REVIEW® of Ophthalmology
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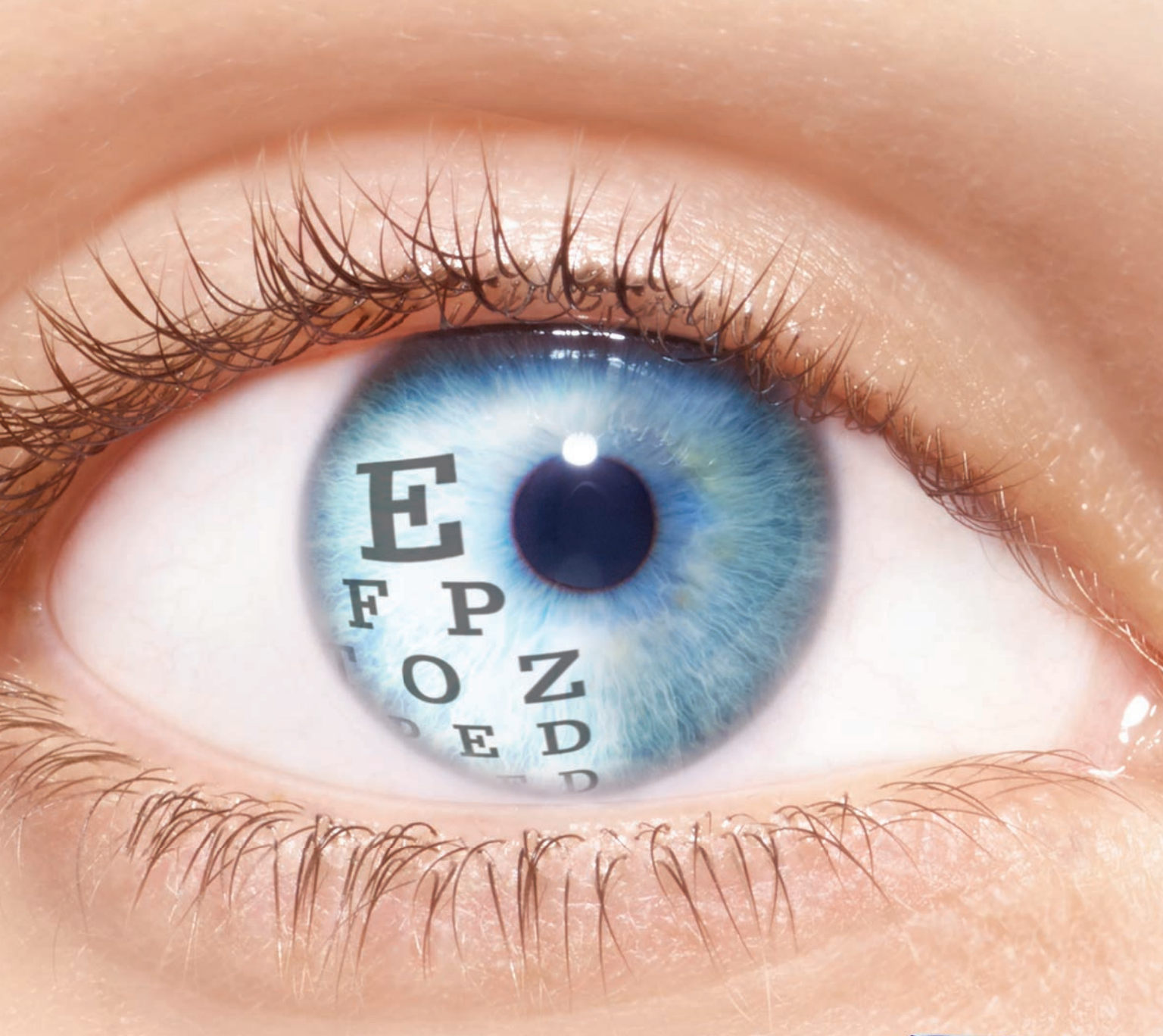
October 2017

ANNUAL DRY-EYE ISSUE

Unboxing the New Approaches to Dry-Eye Treatment

We dig into the latest protocols, drugs and devices you may soon be using.



