous grafts.

Assessing the Conjunctiva

When examining the patient, it's crucial to ask the right questions:

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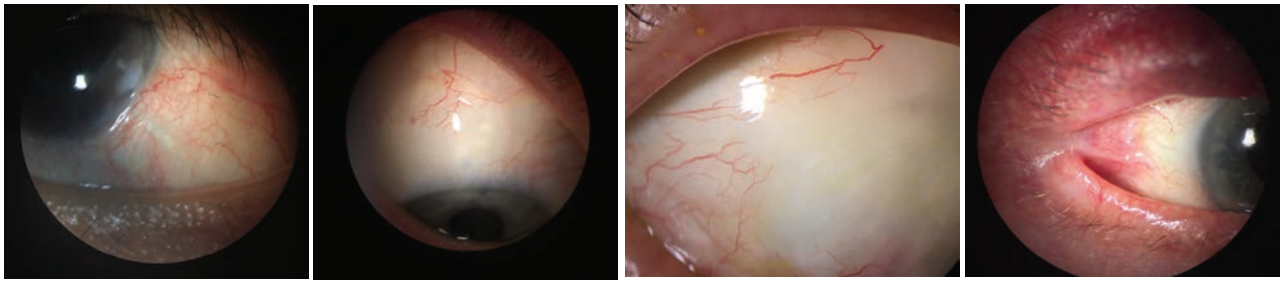


Conjunctival issues a surgeon may encounter during glaucoma surgery include (left to right): Prior glaucoma drainage tube surgery; a prior trabeculectomy with a diffuse filtering bleb; avascular conjunctiva; and conditions such as symblepharon.

• ***Has the patient had prior surgeries?*** This includes any done in childhood: trabeculectomies or tubes; extracap or scleral tunnel cataract surgery; transconjunctival blepharoplasties; pterygium or other excisions; muscle surgery (even as a child, because that will leave areas of conjunctival scarring); and retinal surgery—especially scleral bucking or encircling bands, which can cause 360 degrees of scarring, as well as posterior adhesions behind the muscles.

• ***If the patient's previous surgery involved a conjunctival flap, was it limbus- or fornix-based?*** This is important because the scar lines will be in different places.

• ***If the patient had previous surgery, was mitomycin-C used?*** Mitomycin-C can leave the conjunctiva very vascularized and delicate. You could even see mitomycin toxicity, which causes a very avascular, thick, leathery, white, scarred conjunctiva.

• ***Has the patient used medications that might impact the eye?*** Prior use of glaucoma medications can greatly affect the quality of the conjunctiva and sometimes cause marked scarring.

• ***Does the patient have any relevant concomitant conditions?*** Problems such as pemphigoid, scleroderma, Sjögren's and chemical injuries can cause conjunctival scarring.

The easiest way to directly assess the condition of the conjunctiva during the preop exam is to anesthetize the eye and use a surgical spear or cotton swab to gently move the conjunctiva over the sclera in all four quadrants, looking for mobility, injection, stiffness and inflammation. Check the limbus, but also check high in the fornix. It's helpful to draw a map in the chart showing any prior surgical sites, as well as where you find the conjunctiva to be mobile or scarred.

You'll need to assess the conjunctiva again once you have the patient in the operating room. One of the easiest ways to do that is by injecting fluid under the conjunctiva, which reveals the location of any scar bands. I use mitomycin-C for many of my surgeries, so we dilute it with anesthetic and inject it. It has a therapeutic effect and also helps us to assess where the scar tissue bands are. (I also recheck the condition of the conjunctiva using a surgical spear, as I did during the preoperative exam.)

You should detect most scarring when you're examining the patient in the office. However, if you discover some scarring in the OR that you missed preoperatively, you may need to alter your planned strategy. If the scarring is very extensive, you may have to consider switching to a different quadrant, or even abandoning trabeculectomy and implanting a glaucoma drainage tube instead. A more likely scenario is that you'll discover one or two bands of scarring that you'll have to dissect very carefully. Hopefully, this won't seriously alter your plan.

Of course, it is possible to mobilize even a large area of scarred tissue using very meticulous dissection. However, this can be challenging to accomplish, and even if you succeed the success rate for filtration surgery in that situation decreases dramatically.

Location, Location, Location

When performing glaucoma surgery on an eye with problematic conjunctiva, deciding how to proceed is all about conjunctival real estate. If the patient has had a prior trabeculectomy, can you fit in a second trabeculectomy? Can you implant a tube after a failed trabeculectomy? Can you perform a trabeculectomy after a failed primary tube? Every patient is different, so you have to look carefully to decide what real estate is available to work with.

There are many different scenarios. If you're considering doing a trabeculectomy, you need to be able to mobilize the conjunctival flap without resistance. For example:

• If you find that mobile conjunctiva is only available inferiorly, trabeculectomy is contraindicated. You'll have to alter your surgery and consider placing a glaucoma drainage device inferiorly.

• If there's scarring, but only at the limbus, you can plan a fornix-based conjunctival flap and dissect that scarred conjunctiva off the limbus.

• If the failed surgery was done a little to the temporal or nasal side instead of exactly at 12 o'clock, you can

try to fit in another trabeculectomy in the opposite quadrant. However, you want to be very careful about creating a trabeculectomy that's too nasal or temporal, because that can lead to extension of the bleb into the interpalpebral fissure, which may cause dysesthesia—especially with nasal extension of the bleb.

Other things to consider include:

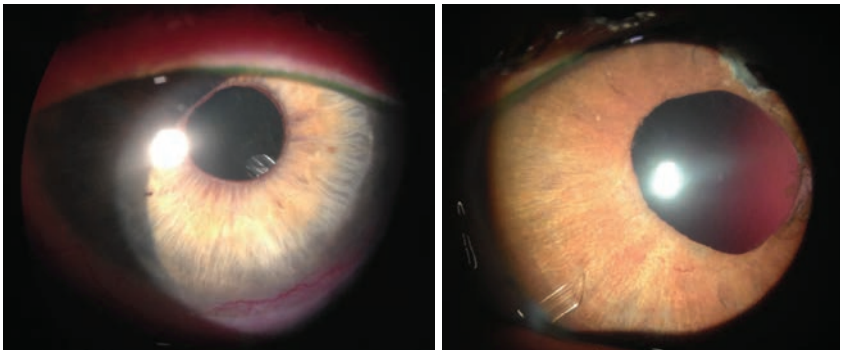
• ***If you're trying to perform a second trabeculectomy, avoid dissecting into the old bleb.*** You could suddenly get that old surgery working again, and that drainage combined with your new surgery could lead to unexpected hypotony that you might not be able to control.

• ***Watch out for a scar band that's high in the fornix.*** This can happen if the prior trabeculectomy was limbus-based.

• ***Consider implanting a XEN.*** When real estate is limited but you have a decent quadrant to work with, a XEN implant might be a good alternative to a trabeculectomy—although the XEN implant is very new, so the decision tree here is still a little unclear. Sometimes it's hard to mobilize a second trabeculectomy flap; a XEN implant avoids the need for conjunctival and scleral dissection.

The role of the XEN implant is going to grow, especially in those patients that have had surgery in one quadrant and still have an available quadrant. You'll still need mobile conjunctiva, however, so you don't want to put the XEN in a quadrant that has significant scarring, and you'll still need mitomycin-C.

• ***If you're dealing with a failed tube, you may be able to do a trabeculectomy, but be aware of the limitations.*** If the tube was placed pretty far temporally or nasally, you may have enough real estate left to make a good trabeculectomy. However, you need to be sure you can mobilize the flap, and the success rate is going to be lower than it would be with a primary trabeculectomy.



If there's too much scar tissue superiorly for a trab or tube, consider placing a glaucoma drainage tube inferiorly. Left: tube placed inferiorly in the ciliary sulcus. Right: tube placed inferiorly in the anterior chamber.

• ***If there's too much superior scarring for a trabeculectomy or a tube, place a glaucoma drainage tube inferiorly.*** However, avoid placing an Ahmed valve inferonasally if the eye is small. The posterior edge of the plate could impinge on the optic nerve.

When Conjunctiva Won't Reach

When a patient has scarred conjunctiva from a previous surgery, you can sometimes create a good flap with the intention of implanting a drainage tube. However, once you put the tube and plate in, you may sometimes find it hard to get the conjunctiva back to the limbus. When the conjunctiva comes up short, here are a few strategies you can try:

• ***Remobilize scarred tissue and perform meticulous dissection.*** Be sure to release the traction suture and rotate the eye back towards the operative quadrant. Then use a blunt cannula or spatula to sweep back deep into the fornix to free the scarred conjunctiva and remobilize the flap; be meticulous in your dissection. Then, use a spear to gently sweep the conjunctiva back towards the limbus.

• ***If the conjunctiva is very friable and thin, use fibrin glue to secure the flap to the limbus.*** Sometimes you start passing sutures through the conjunctiva in these patients and you can see that it's just going to tear the tissue. In this situation, fibrin glue is wonderful; you simply glue the conjunctiva down to the limbus. You still need to anchor the lateral margin to be sure there's tight closure. Fibrin glue can be a real game-changer in those situations. In fact, I use it on all of my tubes. It's a great addition to this type of surgery, but it is expensive, and a lot of surgical centers don't want to have that expense.

• ***If you're placing a patch graft over a tube and you can't get the conjunctiva to reach the limbus, try the "graft and glue" technique.*** I glue a split-thickness corneal graft in place to cover and lock the tube in position. The nice thing about the glue is that when you put the patch graft on, it's not just covering the tube; it's actually sealing it. The whole undersurface of the graft is adherent to the tube and the sclera.

Once you've done that, bring the conjunctiva as close as possible, covering as much of the graft as possible, and glue that into position; then anchor it with a few sutures. The tube is protected and sealed under the flap; the conjunctiva will heal over the corneal graft by secondary intention.