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*Prospective, randomized, double-masked, single-dose, contralateral eye study, N=40. Lipid layer thickness was measured in nanometers, and baseline measurement was 63.38.

1. Korb D, et al. Evaluation of extended tear stability by two emulsion based artificial tears. Poster presented at: 6th International Conference on the Tear Film and Ocular Surface: Basic Science and Clinical Relevance; September 22-25, 2010; Florence, Italy.

The Relief is Real

REVIEW NEWS
Volume XXIV • No. 10 • October 2017

Allergan Files Suit Against Three Competitors

On September 7, 2017, Allergan USA filed lawsuits against three companies: Imprimis Pharmaceuticals; Prescriber's Choice; and Sincerus Florida. The suits allege that the companies—which claim to be compounding pharmacies—aren't producing their drugs in accordance with established compounding regulations, are unlawfully manufacturing and selling unapproved new drugs, and are engaging in unfair competition. The FDA has recently sent several warning letters to these companies relating to the claims in Allergan's legal filings. (The FDA warning letters are available online at FDA.gov.)

Imprimis is widely known for products such as Dropless Therapy, Less-Drops and Simple Drops. (Imprimis has also announced that it has a "development pipeline" that includes a forthcoming compounded eye drop intended to treat dry eye that may compete with Allergan's well-known product Restasis.) Sincerus and Prescriber's Choice are under common ownership; the former creates new drug formulations while the latter markets and distributes them.

Allergan's Imprimis complaint claims that the FDA has found serious deficiencies in Imprimis's production practices, and that Imprimis's use of certain ingredients poses risks to patient safety. (An FDA statement issued on August 4, 2017, linked one of Imprimis's unapproved drugs, an injectable curcumin emulsion, to two severe adverse events; one resulted in death, while the other sent the patient to the emergency room. Other warning letters have described serious health and safety concerns at Imprimis's facilities.) In addition, Allergan states that the three companies are engaging in false and misleading advertising, and that all of these activities are putting both patients and doctors at risk by exposing patients to drugs and drug combinations that have not been shown to be safe or effective.

"In order to be a lawful compounder, you must meet specific regulatory requirements," notes Donald P. Bunnin, Esq., senior counsel-litigation and commercial eye care, at Allergan. "Under certain circumstances, the compounded product must be patient-specific and not mass-produced. As we allege in the complaint, Imprimis is mass-producing a variety of products, including in the ophthalmology space. By doing that in these circumstances, they're not following FDA guidelines."

The complaint alleges that such activities give the defendants an unfair marketplace advantage by allowing them to avoid spending the money required to comply with the appropriate laws and regulations. However, Mark Marmur, a spokesman for Allergan, says that these lawsuits are about more than competition. "The actions that are being taken by these companies are putting patients at risk," he says.

Mr. Bunnin adds that Allergan is not opposed to drug compounding. "We support lawful compounding and believe it provides a valuable service that addresses patient needs and is a valuable tool for physicians," he says. "However, it needs to be done lawfully and in compliance with FDA regulations. The regulations are put in place in part to ensure that patient safety is adequately addressed."

Mark Baum, founder and CEO of Imprimis, contests Allergan's portrayal of his company as being careless about patient safety. "We've invested tremendous sums of money in equipment, facilities, personnel and training to become a GMP [good manufacturing practice] facility," he notes. "Our products are made to the exact same federal standards as Allergan's products. While it's true that our products are not FDA-approved, it's also true that our flagship products, Dropless Therapy formulations, have been used in more than one million eyes. So our products have a significant track record of success in the ophthalmology community."

Regarding the incident cited by Allergan in which a patient died, Mr. Baum says that was a malpractice case that did not involve an ophthalmic product, in which a physician gave a drug prescribed for one patient to a different patient who was allergic to it. "We had nothing to do with that," he says. "In fact, we never formulated a drug for the deceased patient. The FDA recently agreed with our recall statements regarding this case, and we have not been named in any litigation connected to this case.