Note: When we put Baerveldt implants in, we put venting slits in the tube which must be able to drain. Make those far posteriorly and keep

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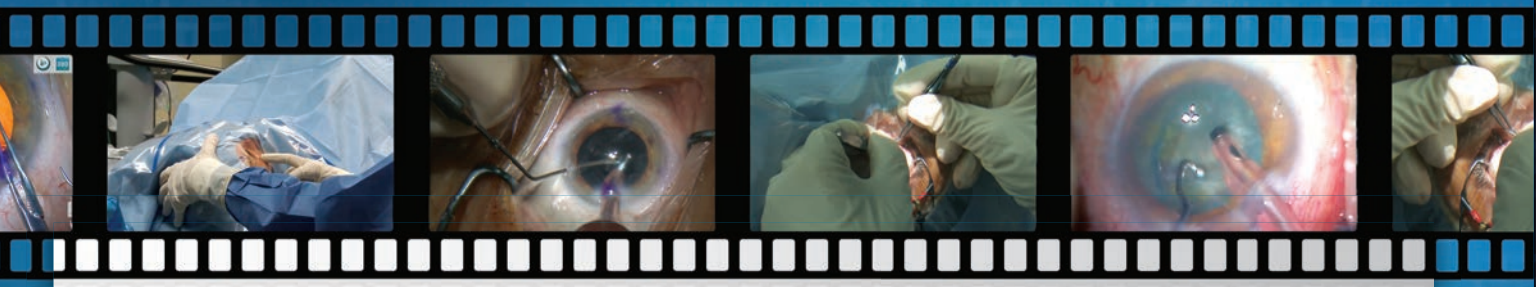

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Episode 19: "Management of Bell's Phenomenon"

Surgical Video by:
Richard J. Mackool, MD

Video Overview:
This month's case features methods for dealing with the problem of a patient with a very active Bell's Phenomenon.

The use and design of my primary chopper to protect the posterior capsule during phacoemulsification, methods to remove extremely adherent lens cortex, and the creation of Penetrating Limbal Relaxing Incisions after implantation of a multifocal IOL are also discussed and demonstrated.

MackoolOnlineCME.com MONTHLY Video Series

Richard J. Mackool, MD

Welcome to the second year of Mackool Online CME! With the generous support of several ophthalmic companies, I am honored to have our viewers join me in the operating room as I demonstrate the technology and techniques that I have found to be most valuable, and that I hope are helpful to many of my colleagues. We continue to edit the videos only to either change camera perspective or to reduce down time – allowing you to observe every step of the procedure.

As before, one new surgical video will be released monthly, and physicians may earn CME credits or just observe the case. New viewers are able to obtain additional CME credit by reviewing previous videos that are located in our archives.

I thank the many surgeons who have told us that they have found our CME program to be interesting and instructive; I appreciate your comments, suggestions and questions. Thanks again for joining us on Mackool Online CME.

CME Accredited Surgical Training Videos Now Available Online: www.MackoolOnlineCME.com

Richard Mackool, MD, a world renowned anterior segment ophthalmic microsurgeon, has assembled a web-based video collection of surgical cases that encompass both routine and challenging cases, demonstrating both familiar and potentially unfamiliar surgical techniques using a variety of instrumentation and settings.

This educational activity aims to present a series of Dr. Mackool's surgical videos, carefully selected to address the specific learning objectives of this activity, with the goal of making surgical training available as needed online for surgeons motivated to improve or expand their surgical repertoire.

Learning Objective:
After completion of this educational activity, participants should be able to:

- Utilize methods to successfully manage Bell's phenomenon during cataract extraction.

Accreditation Statement
This activity has been planned and implemented in accordance with the accreditation requirements and policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint providership of Amedco and Postgraduate Healthcare Education, LLC (PHE). Amedco is accredited by the ACCME to provide continuing medical education for physicians.

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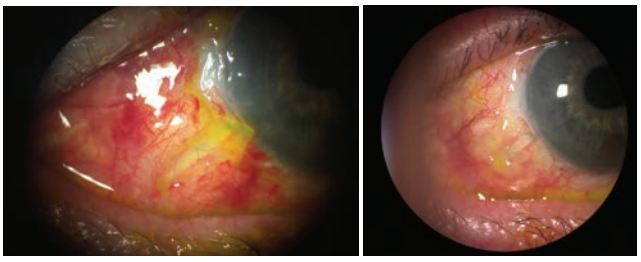
the fibrin glue close to the limbus, away from the venting site.

• ***To repair a tube erosion, know your options.*** In this situation you often have a functioning tube, and the intraocular pressure may be under control, so you don't want to disturb the capsule around the plate. You do want to be able to mobilize the conjunctiva, reposition the tube, and then re-cover everything.



Left: A corneal graft glued over a tube to seal the tube to the sclera, with the conjunctiva glued to cover the edges of the graft, one day postop. Right: The same eye 10 days later with conjunctiva healed over the graft by secondary intention.

If there's too much scarring to re-create a conjunctiva flap, you have several options:

— You can try to mobilize conjunctiva from an adjacent quadrant;

— you can cover the exposed tube with amniotic membrane;

— you can cover it with an adjacent or free conjunctival graft;

— you can use a pedicle graft, in which you slide over a pedicle of conjunctiva; or

— you can use the graft-and-glue technique, which works very well for tube erosion.

• ***Consider other options when repairing a bleb leak.*** Old trabeculectomies sometimes leak, which increases the risk of blebitis and endophthalmitis. In the past we've tried many techniques to manage this that were less than successful, such as autologous blood injections. The mainstay for treating bleb leaks is conjunctival advancement, excising the surface of the old bleb and then remobilizing the flap and bringing it back down to the limbus.

Today I try my best to avoid conjunctival advancement, because there's a significant failure rate for trabeculectomies when you use this technique. Instead, I'll leave the bleb intact and try direct suturing, especially when the leak is limbal or in a somewhat vascular area. I may also needle the bleb, to create more diffuse filtration and put less vertical pressure on it. Then I'll use a mattress suture to either close the leak or wall off the leaking area of the bleb.

• ***If you need to do conjunctival advancement, excision of the old bleb may be best.*** If the bleb is small, extremely thin and walled off with a dense scar band, excision of the old bleb and conjunctival advancement may be your best option. If you need to do conjunctival advancement, dissect posteriorly as far as possible. You want to mobilize a good flap without having traction. The worst thing you can do is to not have good mobilization of the conjunctival flap and just pull the conjunctiva down to the limbus and suture it without relieving the traction first. This will cause the conjunctiva to retract.

• ***Try releasing conjunctiva by making an incision up by the fornix.*** If you can't relieve the traction with simple dissection, make a horizontal incision up in the fornix, allowing the conjunctival tissue to be pulled toward the location at which it's needed. You can suture it at the limbus and then suture the posterior aspect as well. Don't worry about the exposed sclera deep in the fornix; it will heal by secondary intention.

Other options for managing a shortage of tissue include mobilizing conjunctiva from an adjacent quadrant; a Z-plasty or conjunctival rotational graft; using a conjunctiva free graft; or using amniotic membrane. (Peter A. Netland, MD, PhD, who has written about this topic, says he prefers using an autologous patch graft, or free graft, that's oversized by at least 1 mm, taken from an area away from the location of the bleb.)[1]

What if you can't do any of these things? Such cases should be rare, but if they happen, you may have no option except to abandon ship. If that becomes necessary, close the flap, cover it with a donor graft, let things heal over and then plan for a tube in another quadrant.

Going In with Eyes Open

Conjunctival scarring or deficiencies are never fun to manage, but in the vast majority of cases one of these techniques will save the day. Just remember to:

• Be prepared; know what you're getting into. Do a very thorough preoperative assessment and have a clear plan in mind.

• Reassess your plan in the OR.

• Perform meticulous dissection of scarred tissue.

• Know how to make a creative conjunctival flap and what your other options are.

• Be prepared to use autologous or exogenous grafts.

• Remember that fibrin glue is your BFF (Best Friend Forever!). REVIEW

Dr. Piltz-Seymour is an adjunct professor at the Perelman School of Medicine at the University of Pennsylvania, and director of the Glaucoma Care Center at Valley Eye Professionals in Huntingdon Valley. She has no financial ties to any products mentioned.

1. Lawrence SD, Netland PA. Inadequate conjunctival coverage. In: Feldman RM, Bell NP, eds. Complications of Glaucoma Surgery. New York, NY: Oxford University Press, 2013, pp. 258-264.

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The Highlights From ARVO 2017

A review of the hottest research in therapeutics for both the front and back of the eye.

Mark B. Abelson, MD, CM, FRCSC, FARVO, David Hollander, MD, MBA, and Ora Staff
Andover, Mass.

The annual meeting of the Association for Research in Vision and Ophthalmology convened in Baltimore last month, and as usual, the latest in basic and clinical vision science was on display. ARVO is unique among the many annual get-togethers in ophthalmology in that it presents the most diverse perspective on where the field is and where it's going. As in years past, we compiled a collection of presentations that caught our eye, and although ours is not a comprehensive review, we did manage to catch many of the meeting's highlights. (Unless otherwise noted, the abstracts are from this year: *IOVS 2017;58.*)

Retina: Imaging, Endpoints and Anti-VEGF

In recent years there's been a growing focus at ARVO on the back of the eye, especially on those conditions with the fewest therapeutic options and greatest impact on visual health. Age-related macular degeneration, especially the non-exudative, or dry, form of the disease, is increasingly a focus of both basic and clinical research.[1,2] As such, understanding the course and risk factors of AMD, as well as evaluating new imaging techniques and clinical endpoints, were hot topics at this year's meeting.

AMD is a slowly progressive disease characterized in its early stage by extracellular drusen deposits and pigmentary changes in the macula. Drusen features, including size, are important risk factors for the progression of more-advanced forms of AMD. However, the exact role of drusen in the pathogenesis of AMD is not fully understood. One report (*Baratsits, et al;ARVO E-abstract 1579*) demonstrated that eyes from early AMD subjects showed both a dynamic progression and a regression of drusen volume, which, surprisingly, occurred simultaneously at different locations within the same retina. Another group looked for molecular changes in drusen using fluorescence lifetime imaging ophthalmology (FLIO) (*Sauer, et al;ARVO E-abstract 3399*). This technique distinguishes soft and hard drusen based upon autofluorescence; using this method it was possible to differentiate drusen types, distinguishing those in patients with AMD from those with healthy retinas; thus, giving FLIO the potential to provide information on individual risks for the progression to later stages of dry AMD.