"Let me be clear: We abide by federal and state laws," he continues. "Imprimis Pharmaceuticals has never been sued or paid out a nickel in settle-

ments relating to any drug we've dispensed—not the one Allergan cites in their complaint, not any ophthalmology product, not anything. I'm very proud of that. It says a lot about the quality of our products—and I don't think Allergan can make the same statement."

Regarding Allergan's claim that Imprimis is not abiding by the laws governing compounding pharmacies, Mr. Baum notes that FDA inspectors recently spent three months at Imprimis's New Jersey manufacturing facility. "The FDA knows everything about what we make, what we dispense, how we train our people and our equipment," he says. "Do you think they would let us stay in business if they believed we were putting patients at risk or not abiding by the law?"

Mr. Baum says Allergan's lawsuit is not about Imprimis's business model or patient safety, but about the possibility of competition for Allergan's drug Restasis. "Allergan derives 9 percent of its revenue and 16 percent of its profits from Restasis," he points out. "It's a billion-and-a-half-dollar franchise, and they know that competition is coming. This lawsuit is an attempt to prevent lower-cost providers from entering the market. Our more than 1,700 physician customers know that Imprimis products work really well for their patients. Our formulations are affordable and innovative, and we do a great job in terms of servicing our customers."

Mr. Baum adds that the idea that his company has an unfair advantage over Allergan because it doesn't have to run clinical trials is absurd. "Allergan is an $85 billion corporation with thousands of salespeople and significant financial resources," he says. "I think they have more lobbyists and government-relations people than we have employees in our entire company. They have every single advantage that we don't have. The idea that we're taking unfair advantage of them is absurd. That would be the equivalent of the United States complaining to the United Nations that East Timor was trying to take advantage of it."

Allergan also made headlines in September when, in a surprise, unprecedented (at least in ophthalmology) move, it sold the key patents related to Restasis to the Saint Regis Mohawk tribe of Akwasasne, N.Y. The tribe, in turn, granted Allergan exclusive use of the patents. Under the terms of the agreement, the tribe will receive $13.75 million upon the finalization of the agreement, and is eligible to receive $15 million in annual royalties.

According to a company statement, the tribe, a recognized sovereign tribal government, is filing a motion to dismiss the ongoing *inter partes* review of the patents based on their sovereign immunity. The agreement with the tribe has no impact on the pending abbreviated new drug application patent litigations regarding the patent family, which recently completed a five-day trial in Federal District Court in Marshall, Texas. REVIEW

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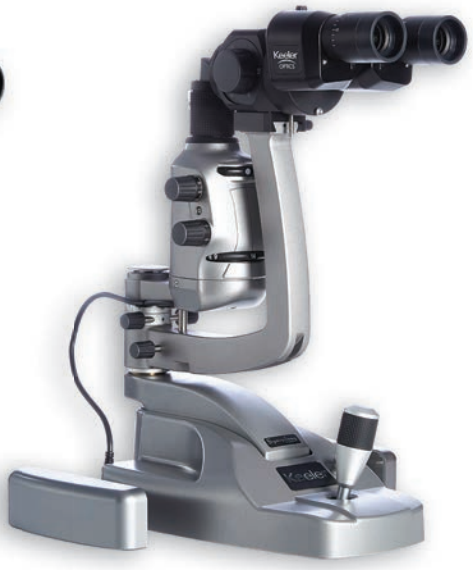

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REVIEW® of Ophthalmology

REVIEW Editor's Page

Walter C. Bethke, Editor in Chief

One Chapter Opens, Another Closes

For the busy clinician in ophthalmology, it helps to have some commonly accepted protocols to guide his or her diagnostic and treatment decisions regarding a given disease state. In the arena of ocular surface disease, these protocols have often come in the form of reports from the Tear Film and Ocular Surface Society's Dry Eye Workshop.