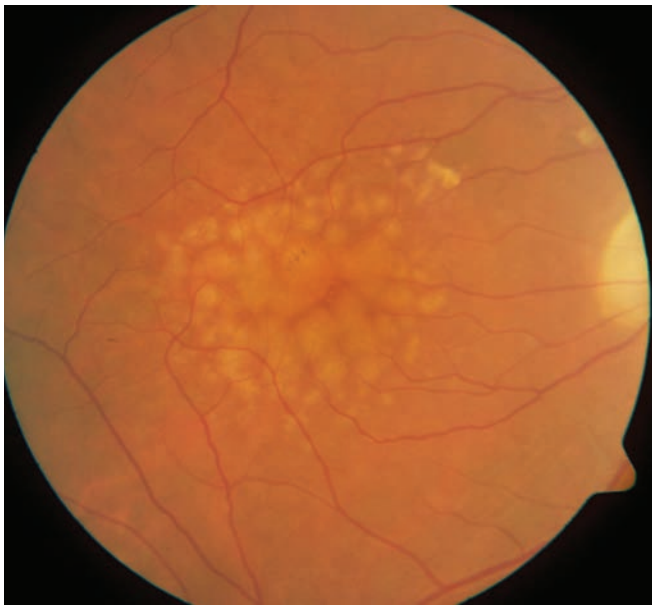
Progression to more advanced stages of AMD is characterized by geographic atrophy and choroidal neovascularization. In patients with intermediate AMD, the risk and speed of progression to GA or CNV is highly variable. A study by Erfurth, et al (*ARVO E-abstract 3398*) showcased a fully automated machine-learning method that was developed to predict progression to AMD based on retinal imaging and genetics. Fellow eyes with intermediate AMD from subjects enrolled in the HARBOR trial were used to demonstrate that an automated analysis of OCT biomarkers allowed for a personalized prediction of AMD progression. Interestingly, genetic characterization didn't add additional accuracy to the prediction of AMD conversion.

As another means of predicting progression of GA or CNV, Chakravarthy, et al (*ARVO E-abstract 2979*) presented results from a large U.K.

This article has no commercial sponsorship.

cohort study (83,425 persons from 10 U.K. eye clinics) demonstrating that progression to GA or CNV was frequently observed in eyes with early to intermediate AMD, and was more common in patients with advanced disease in the contralateral eye.

A major limitation in the development of novel therapeutic options for AMD has been a lack of sensitive endpoints to evaluate their therapeutic efficacy. Although using GA growth rate is currently an accepted endpoint in clinical trials, therapeutic intervention at this advanced stage may have little impact on preserving a patient's sight. A study by Bagheri, et al (*ARVO E-abstract 3400*), carried out a retrospective review of blue autofluorescence fundus images, optical coherence tomography and Snellen visual acuity in patients with GA due to AMD (18 subjects) in order to understand the relationship between total GA, foveal GA and VA in AMD. Results suggest that the percentage of GA within the fovea may be more sensitive in predicting the degree of visual acuity impairment than the total GA area or foveal involvement; however, further validation is needed in larger cohorts. Another study, by Colijin, et al (*ARVO E-abstract 2980*), also assessed GA in relation to foveal involvement. Here the relationship between foveal involvement and GA was examined in subjects who had developed GA in the Rotterdam Study I, a population-based, prospective cohort that started in 1990 with follow-up visits every five years. This study demonstrated that the first presentation of GA is mostly outside of the fovea and the average time to reach the fovea is 5.8 years; thereby suggesting that future trials for GA to reduce the risk of foveal development should consider that this clinical endpoint takes a rather long time to develop.



One of the highlights from this year's ARVO meeting was a report that found that taking a closer look at drusen characteristics may provide an improved diagnostic protocol for the non-exudative form of age-related macular degeneration.

An additional study by Cocce, et al (*ARVO E-abstract 3765*), further elaborated on the lack of reliable functional endpoints for proof of concept clinical trials in AMD through the evaluation of visual function metrics. This study demonstrated that low-luminance visual acuity, mesopic microperimetry with eye tracking, cone contrast test, or dark adaptation may be used as potential functional measures in clinical trials involving patients with early and intermediate AMD. The theme of developing sensitive endpoints for the clinical study of retinal degeneration was demonstrated in a number of presentations. These studies evaluated the use of a variety of visual tests including critical flicker fusion (*Slocum, et al;ARVO E-abstract 2347; Lane, et al;ARVO E-abstract 4714*), photostress and photobleach *(Rodriguez, et al;ARVO E-abstract 4715)*, or critical flicker fusion combined with photobleach (*Sundstrom, et al;ARVO E-abstract 4713*) to examine the potential of these visual tests to serve as sensitive endpoints for AMD.

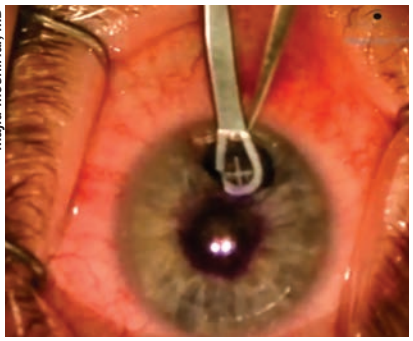
Although there are no currently approved treatments for dry AMD, there are several commonly prescribed treatments for the neovascular, or wet, form. These include: ranibizumab (Lucentis) and aflibercept (Eylea). Both therapies are intravitreal injections that antagonize the angiogenic factor, VEGF. While data from clinical trials have demonstrated the effectiveness of these therapies for the treatment of wet AMD, real-world data on the long-term effects of treatment are lacking.

Several studies at ARVO evaluated the effectiveness of aflibercept after long-term treatment. These studies demonstrated the long-term effectiveness of aflibercept in the treatment of wet AMD after three years *(Babalola, et al;ARVO E-abstract 423)*; however, visual acuity was lower for subjects who didn't complete three years of treatment (*Vig, et al;ARVO E-abstract 411*) and longer treatment was needed for subjects with persistent disease activity (*Eleftheriadou, et al;ARVO E-abstract 874*). A study by Queguiner, et al *(ARVO E-abstract 414)*, demonstrated that ranibizumab injections were effective for up to five years of treatment, raising the question of whether ranibizumab is a more effective treatment than aflibercept for wet AMD. Interestingly, Gillies,

et al *(ARVO E-abstract 896)*, did a 12-month, head-to-head comparison that looked at visual acuity changes in 394 eyes with wet AMD; there were no significant differences in acuity between patients treated with ranibizumab compared to aflibercept for 12 months, suggesting both drugs are effective for the treatment of wet AMD in real-world clinical practice.

Since current therapies for wet AMD require repeated intravitreal injections of anti-VEGF, numerous presentations at ARVO focused on new delivery mechanisms, many of which focused on extended-release formulations that would not only reduce patient burden but potentially provide improved clinical outcomes. Owens, et al (*ARVO E-abstract 409*), from Envisia Therapeutics demonstrated a proof-of-concept, multi-month release of aflibercept from a biodegradable hydrogel matrix *in vitro* that was further supported by three-month-release data in non-human primates. A bio-absorbable hydrogel depot delivery system was also described in a presentation by researchers from Ocular Therapeutix, but in this case the device was used to deliver a tyrosine kinase inhibitor (*Jarett, et al;ARVO E-abstract 1956*). In rabbits, the device delivered and maintained high levels of tyrosine kinase inhibitors in the vitreous humor, retina and choroid for six months. Parallel studies of this same delivery system demonstrated that it could provide six months of therapeutic levels of drug treatment for wet AMD using a VEGF-induced retinal leakage model (*Elhayek, et al;ARVO E-abstract 1968*).

There was also great interest in studies and treatments for inherited retinal disease. While this group of disorders doesn't have the prolonged natural history that makes AMD so difficult, developing treatments and establishing valuable clinical endpoints remain a challenge. One exciting gene therapy approach may soon bring a new treatment option for retinitis pigmentosa patients to clinical trials. ProQR Therapeutics presented new data demonstrating that their antisense oligonucleotide product, QRX411, restores wild-type USH2A RNA in RP patient-derived optic cups (*van Diepen, et al;ARVO E-abstract 1203*). As mutations in the USH2A gene are known to be a cause of RP, the ability to correct mutations *in vivo* might make it possible to stop disease progression and vision loss in these patients. QRX411 was also effective *in vivo* in a USH2A mutant zebrafish model. QRX411 has obtained orphan designation from the European Medicines Agency, and we are excited to watch this new therapy make its way to the clinic.



Majid Moshirfar, MD

Researchers have found that the AcuFocus Kamra inlay may benefit from incremental design changes.

Of course the ultimate retinal therapy, stem cell replacement of damaged retinal tissues, is still years away. This field was on the front burner in two recent, back-to-back papers that described two different approaches to stem cell replacement in patients with AMD.[3,4] In one study, autologous fibroblasts were differentiated into a sheet of retinal pigmented epithelial cells; the transplanted cellular sheet was healthy one year after transplant, though the patient didn't achieve any improvement in vision.[3] The second paper described the adverse effects of injection of adipose-derived stem cells in three patients, all of whom developed ocular hypertension, hemorrhagic retinopathy and severe vision loss.[4] In this setting the mini-symposium, Novel Therapies and Imaging Techniques for Retinal Disorders (*Sohn, E;ARVO E-abstract 2467; and others*) provided a comprehensive background on the status of this groundbreaking therapeutic path.

Even the most promising new therapeutic candidates suffer setbacks when it comes to clinical trials. Functional endpoints often aren't sensitive enough to detect clinically meaningful changes in patients' visual function with certain retinal diseases, especially in early stages of the disease. One presentation described development of a portable Visual Navigation Challenge (VNC), through which subjects must navigate a marked path with a series of obstacles under homogenous, modifiable lighting conditions (*Shapiro, et al;ARVO E-abstract 3290*). This device was able to detect significant differences between three cohorts of subjects navigating the path: normal vision subjects and those with simulated mild or severe RP. Having a portable and effective test that's able to detect differences between healthy subjects and those with varying degrees of visual function due to RP could decrease the cost and time constraints that are often barriers to clinical trials.

Cyclosporin A is now commercially available as an oil-based surfactant for dry eye and other inflammatory disorders, but its use is limited by low aqueous solubility. Surfactants that are used to improve solubility can irritate the surface of the eye, causing burning, itching and irritation of the conjunctiva. One presentation (*Johannsdottir, et al;ARVO E-abstract 4442*) reported on a preclinical study designed to develop a surfactant-free drop by delivering cyclosporin A via cyclodextrin nanoparticles. The eye-

drop formulation with cyclodextrin nanoparticles exhibited no ocular irritation in rabbits after three months of treatment. A similar clinical study compared the postoperative use of 1.5% dexamethasone nanoparticle-containing eye drops (Oculis; Reykjavik, Iceland) with mitomycin-C and Maxidex as follow-up after trabeculectomy (*Stefansson, et al;ARVO E-abstract 4947*). This was a randomized, double-masked clinical trial with 25 patients undergoing trabeculectomy for poorly controlled primary open angle glaucoma. (The study team was composed of both consultants and employees of Oculis.) The researchers say that DexNP eye drops were an effective post-trabeculectomy treatment and may serve as an alternative to current treatment used in conjunction with glaucoma surgery and other conditions where anti-inflammatories are indicated.

The Front of the Eye

Presbyopia isn't as debilitating as retinitis pigmentosa or AMD, but the decrease in near vision that accompanies it does result in some level of disability that can impact one's quality of life. A presentation by Aston University's James Wolffsohn, PhD, from Birmingham, U.K., (*ARVO E-abstract 2996*) was part of a larger mini-symposium on the aging eye that discussed the optical and visual trade-offs associated with lenses for presbyopia correction. These included well-known non-surgical options such as contact and spectacle lenses, as well as more novel surgical approaches like diffractive/refractive aspheric optics, trifocal lenses, and "accommodating" intraocular lenses. Gutierrez-Contreras, et al (*ARVO E-abstract 1246*), demonstrated the promise of accommodating intraocular lenses for restoring accommodation levels similar to the crystalline lens's at a presentation session focused on intraocular lenses and presbyopia correction.

One of the latest solutions for presbyopia is the Kamra inlay. This inlay works by limiting the size of the effective pupil to 1.6 mm, thereby taking advantage of the paraxial behavior of light. Work presented by de Gracia and Hartwig (*ARVO E-abstract 327*) sought to optimize the optical design of the Kamra inlay. This study used computer-simulated variations of the inlay design, then tested their fit and performance *in silico* for 1,299 subjects. They were able to show that slight incremental design changes such as a reduction in the number of holes could improve the optical properties of the inlay.

Due to the limitations inherent in the surgical correction of presbyopia, the use of pharmaceutical therapy has been explored but, thus far, continues to be limited. Encore Vision/Novartis had a strong presence during the presbyopia poster session with the presentation of their novel eye drop for presbyopia correction: EV06. In a Phase I/II study, treatment of presbyopes with EV06 resulted in a statistically and clinically significant improvement in distance-corrected near visual acuity when compared to placebo (*Korenfeld, et al;ARVO E-abstract 331*). A seven-month follow-up of this Phase I/II study demonstrated that the gains in distance-corrected near visual acuity, attributed to dosing with EV06 for 90 days, persisted for at least an additional 210 days after final exposure to the drug (*Stein, et al;ARVO E-abstract 330*).

Dry Eye

Efforts to characterize dry eye at the gene and protein level are being met with increased interest as clinicians and basic scientists alike look for new ways to diagnose and describe the disease. For those developing new therapies for dry eye, the discovery of differential gene/protein expression between healthy subjects and those with the disease might mean new therapeutic targets. One group used a mouse model of severe dry eye to explore changes in the expression of inflammation-associated genes *(Daull, et al;ARVO E-abstract 797)*. Inflammation is a key driver of some of the signs and symptoms of dry eye. Results from the study showed either an up- or downregulation of 34 genes, which may translate to therapeutic targets or diagnostic markers after future studies assess the role that these genes play in human disease.

In a study investigating differences in protein expression between healthy subjects and those with dry eye, differentially expressed proteins were discovered in tear samples from the two groups (*Perumal, et al;ARVO E-Abstract 796*). Proteins associated with increased inflammation were significantly increased in the dry-eye group, while some proteins necessary for tear function and ocular health, such as lysozyme and proline-rich protein 4, were significantly decreased. In total, 76 differentially expressed proteins were discovered in three main categories: inflammation; apoptosis; and metabolism. The results of these studies may lead to clinically useful biomarkers for patient diagnosis and clinical trial endpoints.

Results from tests of a new lubricant eye drop for patients with lipid-deficient tears were shown this year (*Hom, et al;ARVO E-Abstract 2671*). The novel eye drop contains lubricant polymers along with omega-3 fatty acids and trehalose. When compared to a marketed eye drop, the investigational drop proved non-inferior for symptomatic dry-eye relief. Further, subjects using the investigational drop saw significant improvement in corneal and conjunctival staining

when compared to the control drops at all follow-up visits.

One particularly exciting topic in the clinical dry-eye community at ARVO this year was Allergan's TrueTear Intranasal Tear Neurostimulator. The TrueTear is a small, handheld device with two slim prongs that deliver a small electrical current to sensory neurons in the nasal cavity. This stimulation induces the nasolacrimal reflex, resulting in tear formation. In a trial of 25 dry-eye subjects, the TrueTear was shown to significantly increase tear production when measured by Schirmer's test and tear meniscus height measured by optical coherence tomography imaging (*Orrick, et al;ARVO E-Abstract 2692*). In the same study, it was shown that TrueTear use also significantly increased tear film lipid layer thickness, a finding that may have implications in tear-film stability for patients with evaporative dry eye (*Watson, et al;ARVO E-Abstract 4387*). A separate study analyzed meibomian gland morphology before and after TrueTear stimulation in subjects with dry eye (*Pondelis, et al;ARVO E-Abstract 2235*). The group used OCT imaging to measure the size of the glands and found that overall gland area and perimeter was significantly smaller after stimulation. The authors suggest that this is due to expression of meibum from the glands, a finding that corroborates the results from the Watson study described above. With the recent FDA market authorization, we're sure to see much more of the TrueTear in the clinic very soon.

We also saw positive results presented from Regentree's ARISE-I Phase IIa study evaluating RGN-259 (Thymosin β-4) ophthalmic solution for the treatment of dry-eye syndrome (*Ousler, et al;ARVO E-Abstract 2668*). This five-week, multicenter study evaluating 317 subjects in three arms (placebo and 0.05% and 0.10% RGN-259) showed positive results for RGN-259 in measures of ocular discomfort and ocular surface staining compared to placebo. The 0.05% and 0.10% solutions reduced ocular discomfort on day 28 both before and, in patients more symptomatic at baseline, after exposure to a controlled adverse environment. Additionally, subjects in the 0.05%- and 0.10%-RGN-259 groups with worse tear-film breakup time at baseline saw improved corneal staining scores by the end of the study. We're looking forward to more positive results from future studies.

Allergan's TrueTear is a small handheld device with two slim prongs that deliver a small electrical current to sensory neurons in the nasal cavity, resulting in tear formation.

ARVO 2017 also hosted a special-interest group in which conclusions and recommendations from the TFOS Dry Eye Workshop II were presented (*Sullivan, et al*). This update of the 2007 DEWS report includes refinements in endpoints and greater emphasis on neuropathic aspects of dry eye. Details should be available with publication of the full report later this summer. Allergy and dry eye were also highlighted in a mini-symposium focused on the relation of these conditions to ocular surface health. It's well known that the allergic response begins with the engagement of allergen by IgE receptors on the surface of mast cells, resulting in an inflammatory cascade primarily composed of histamine and other local mediators. Symposium presenters described the latest work on shared immune mechanisms seen in both allergic disease and dry eye. In one of these presentations, Andrea Leonardi, MD, of Italy's Padua University, discussed how disruption of cell-cell junctions on the ocular surface is pivotal to the immune response, and how analysis of patterns of tissue RNA from the conjunctival surface has provided clues to the underlying etiology of the severe allergic disorder vernal keratoconjunctivitis (*ARVO E-Abstract 1599*). These results demonstrated a distinct conjunctival transcriptome involved in immune signaling, and thus they've provided new potential drug targets for the treatment of severe ocular allergy.

In this report, we've only covered a tiny fraction of the posters, talks, symposia and special-interest groups that were on display at this year's ARVO meeting. Looking ahead, although Baltimore was a great venue, it will be hard-pressed to compete with next year's meeting in Hawaii. See you there. REVIEW

Dr. Abelson is a clinical professor of ophthalmology at Harvard Medical School. Dr. Hollander is chief medical officer at the ophthalmic consulting firm Ora in Andover, Mass., and an assistant clinical professor of ophthalmology at the Jules Stein Eye Institute at the University of California, Los Angeles.

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2. Villegas VM, Aranguren LA, Kovach JL, Schwartz SG, Flynn HW Jr. Current advances in the treatment of neovascular age-related macular degeneration. Expert Opin Drug Deliv 2017;14:2:273-282.
3. Mandai M, Watanabe A, Kurimoto Y, et al. Autologous induced stem-cell-derived retinal cells for macular degeneration. N Engl J Med. 2017;16:376:11:1038-1046.
4. Kuriyan AE, Albini TA, Townsend JH et al. Vision loss after intravitreal injection of autologous stem cells for AMD. N Engl J Med 2017;16:376:11:1047-1053.

Continued from pg. 5

couldn't afford treatment and were delaying it," he explains. "Also, some patients started submitting claims for reimbursement on their own. We decided to take the lead in the effort to obtain reimbursement so that more patients could have access to this procedure, including submitting to obtain a J-code for the drugs. In January, there were three insurance companies covering cross-linking. As of May, there are 14 companies across the country covering cross-linking, including Aetna. We're working hard to get more companies to cover it, and do so at a payment that's uniform and appropriate. This is not an elective procedure; it's treating a progressive, sight-threatening disease, so it should be covered.

"For this program to work, all parties should benefit," he adds. "Patients should have access to it; our ARCH program will help with that. Physicians should be reimbursed for the procedure. Payers should save money by avoiding paying for corneal transplants. And it should make sense for us, the manufacturer, so that we can continue developing this technology for the future."

Remembering Roger Steinert, MD

On June 6, 2017, the field of ophthalmology lost one of its most respected members: Roger F. Steinert, MD, known for his leadership and expertise in the areas of cataract, refractive and corneal surgery. He was a pioneer in LASIK, laser refractive surgery and corneal transplantation, developing new techniques that have preserved and improved vision for millions. He died peacefully at his home in Vail, Colorado, from complications of glioblastoma. He was 66 years old.

Dr. Steinert obtained a BA in psychology from Harvard in 1973 and his MD from Harvard Medical School in 1977; he then completed his residency at the Massachusetts Eye & Ear Infirmary. He began teaching at Harvard Medical School in 1981. In 2004 he became a professor of ophthalmology at the University of California, Irvine.

His list of accomplishments is remarkable. They include being the Irving H. Leopold Professor and chair of the ophthalmology department at UC-Irvine School of Medicine, as well as a professor of biomedical engineering; being the founding director of The Gavin Herbert Eye Institute; and being chief of staff at UC-Irvine's Medical Center. His awards include the AAO's 2008 Barraquer Award and 2009 Lifetime Achievement Award; and the ISRS's Lifetime Achievement Award in 2015. He was also president of ASCRS from 2005 to 2006.