As our understanding of dry eye has evolved over the years, the DEWS has changed too, shedding new light on heretofore unknown aspects of the disease and helping clinicians integrate that new knowledge into their treatment decisions. Recently, the Workshop started a new chapter on dry eye with its latest report, DEWS II.

In addition to a new definition of the disease, which incorporates such concepts as "homeostasis of the tear film" and "neurosensory abnormalities" (which may help explain why signs and symptoms don't always match up in both the clinic and in large-scale, prospective clinical trials), the researchers in DEWS II also use an exhaustive literature search to ferret out the treatment approaches that work best.

As Senior Editor Christopher Kent points out in his feature on three of the latest dry-eye treatment algorithms *(p. 24)*, the DEWS II protocol tries to impress upon physicians the value of starting out with less intensity—perhaps discussing how the patient's work and leisure environments might be contributing to his or her dryness—before moving on to more intense treatments such as punctal occlusion. Chris' article walks the reader through each of the algorithms' recommendations in a stepwise fashion, allowing the reader to take the concepts back to the clinic immediately.

However, a treatment algorithm is only as good as the treatments that are used. With this in mind, on page 42 of this month's issue Senior Associate Editor Kristine Brennan gives readers a sneak peak at several dry-eye therapies—one that's recently become available and others that are still in the research pipeline—that may prove to be game changers in the quest for relief from signs and symptoms. It might pay to save some space for these new approaches in your personal protocol.

As DEWS II writes a new chapter in our ongoing understanding of the ocular surface, another chapter ends. This time, though, it's much closer to home: After 23 years, Mark B. Abelson, MD, is stepping away from writing our monthly column on ocular therapeutics, Therapeutic Topics. During his tenure with *Review*—which began with the magazine's first issue and in which he's never missed a month—he generously shared his wisdom on topics ranging from dry eye to infection. Taken together, his columns are like a mini-fellowship in the pharmaceutical management of diseases of the anterior segment.

I'd like to take this opportunity to thank Dr. Abelson for his valuable contributions to *Review*, and for allowing us to take part in the creation of his own unique chapter on ocular care.

—Walt Bethke, Editor in Chief

EYLEA®
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For Intravitreal Injection

Feel the Power at AAO 2017. Regeneron Booth 4239

POWER TO PREVAIL

As demonstrated in phase 3 clinical trials evaluating BCVA,* as measured by ETDRS letters, in patients with Wet AMD, Macular Edema following RVO, DME, and by ETDRS-DRSS† in DR in Patients with DME,[1] as well as your clinical experience

Start with EYLEA for proven efficacy outcomes[1]

AMD = Age-related Macular Degeneration; DME = Diabetic Macular Edema; DR = Diabetic Retinopathy.

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 adjacent Brief Summary.

*Best-corrected visual acuity.
†Early Treatment Diabetic Retinopathy Study–Diabetic Retinopathy Severity Scale: an established grading scale for measuring the severity of DR.

Reference: 1. EYLEA® (aflibercept) Injection full U.S. Prescribing Information. Regeneron Pharmaceuticals, Inc. May 2017.

REGENERON

777 Old Saw Mill River Road, Tarrytown, NY 10591

09/2017
US-LEA-13915

EYLEA®
(aflibercept) Injection
For Intravitreal Injection

BRIEF SUMMARY—Please see the EYLEA package insert for full Prescribing Information.

1 INDICATIONS AND USAGE

EYLEA is a vascular endothelial growth factor (VEGF) inhibitor indicated for the treatment of:

Neovascular (Wet) Age-Related Macular Degeneration (AMD); Macular Edema Following Retinal Vein Occlusion (RVO); Diabetic Macular Edema (DME); Diabetic Retinopathy (DR) in Patients with DME

4 CONTRAINDICATIONS

4.1 Ocular or Periocular Infections

EYLEA is contraindicated in patients with ocular or periocular infections.