"Roger was more than my mentor; he was one of my best friends," says Sumit Garg, MD, medical director and associate professor at the Gavin Herbert Eye Institute. "I learned so much from him, not just as a doctor, but as a person. He approached obstacles with a friendly smile, always taking the long view, keeping things in perspective. He was a creator of possibilities. It was largely because of his dedication that we were able to construct the Gavin Herbert Eye Institute. One of the things I will miss most is his sense of humor. We shared many good times together.

"Roger was more than the sum of his accomplishments," he adds. "For a generation of ophthalmologists, including me, he was a leader, teacher, mentor, friend and colleague whose daily commitment to excellence provided inspiration and guidance. Roger: One of the greatest gifts ever given to me was to be mentored by you and to call you a friend. Your legacy will live on in those you have trained and we will strive to make you proud. I will miss you. Rest in Peace." REVIEW

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Find Common Ground With Premium Patients

An update to the venerable Dell Patient Questionnaire may help you crack the code of proper preop patient communication.

Walter Bethke, Editor in Chief

For many years, much of the culture and history of ancient Egypt was shrouded in mystery, due in large part to researchers' inability to translate Egyptian writing. This all changed with the discovery and translation of the Rosetta Stone, which gave researchers and the ancient Egyptians a common language—Greek—to help the former better understand the latter.

Similarly, over a decade ago, when presbyopic intraocular lenses began to appear, neither patients nor their ophthalmologists spoke the same language, and it took surgeons large chunks of chair time to provide the many details and definitions the patients needed just to understand the basics of presbyopic IOL surgery. In response, Austin surgeon Steve Dell devised a preop patient questionnaire to act as an ophthalmic Rosetta Stone of sorts—getting patients on the same page as their doctors. Recently, Dr. Dell rewrote the questionnaire to keep pace with changes in cataract surgery. In this article, we'll take a look at the changes and how they improve the preop patient/doctor interaction.

The Problem

Dr. Dell explains the specifics of why he came up with the questionnaire in the first place. "Prior to the introduction of presbyopic IOLs in 2004, we really had a pretty simple discussion with most of our cataract surgery patients," he says. "It was limited to the decision about whether to have their postop vision set mostly for distance or mostly for near, and spectacle independence wasn't nearly as common a goal as it is now. Also, our refractive surgery offerings at that time were limited just to AK to try to provide good distance vision, so it was really a discussion about if the patient wanted to have good distance vision or wanted to wear glasses for everything. Then, when presbyopic IOLs came onto the scene, it was great. I had participated in some of the FDA trials of these lenses, and patients were excited about the new opportunities. However, their introduction created a massive logjam in my clinic because these consultations were now taking up all kinds of time. It was a situation that needed to be changed.

"I tried using counselors, videos and the like, but inevitably the patients still needed a discussion with a surgeon to go over their various options. Also, I wanted to develop a common vocabulary with the patients quickly. For instance, when I say, 'intermediate vision,' I know that I'm referring to a computer screen's distance. A patient, however, might think I mean a TV set that's 10 feet away, as opposed to 'distance' vision, which might be a mile away. And all this needed to be communicated quickly." To accomplish this, the questionnaire was born.

The Solution

The original Dell questionnaire was aimed at succinctly explaining the concept of cataract surgery or refractive lens exchange, explains Dr. Dell, and then to force the patient to prioritize his postop visual goals, using clear definitions of distance, intermediate and near tasks.

"The questionnaire then began to explore the various levels of visual compromise that the patient would be willing to accept in pursuit of these goals," he says. "For instance, would they accept giving up stereopsis/depth

perception? Would they be willing to put up with some dysphotopsias? We wanted to understand their thoughts about such compromises before even beginning the discussion.

"We also put in a personality test," Dr. Dell continues. "In it, the patient rates his personality on a scale from easygoing to perfectionist. However, though these questions were helpful, we found the real utility of the questionnaire was its ability to get both of us on the same page very quickly. We established a common vocabulary, of course, but the patients knew—even before they met me—that some sorts of compromises might be required. Just the act of filling out the questionnaire, reading the questions, tells them that maybe they can't have everything they imagined without any form of visual compromise. It alters their expectations a little bit, making for a much simpler discussion."

The New Questionnaire

Even though the questionnaire proved effective, the changing world of refractive-cataract surgery led Dr. Dell to revamp it and make the new version available to his fellow surgeons. Following are the key modifications and areas Dr. Dell focuses on when a patient fills out the questionnaire.

• ***Key differences.*** "We updated the terminology to reflect current methods of accessing reading material," Dr. Dell explains. "So, we talk about things like tablets, smartphones and e-readers. Those things didn't really exist in 2004 when we first published the questionnaire.

"We also included a self-test for the patient's habitual reading distance," Dr. Dell adds. "With this, the patient uses the physical piece of paper the questionnaire is written on as a rough ruler to estimate how far from his face he typically holds the reading material. We validated this method in our clinic over a period of several months and patients were quite good at estimating whether it was one vertical paper length, 1.5 or two. This is an important question, because we now have a variety of presbyopic lenses with different add powers. We have extended-depth-of-focus lenses that are geared more toward intermediate, accommodative lenses that are better for intermediate and some multifocals that allow patients to read very close."

The design of lenses has changed slightly over the intervening years, too, so questions regarding adverse events changed, too. "We've upgraded the descriptions of dysphotopsias to include starbursts, which are more of an EDOF-type phenomenon as opposed to halos and rings, and we've slightly reduced the severity of dysphotopsias to reflect the improved performance of modern presbyopia-correcting IOLs." Also, in terms of logistics, if a surgeon would rather present the questionnaire digitally, such as on a tablet or laptop, Dr. Dell says he or she can use a calibrated piece of string for the estimation of the reading distance.

• ***Important question(s).*** Though the questionnaire was created so that each question is important in its own way, Dr. Dell says he finds his eyes seeking out certain questions. "I actually look at the first question, 'Are you trying to achieve good vision without glasses at distance, mid-range and near?' " he says. "They then have to make a selection for each of these distances. I also pay a fair bit of attention to question three, which some patients find difficult to answer: 'If you had to wear glasses after surgery for one activity, for which distance would you be most willing to wear them?' They then are forced to pick distance, mid-range or near. Their response can be very telling, and you sometimes get an answer that completely surprises you. For example, we sometimes get a patient who currently has good distance vision without glasses, but who really wants to be nearsighted—they'd really prefer to read up close. It's an unusual request, but I've seen it many times. And, if they do provide a weird answer like that, it stimulates a conversation about that issue, which is good. Having such a conversation after they've already had their surgery is very awkward—'I really wanted X but you gave me Y.' That's not good."

• ***Red flag responses.*** Certain responses to the questions can be a cause for concern. "When I review the completed questionnaire, there are some things that are worrisome," Dr. Dell says, "such as when the patient actually refuses to fill it out. This can be a warning sign that they're obstinate. We also see people who change their minds many times during the course of filling it out. These patients will cross out an answer, select a new one, but then go back and re-select their first answer. This is a little concerning as well. Some people fill out the questionnaire in a way that lets you know they don't really understand what they're reading. They appear to be completely confused about it. However, this can be helpful because it tells you that you've got more work to do to educate the patient on what his options are. This confusion will often take the form of contradictory answers. There are also the patients who write editorial commentary about the questions in the margins, and those who mark up the page to correct my—already correct—grammar."

Ultimately, Dr. Dell says the questionnaire helps make a weighty decision easier for both patient and doctor. "The thing is, as a cataract surgeon, you're sometimes making important, lifetime-long vision decisions with a patient you've only known for about 10 minutes," he says. "The questionnaire helps you quickly suss out what this person is about and what his vision needs are." REVIEW

A downloadable version of the new questionnaire accompanies the online version of this article on our website.


High-dose Anti-VEGF in Refractory Wet AMD

Researchers say that, for certain cases, increased doses of these drugs may yield better results than a standard regimen.

Intira Sukpen, MD, and Jay M. Stewart, MD, San Francisco

Choroidal neovascularization, the hallmark of neovascular AMD, is the major cause of severe vision loss in the disease, and research has shown that the development of CNV lesions is stimulated by increased secretion of vascular endothelial growth factor A.[1,2] The goal of anti-VEGF therapy is to stabilize or improve vision by inhibiting the growth of CNV, which reduces the complications induced by the neovascular complex that can lead to loss of vision, such as macular hemorrhage, macular edema and subretinal fluid (SRF). Although anti-VEGF therapy has improved the visual prognosis for patients with AMD, not all eyes with exudative disease experience full anatomic resolution of macular hemorrhage, macular edema or intraretinal fluid/SRF on OCT with standard-dose therapy (ranibizumab 0.5 mg, bevacizumab 1.25 mg or aflibercept 2 mg). Using a higher dose of anti-VEGF therapy may enhance the effectiveness of these drugs in some cases of neovascular AMD. In this article, we'll explain what we know so far about this treatment option.

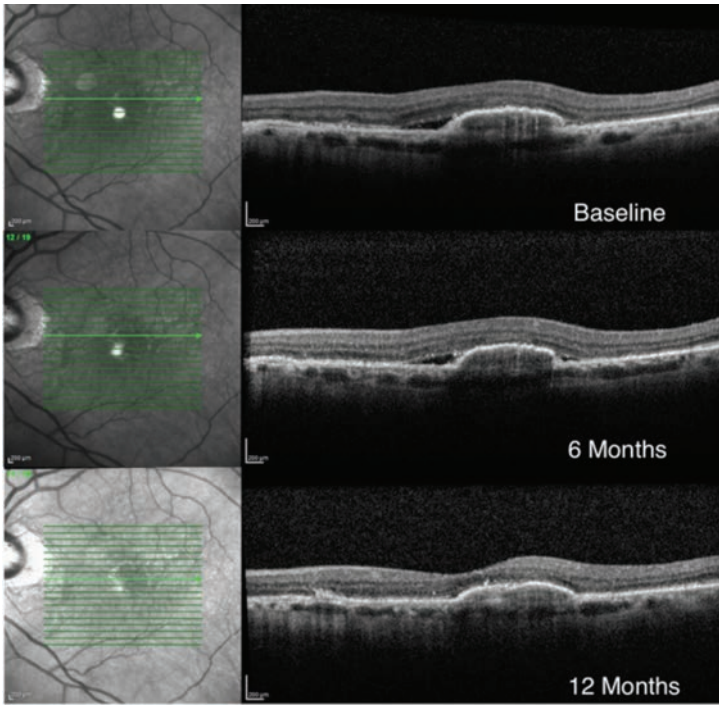

Figure 1. An 83-year-old man who had suboptimal response to anti-VEGF monotherapy for six months (vision 20/25 at baseline and six months). After switching to a double-dose regimen the subretinal fluid resolved and vision improved to 20/20.