4.2 Active Intraocular Inflammation

EYLEA is contraindicated in patients with active intraocular inflammation.

4.3 Hypersensitivity

EYLEA is contraindicated in patients with known hypersensitivity to aflibercept or any of the excipients in EYLEA. Hypersensitivity reactions may manifest as rash, pruritus, urticaria, severe anaphylactic/anaphylactoid reactions, or 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 (6.1)*]. 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 (2.7) and Patient Counseling Information (17)*].

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 (6.1)*]. Sustained increases in intraocular pressure have also been reported after repeated intravitreal dosing with vascular endothelial growth factor (VEGF) inhibitors. Intraocular pressure and the perfusion of the optic nerve head should be monitored and managed appropriately [*see Dosage and Administration (2.7)*].

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 potentially serious adverse reactions are described elsewhere in the labeling:

- Hypersensitivity [*see Contraindications (4.3)*]
- Endophthalmitis and retinal detachments [*see Warnings and Precautions (5.1)*]
- Increase in intraocular pressure [*see Warnings and Precautions (5.2)*]
- Thromboembolic events [*see Warnings and Precautions (5.3)*]

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.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Adequate and well-controlled studies with EYLEA have not been conducted in pregnant women. Aflibercept produced adverse embryofetal effects in rabbits, including external, visceral, and skeletal malformations. A fetal No Observed Adverse Effect Level (NOAEL) was not identified. At the lowest dose shown to produce adverse embryofetal effects, systemic exposures (based on AUC for free aflibercept) were approximately 6 times higher than AUC values observed in humans after a single intravitreal treatment at the recommended clinical dose [*see Animal Data*].

Animal reproduction studies are not always predictive of human response, and it is not known whether EYLEA can cause fetal harm when administered to a pregnant woman. Based on the anti-VEGF mechanism of action for aflibercept [*see Clinical Pharmacology (12.1)*], treatment with EYLEA may pose a risk to human embryofetal development. EYLEA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. The background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Animal Data

In two embryofetal development studies, aflibercept produced adverse embryofetal effects when administered every three days during organogenesis to pregnant rabbits at intravenous doses ≥3 mg per kg, or every six days during organogenesis at subcutaneous doses ≥0.1 mg per kg.

Adverse embryofetal 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 not identified. At the lowest dose shown to produce adverse embryofetal effects in rabbits (0.1 mg per kg), systemic exposure (AUC) of free aflibercept was approximately 6 times higher than systemic exposure (AUC) observed in humans after a single intravitreal dose of 2 mg.

8.2 Lactation

Risk Summary

There is no information regarding the presence of aflibercept in human milk, the effects of the drug on the breastfed infant, or the effects of the drug on milk production/excretion. Because many drugs are excreted in human milk, and because the potential for absorption and harm to infant growth and development exists, EYLEA is not recommended during breastfeeding.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for EYLEA and any potential adverse effects on the breastfed child from EYLEA.

8.3 Females and Males of Reproductive Potential

Contraception

Females of reproductive potential are advised to use effective contraception prior to the initial dose, during treatment, and for at least 3 months after the last intravitreal injection of EYLEA.

Infertility

There are no data regarding the effects of EYLEA on human fertility. Aflibercept adversely affected female and male reproductive systems in cynomolgus monkeys when administered by intravenous injection at a dose approximately 1500 times higher than the systemic level observed humans with an intravitreal dose of 2 mg. A No Observed Adverse Effect Level (NOAEL) was not identified. These findings were reversible within 20 weeks after cessation of treatment [*see Nonclinical Toxicology (13.1)*].

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 (5.1)*].

Patients may experience temporary visual disturbances after an intravitreal injection with EYLEA and the associated eye examinations [*see Adverse Reactions (6)*]. Advise patients not to drive or use machinery until visual function has recovered sufficiently.

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

Issue Date: June 2017
Initial U.S. Approval: 2011

Based on the May 2017 EYLEA® (aflibercept) Injection full Prescribing Information.

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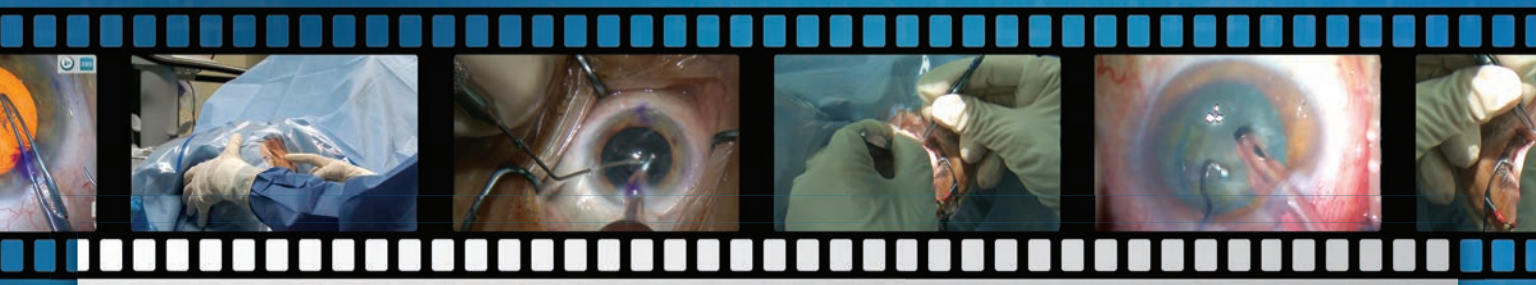

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Episode 22:
"Negative Dysphotopsia: Reverse Optic Capture Techniques"

Surgical Video by:
Richard J. Mackool, MD

Video Overview:
This patient has persistent negative dysphotopsia after cataract-implant surgery performed 18 months ago. A combination of techniques is used to achieve the desired reposition of the IOL optic (reverse optic capture). Treatment of one diopter of astigmatism is also demonstrated by the placement of 2 penetrating limbal relaxing incisions (PLRIs) at the steep corneal meridian.

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:

- Demonstrate techniques for achieving reverse optic capture of an IOL

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ZYLET®

"A One-Two Combo"

VS

STEROID-RESPONSIVE INFLAMMATORY OCULAR CONDITIONS WITH RISK OF INFECTION

HELP PUT RELIEF IN YOUR CORNER

INDICATIONS AND USAGE

ZYLET® (loteprednol etabonate 0.5% and tobramycin 0.3% ophthalmic suspension) is a topical anti-infective and corticosteroid combination for steroid-responsive inflammatory ocular conditions for which a corticosteroid is indicated and where superficial bacterial ocular infection or a risk of bacterial ocular infection exists.

Ocular steroids are indicated in inflammatory conditions of the palpebral and bulbar conjunctiva, cornea and anterior segment of the globe such as allergic conjunctivitis, acne rosacea, superficial punctate keratitis, herpes zoster keratitis, iritis, cyclitis, and where the inherent risk of steroid use in certain infective conjunctivitides is accepted to obtain a diminution in edema and inflammation. They are also indicated in chronic anterior uveitis and corneal injury from chemical, radiation or thermal burns, or penetration of foreign bodies.

The use of a combination drug with an anti-infective component is indicated where the risk of superficial ocular infection is high or where there is an expectation that potentially dangerous numbers of bacteria will be present in the eye.

The particular anti-infective drug in this product (tobramycin) is active against the following common bacterial eye pathogens: Staphylococci, including *S. aureus* and *S. epidermidis* (coagulase-positive and coagulase-negative), including penicillin-resistant strains. Streptococci, including some of the Group A-beta-hemolytic species, some nonhemolytic species, and some *Streptococcus pneumoniae, Pseudomonas aeruginosa, Escherichia coli, Klebsiella pneumoniae, Enterobacter aerogenes, Proteus mirabilis, Morganella morganii,* most *Proteus vulgaris* strains, *Haemophilus influenzae,* and *H. aegyptius, Moraxella lacunata, Acinetobacter calcoaceticus* and some *Neisseria* species.