The response to anti-VEGF therapy depends on a variety of factors, including the patient's age, lesion characteristics, lesion duration, baseline best-corrected visual acuity and anatomic improvement on optical coherence tomography. We know from clinical trials that anti-VEGF therapies given as a standard regimen of monthly injections fail to control exudation in all patients. For example, the Comparison of Age-Related Macular Degeneration Treatment Trials research group reported that despite a monthly dosing regimen with anti-VEGF for a year,

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53.2 percent of patients receiving ranibizumab 0.5 mg and 70.9 percent of patients receiving bevacizumab 1.25 mg had evidence of persistent subretinal fluid on OCT.[3]

Because of the lack of complete response to standard therapy in some patients with AMD, some clinicians and researchers have investigated the possibility of using higher-dose treatment. The LAST trial, the first prospective clinical trial of neovascular AMD to publish results of high-dose (2 mg) ranibizumab, reported that it has the potential to maintain or improve BCVA and anatomical outcomes in some patients with persistent or recurrent SRF or IRF secondary to neovascular AMD despite prior monthly intravitreal anti-VEGF therapy with the standard dose.[4] Bascom Palmer retina specialist Phil Rosenfeld and his colleagues examined the tolerability of higher dose ranibizumab (up to 2 mg) and found that increasing the dose was well-tolerated, with a 40-percent rate of improvement in visual acuity that was similar to the standard regimen.[5] Another study recently demonstrated improved visual acuity and anatomic response with 2-mg ranibizumab injections in patients who demonstrated persistent disease despite standard dosing therapy.[6] Other researchers reported the use of double-dose ranibizumab in a retrospective chart review of 10 eyes (eight subjects) with exudative AMD that had persistent macular fluid on spectral-domain OCT after at least three monthly intravitreal ranibizumab (0.5 mg) or bevacizumab (1.25 mg) injections. In this cohort, central macular thickness was significantly lower after two monthly double-dose intravitreal ranibizumab injections (0.1 mg, DDR) (324 ±77 µm at baseline vs. 248 ±50 µm, p=0.02). All eyes demonstrated improvement on SD-OCT after the first two doses of DDR. Central macular thickness demonstrated a statistically significant decrease following the second DDR injection, while the decrease was smaller and not significant after the third double dose of ranibizumab. Paracentesis was performed frequently for acute intraocular pressure elevation or as prophylaxis in eyes receiving DDR, due to the higher volume injected intravitreally, but no other ocular or systemic adverse effect was noted with double-dose ranibizumab.[7]

In our clinical practice, we've used high-dose anti-VEGF agents with some success in a small cohort of cases of recalcitrant exudation in neovascular AMD *(See Figures 1 and 2)*. This has provided us with an additional treatment option to consider in patients with an unsatisfactory response to standard therapy. A larger prospective, randomized clinical study will be necessary to validate this therapeutic approach and to identify features predicting a response to a high dose anti-VEGF therapy regimen. REVIEW

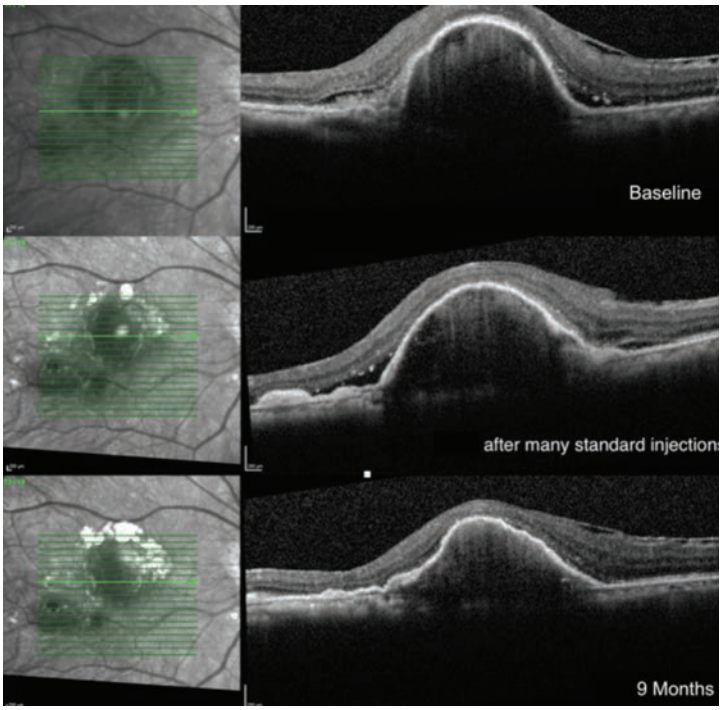

Figure 2. A case of good response after switching to a double-dose regimen of anti-VEGF therapy. The images show resolution of subretinal fluid in a 73-year old woman with wet AMD and large pigment epithelial detachment despite many injections of anti-VEGF agents on a monthly regimen. Vision remained stable at 20/100 at all visits.

Dr. Sukpen is a fellow and Dr. Stewart a professor in the Department of Ophthalmology at the University of California, San Francisco Medical Center. Dr. Stewart can be reached at Jay.Stewart@ucsf.edu

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Boston KPro: Current And Future Directions

An in-depth look at this innovative device's design, recent modifications, implantation techniques and outcomes.

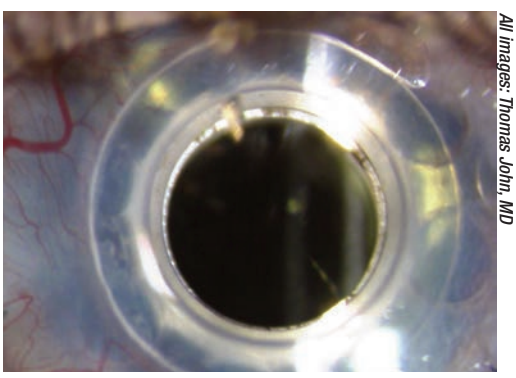
Thomas John, MD, Chicago

Though replacing a patient's diseased or damaged cornea with an artificial one may seem modern and high-tech, the concept of an artificial cornea is more than two centuries old,[1] dating back to Guillaume Pellier de Quengsy's description of the first keratoprosthesis (KPro) in 1789.[2] However, it wasn't until 1855 that a quartz crystal implant was used in the first human KPro procedure. Since then, artificial corneas have helped numerous patients recover vision lost to corneal diseases, and the design of the devices continues to evolve.

In this article, I'll review the indications for the use of a keratoprosthesis, list the available devices and outline the results you can expect to achieve with them.

KPro Indications

Diseases affecting the cornea are a major cause of global vision loss, second only to cataract in overall importance, and both inflammatory and infectious etiologies resulting in corneal scarring can cause functional blindness.[3] Globally, bilateral corneal blindness is estimated to be 4.9 million persons, or 12 percent of the total 39 million blind, based on the World Health Organization's 2010 global blindness data.[4] A KPro, however, can reverse corneal blindness and restore eyesight, and it's most useful in cases where conventional surgical techniques such as penetrating keratoplasty or limbal stem cell transplantation are most often projected to fail due to the adverse ocular surface conditions that prevail in a subset of patients with corneal blindness. Recent data appear to suggest that Boston KPro (BKPro) *(See Figure 1)* may be superior to conventional corneal transplant for a previously failed corneal graft. However, one should consider the potential postoperative challenges with BKPro, namely possible retroprosthetic membranes (RPM) *(See Figure 2, facing page)*, glaucoma and BKPro extrusion.



All images: Thomas John, MD

Figure 1. Slit-lamp photograph of a Boston Kpro in a highly vascularized cornea with multiple prior failed corneal grafts.

The clinical indications for a keratoprosthetic device such as the BKpro include refractory corneal blindness with very poor prognosis for conventional penetrating keratoplasty, such as failed corneal grafts, autoimmune ocular disorders such as Stevens-Johnson syndrome, toxic epidermal necrolysis, herpetic keratitis, congenital anomalies such as aniridia; chemical or thermal injury and pediatric corneal opacities.

BKPro Type II is especially indicated in the rarer cases of symblepharon, severe dry eyes and significant corneal scarring associated with autoimmune and inflammatory diseases. Recent reports indicate type II BKPro is indicated most commonly for Stevens-Johnson syndrome (41.7 percent) and mucous membrane pemphigoid (41.7 percent).[5]

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Patients who have a high risk of failure with conventional penetrating keratoplasty, and therefore might require an artificial cornea, fall into two categories: those with optimal tear function and those who don't have lubricating tears and therefore run the risk of surface keratinization and corneal blindness.

The BKPro

Globally, the BKPro has the highest ocular implantation rate,[6] with more than 12,000 devices implanted worldwide as of March 2015.[7] This device was initially developed at the Massachusetts Eye and Ear Infirmary in 1960s, and was Food and Drug Administration-approved in 1992 and CE-marked in 2014.

Other types of keratoprostheses of interest include: AlphaCor artificial cornea; osteo-odonto keratoprosthesis (OOKP);[8] KeraKlear (Keramed); Micro Cornea;[9] Auro KPro (BKPro type 1-based KPro);[10] LVP KPro (Auro KPro with a longer optical stem);[11] and the MICOF (from Russia's Moscow Eye Micro Surgery Complex).[12] The AlphaCor was FDA approved in 2002, while the rest aren't approved in the United States.

The BKPro consists of model types I and II, the former being used in patients with adequate tear function and the latter being used in ocular conditions with no surface tears and the presence of a keratinized ocular surface, where the device is placed through the eyelids to provide vision in an otherwise functionally blind eye.

The device has a collar-button configuration; the two main parts of the BKPro are the front plate with its integral optical cylinder or optical stem (3.35-mm diameter) that's made of poly(methyl methacrylate), and the backplate that can be either PMMA or titanium. The recent introduction of an enlarged titanium backplate to clamp the donor-host junction is aimed at decreasing the rate of RPM. However, currently there is no definitive comparative evidence that a titanium backplate is superior to a PMMA backplate in reducing RPM formation. Because of this, the PMMA backplate is still a viable surgical option due to its relatively long-term track record of proven safety.

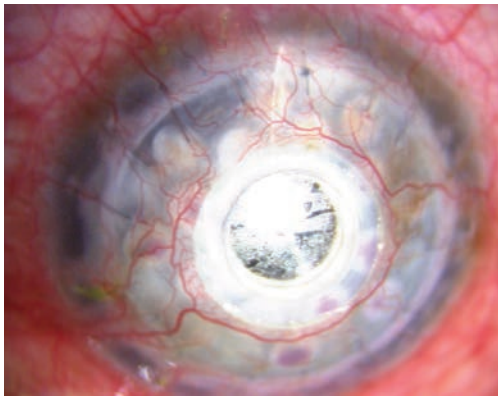

Figure 2. A Boston Kpro with a thick retro-prosthetic membrane.

While the PMMA backplate is cosmesis-neutral for the most part, the blue titanium backplate—which works well for for blue and hazel eyes—can potentially be a cosmetic issue where the contralateral iris color is brown. Although a painted contact lens can mask the blue color of the titanium backplate, having a lens made can make the whole process very expensive for the patient. In these instances, a PMMA backplate may be a consideration. In the future, however, brown and blue titanium backplates may become available.

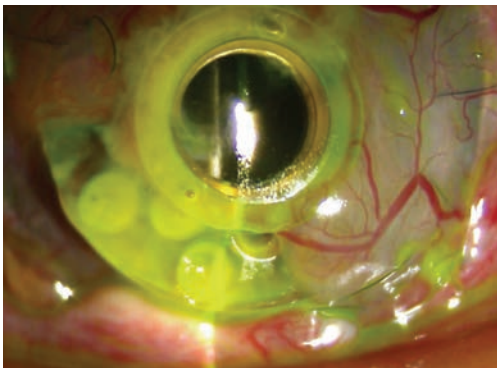

Figure 3. Slit-lamp photograph displaying corneal melt with significant PMMA backplate exposure and partial forward tilt of a Boston Kpro.

A titanium backplate is thinner than a PMMA model, and therefore occupies less anterior chamber space, is considered to be more tissue-friendly, and is thought to be associated with less RPM than the medical-grade, transparent, biologically inert PMMA, which has been associated with many postoperative complications.[13] In contrast, titanium has been shown to have superior biocompatibility and demonstrates increased corrosion resistance compared to other materials.[14,15]

The assembly of a BKPro consists of a donor cornea sandwiched between the front plate and backplate of the device. The central rigid optical cylinder of the BKPro passes through the central, surgically created 3-mm opening in the donor cornea. The front plate diameter is 5.5 to 7 mm,[16] while the backplate is available in adult and pediatric sizes—8.5- and 7-mm diameters, respectively.[17] The backplate of the adult Boston KPro contains 16 1.3-mm diameter holes, while the pediatric model has eight. These openings provide a pathway for nutrition and hydration for the donor corneal graft.

There are two types of backplate attachments: the newer click-on type that clicks onto the optic of the front plate and is made of titanium; and the older snap-on type of backplate that snaps onto the optic and is further secured with a locking ring. The newer model is threadless, while the older model is threaded on. The former's backplate is 8.5 mm in diameter, while the older model comes in either a 7- or 8.5-mm diameter backplate made of either PMMA or titanium.

Once the Boston KPro and the donor cornea are put together in one assembly, the surgeon attaches the entire unit to the patient's cornea, which has been trephinated to full-thickness in a manner similar to conventional penetrating keratoplasty. The surgeon approximates and then connects the donor corneal rim and recipient cornea with interrupted 10-0 nylon sutures like a routine PK with corneal neovascularization. This type I KPro is manufactured in a single standard pseudophakic plano power or with customized aphakic powers based on the eye's axial length. With the type I device, the maximum visual field is 60 degrees.[16] Boston KPro type II has a through-the-lid design that incorporates a 2-mm anterior nub that penetrates through a tarsorrhaphy and has a visual field of 40 degrees.[18]

Surgical Pearls

Centration of the BKPro is important both for the donor and recipient. Recipient corneal centration of the trephination may be achieved by measuring with surgical calipers in a way similar to that used when performing a PK. For the donor cornea, the full-thickness trephination is carried out in the usual surgical manner for donor corneal disc preparation. It's important that the central 3-mm trephination be performed in the center of the donor corneal disc. This ensures that the Boston KPro achieves uniform centration with the donor corneal disc. A device I helped design, the John Centration Ring (ASICO), is helpful in centering the central 3-mm trephination on the donor corneal disc.

To help with visualization, you can dye the donor cornea blue by immersing it in trypan blue, followed by BSS irrigation. This facilitates visualization of the donor disk during the central trephination and while suturing the assembled KPro donor corneal disk unit to the recipient peripheral corneal rim.

Suture the donor corneal rim and the recipient cornea using interrupted 10-0 nylon sutures, making sure that the surface at the donor-recipient junction is uniform without any step formation, to ensure postoperative uniform tear-film distribution on the newly created ocular surface.

To help with visualization during trephination, you can dye the donor cornea blue by immersing it in trypan blue, followed by BSS irrigation.

Hemostasis is essential before the Boston KPro is sutured onto the recipient corneal rim. Using fine-needle-tip cautery can help achieve effective hemostasis of the recipient corneal rim, as most of these corneas may be associated with extensive corneal neovascularization. Prevent any blood from entering the vitreous cavity, as postoperative clearance of the introduced hemorrhage can be slow and often has a direct detrimental effect on the patient's immediate postoperative vision and visual recovery.

The use of a postoperative large contact lens, such as the Kontur lens (Kontur Kontact Lens Co.), is important to keep the Boston KPro surface clean and smooth, which results in the best post-surgical visual acuity.

Results and Complications

The spectrum of postoperative complications associated with artificial corneas include RPM *(Figure 2)*, corneal melt *(Figure 3)*, corneal infection, extrusion of the KPro, secondary glaucoma and endophthalmitis.

A multicenter Boston KPro study published in 2006 featured a large series with 141 Boston type I keratoprostheses comprising 39 different surgeons from 17 surgical sites. The researchers reported an overall Boston KPro retention rate of 95 percent, and more than half of the patients (57 percent) had a best corrected visual acuity of equal to or better than 20/200. Postoperative complications included elevated intraocular pressure in 15 percent of patients, retroprosthetic membranes in 25 percent and sterile vitritis in 5 percent.[19] None of the cases had endophthalmitis following Boston KPro implantation.

In another study, the incidence of endophthalmitis associated with the Boston KPro was 3.67 percent (five of 136 eyes) and the average time to development of endophthalmitis was 5.62 months (range: two days to eight months).[20]

Modified KPro

Recently, researchers at the LV Prasad Eye Institute in India attempted to use a modified type I Boston KPro, called the LVP KPro, in severe dry eye that normally would be an indication for Boston type II KPro or the OOKP.

In the trial, surgeons first covered the ocular surface of these eyes with a mucous membrane graft[21] to provide a stable epithelial cover for the device. In order to accommodate the extra thickness of the mucous membrane graft, the researchers lengthened the optical stem.[21] This increased stem length provides extra space around the stem beneath the front plate where the edges of the mucous membrane graft remain tucked under the front plate of the optical cylinder.[21] The study's authors reported survival of

the device for more than a year without any surface breakdown, infection, extrusion or glaucoma. Larger-scale studies with longer follow-up times should provide a better idea of the safety and efficacy of the LVP KPro.

Boston keratoprosthesis has contributed significantly to the overall retention and successful visual restoration in cases of corneal blindness that are at high risk for failure of a conventional PK. Continued innovation and modifications in the surgical technique will improve the procedure's outcomes, increase device retention times and, hopefully, decrease complications such as secondary glaucoma, RPM, infection, corneal melts and device extrusion. REVIEW

Dr. John is a clinical associate professor at Loyola University at Chicago, and is in private practice in Oak Brook, Tinley Park, and Oak Lawn, Illinois. He can be reached at 708-429-2223; fax: 708-429-2226; e-mail: tjcornea@gmail.com. He receives a small royalty on his devices from ASICO.

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Career Opportunities

An elderly woman presents with complaints of unilateral glare and photophobia.

Lucas Bonafede, MD, and Carol L. Shields, MD

Presentation

An 84-year-old Caucasian female presented for evaluation of a right iris lesion with associated symptoms of glare and light sensitivity for the preceding three months. She had had a similar occurrence approximately two years earlier, and vaguely recalled that it resolved after treatment with a laser procedure. The patient was referred to the Ocular Oncology Service at Wills Eye Hospital for further evaluation and management.

Medical History

Her past ocular history was notable for previous uncomplicated cataract surgery in both eyes, as well a giant retinal tear with detachment in the right eye that required surgical repair. She had bilateral blepharopigmentation (eyeliner tattoos). Her medical history was notable only for hypertension, controlled with atenolol. She had no known allergies, and her family and social history were unremarkable.

Examination

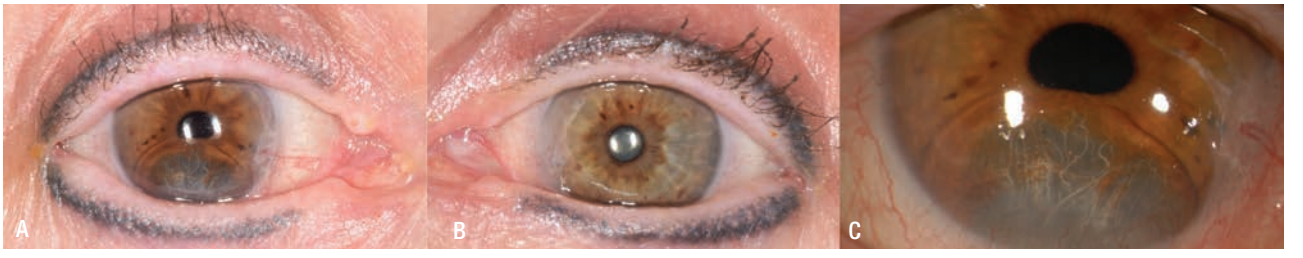

Figure 1. External photography of the right eye (A) shows a cystic iris lesion inferiorly measuring 10 mm x 6 mm, as well as blepharopigmentation in the upper and lower eyelids. The left eye (B) reveals similar blepharopigmentation. A magnified view of the right eye (C) depicts the cystic lesion protruding into the anterior chamber and distorting the pupil.

On ocular examination her best corrected visual acuity was 20/60 OD and 20/30 OS. Intraocular pressures were 8 mmHg OD and 9 mmHg OS. The right pupil was irregularly shaped but reactive and the left pupil was round and reactive. There was no afferent pupillary defect. Extraocular movements were intact and her visual fields were full to confrontation in both eyes. External and slit lamp examination revealed the blepharopigmentation of the bilateral upper and lower eyelids *(Figure 1A and 1B)*. Examination of

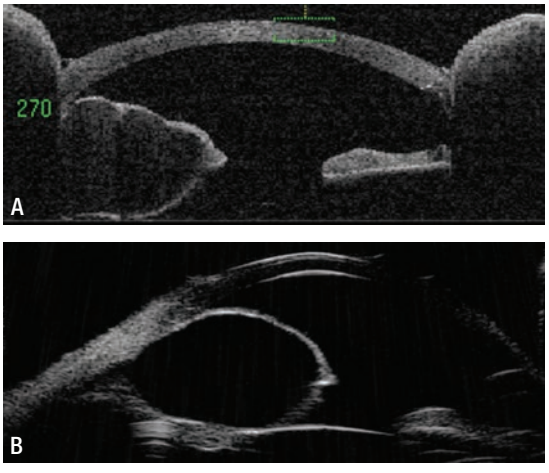

Figure 2. Anterior segment optical coherence tomography of the right eye (A) shows an iris cyst originating from the stroma and occupying the anterior chamber. Ultrasound biomicroscopy of the right eye (B) confirms an iris cystic lesion extending anteriorly with associated endothelial touch.

the right eye was further notable for a cystic mass in the iris protruding into the anterior chamber inferiorly and causing distortion of the pupil *(Figure 1C)*. The iris lesion measured approximately 10 mm x 6 mm and endothelial touch was noted inferiorly. The left anterior segment was unremarkable. Dilated fundus examination of each eye demonstrated a flat retina and intact macula.

Anterior segment optical coherence tomography was performed OD and demonstrated a thin-walled, fluid-filled, cystic lesion in the iris stroma distorting the iris both anteriorly and posteriorly *(Figure 2A)*. Ultrasound biomicroscopy OD confirmed the cystic iris stromal lesion with endothelial touch *(Figure 2B)*.

What is your differential diagnosis? What further workup would you pursue?

Diagnosis and Workup

These features were suggestive of an epithelial downgrowth cyst or, more likely, a late-onset acquired iris stromal cyst. Several treatment options were discussed, including observation, repeat Nd:YAG laser treatment, aspiration of the cyst, aspiration combined with cryotherapy and aspiration combined with ethanol irrigation. The patient underwent aspiration of the cyst with complete deflation followed by cryotherapy to stimulate adhesion of the cyst walls. Cytopathology of the aspirated fluid identified benign epithelial cells and macrophages with no malignant cells. Postoperatively, the patient noted marked improvement in symptoms.

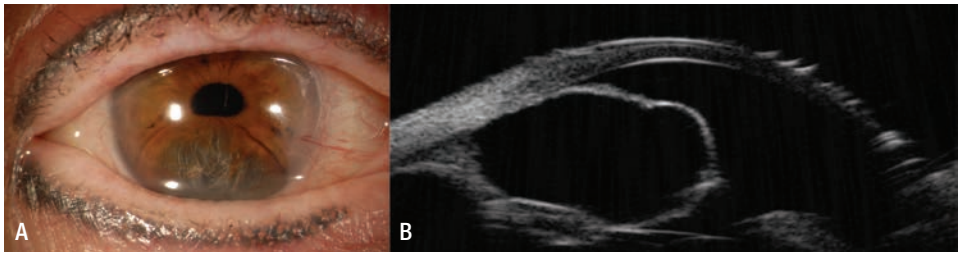

Figure 3. One year after aspiration and cryotherapy, the right eye shows recurrence of the cyst (A). On UBM, the cyst was extending into the anterior chamber, distorting the pupil and adherent to the endothelium (B). However, it was smaller than it had been prior to treatment.

One year later, the patient returned with recurrent symptoms. On examination, her best corrected visual acuity was 20/80 OD and 20/30 OS. Anterior segment assessment OD again revealed a large cystic mass at the inferior region of the iris measuring 7 mm x 4 mm and with endothelial touch inferiorly *(Figure 3A)*. UBM disclosed recurrence of the cystic iris lesion with endothelial touch *(Figure 3B)*. Treatment options were reviewed, and the patient underwent fine needle aspiration with ethanol irrigation (alcohol sclerosis of the cyst wall). Postoperatively, the patient noted improvement of symptoms.

On one month follow-up, there were no visual symptoms and visual acuity and intraocular pressures remained stable. External and slit lamp examination showed that the partially deflated flat-surfaced cyst was hung up on the endothelium anteriorly and the lens capsule posteriorly. There was no pupillary distortion *(Figure 4A)*. AS-OCT confirmed the residual cyst with partial collapse and endothelial adhesion *(Figure 4B)*. Observation of the asymptomatic, partially-collapsed cyst was advised.

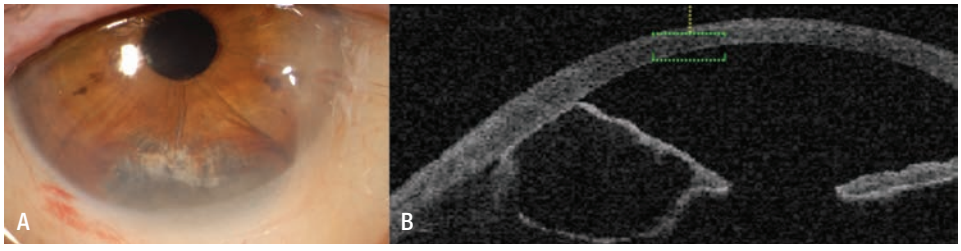

Figure 4. One month after aspiration and alcohol-induced sclerosis, the right eye shows clinical resolution (A), but OCT documents a partially involuted, flat-surfaced cyst adherent to the endothelium and the lens capsule (B).

Discussion

Iris tumors are characterized as either solid or cystic.[1-4] Solid iris tumors are more common than cystic, accounting for 79 percent vs. 21 percent of cases, respectively.[2-4] Iris cysts can be further classified as primary or secondary cysts.[1-6] Primary cysts are categorized anatomically into iris pigment epithelium (IPE) cysts and iris stromal cysts. Secondary cysts are categorized by etiology into epithelial downgrowth cysts, cysts secondary to intraocular tumors,

and parasitic cysts.[1-4]

Primary IPE cysts are the most common type of iris cyst and the second most common iris tumor, following iris nevus, accounting for 19 percent of all iris tumors.[3-5] IPE cysts are classified as pupillary margin, midzonal, peripheral, dislodged and free-floating.[1-5] Peripheral and midzonal cysts are the most frequent, accounting for 72 and 21 percent of IPE cysts, respectively.[1-5] IPE cysts tend to have a benign clinical course. Importantly, pupillary margin IPE cysts can be associated with a mutation of smooth muscle alpha-actin2 (ACTA2) and the smooth muscle gene (MYH11), which have been associated with thoracic aortic artery aneurysm and dissection.[7-10]

Iris stromal cysts are far less common than IPE cysts, representing only 3 percent of all iris tumors. These cysts are categorized as either congenital or acquired.[1-4,6] Iris stromal cysts are characterized as a unilateral, smooth-surfaced, translucent mass and often contain a fluid-debris level.[1,3,4,6] A series of 17 congenital iris stromal cysts found that, compared to older patients, patients younger than 10 had a more aggressive cyst that resulted in worse visual prognosis.[6] Iris stromal cysts have a propensity to recur, and there are several proposed treatments in the literature.[6,11-19]

The appearance of the cystic lesion in our patient is classic for an acquired iris stromal cyst. However, the patient's history of previous ocular surgery encourages the consideration of an epithelial downgrowth cyst. Similar treatment modalities can be considered for both entities. The patient initially underwent treatment elsewhere with Nd:YAG laser prior to presentation. Nd:YAG laser cystotomy involves laser-induced puncture of the cyst wall in a non-invasive manner, but this tends to have a high rate of recurrence due to healing of the rupture and reformation of the cyst.[11-13]

Fine needle aspiration of the cyst can also be performed but tends to result in a fairly high recurrence rate, especially if the cyst occurs in a younger individual.[6] Multiple surgical resection techniques have been described for simple unroofing of a cyst, complete cyst removal, and en bloc cyst plus partial cornea/sclera removal.[6,14-18] Shen et al., described four cases of congenital iris cysts that underwent surgical excision and microdiathermy which resulted in no recurrence on one to six years of follow-up.[14] Shin et al., described aspiration combined with endophotocoagulation and cryoablation for recurrent iris stromal cyst that resulted in resolution and no recurrence at 43 months of follow-up.[15] There have been attempts to treat both iris stromal cysts and epithelial downgrowth cysts with aspiration and chemical irrigation using agents such as 5-fluorouracil, mitomycin-C and absolute ethanol.[16-19] One study described using intracystic ethanol irrigation to treat 99 epithelial iris cysts, which led to resolution in 93 of 99 after one procedure, 96 of 99 after two procedures and 98 of 99 after three procedures.[18] One of this case report's co-authors, Dr. Shields, utilized a modified technique in the treatment of 16 patients with iris stromal cyst using aspiration and alcohol-induced sclerosis with special T-connector tubing.[19] Control of the cyst with involution or stabilization was achieved in 14 of 15 patients, 10 of which improved after a single treatment.[19]

In conclusion, iris cysts represent a broad group of lesions with a varied natural course, systemic associations, prognoses and treatment modalities. Iris stromal cysts and epithelial downgrowth cysts are often burdened with a high rate of recurrence and may require multiple procedures to control. Aspiration with alcohol-induced sclerosis appears to be an effective alternative in the management of these lesions without the need for open surgical resection. REVIEW

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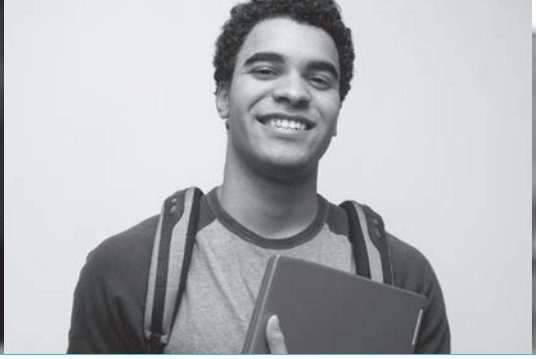


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