IMPORTANT SAFETY INFORMATION

- ZYLET® is contraindicated in most viral diseases of the cornea and conjunctiva, including epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, and varicella, and also in mycobacterial infections of the eye and fungal diseases of ocular structures.

IMPORTANT SAFETY INFORMATION (continued)

- Prolonged use of corticosteroids may result in glaucoma with damage to the optic nerve, and defects in visual acuity and fields of vision. Steroids should be used with caution in the presence of glaucoma. If this product is used for 10 days or longer, intraocular pressure should be monitored.
- Use of corticosteroids may result in posterior subcapsular cataract formation.
- The use of steroids after cataract surgery may delay healing and increase the incidence of bleb formation. In those diseases causing thinning of the cornea or sclera, perforations have been known to occur with the use of topical steroids. The initial prescription and renewal of the medication order should be made by a physician only after examination of the patient with the aid of magnification such as a slit lamp biomicroscopy and, where appropriate, fluorescein staining.
- Prolonged use of corticosteroids may suppress the host response and thus increase the hazard of secondary ocular infections. In acute purulent conditions, steroids may mask infection or enhance existing infections. If signs and symptoms fail to improve after 2 days, the patient should be re-evaluated.
- Employment of corticosteroid medication in the treatment of patients with a history of herpes simplex requires great caution. Use of ocular steroids may prolong the course and exacerbate the severity of many viral infections of the eye (including herpes simplex).
- Fungal infections of the cornea are particularly prone to develop coincidentally with long-term, local steroid application. Fungus invasion must be considered in any persistent corneal ulceration where a steroid has been used or is in use.
- Most common adverse reactions reported in patients were injection and superficial punctate keratitis, increased intraocular pressure, and burning and stinging upon instillation.

Please see Brief Summary of full Prescribing Information for ZYLET® on adjacent page.

BAUSCH+LOMB

Zylet®
loteprednol etabonate 0.5% and
tobramycin 0.3% ophthalmic suspension

BRIEF SUMMARY OF PRESCRIBING INFORMATION

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

Zylet® (loteprednol etabonate 0.5% and tobramycin 0.3% ophthalmic suspension)

Initial U.S. Approval: 2004

DOSAGE AND ADMINISTRATION

2.1 Recommended Dosing

Apply one or two drops of Zylet into the conjunctival sac of the affected eye every four to six hours. During the initial 24 to 48 hours, the dosing may be increased, to every one to two hours. Frequency should be decreased gradually as warranted by improvement in clinical signs. Care should be taken not to discontinue therapy prematurely.

2.2 Prescription Guideline

Not more than 20 mL should be prescribed initially and the prescription should not be refilled without further evaluation [*see Warnings and Precautions (5.3)*].

CONTRAINDICATIONS

4.1 Nonbacterial Etiology

Zylet, as with other steroid anti-infective ophthalmic combination drugs, is contraindicated in most viral diseases of the cornea and conjunctiva including epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, and varicella, and also in mycobacterial infection of the eye and fungal diseases of ocular structures.

WARNINGS AND PRECAUTIONS

5.1 Intraocular Pressure (IOP) Increase

Prolonged use of corticosteroids may result in glaucoma with damage to the optic nerve, defects in visual acuity and fields of vision. Steroids should be used with caution in the presence of glaucoma.

If this product is used for 10 days or longer, intraocular pressure should be monitored.

5.2 Cataracts

Use of corticosteroids may result in posterior subcapsular cataract formation.

5.3 Delayed Healing

The use of steroids after cataract surgery may delay healing and increase the incidence of bleb formation. In those diseases causing thinning of the cornea or sclera, perforations have been known to occur with the use of topical steroids. The initial prescription and renewal of the medication order should be made by a physician only after examination of the patient with the aid of magnification such as a slit lamp biomicroscopy and, where appropriate, fluorescein staining.

5.4 Bacterial Infections

Prolonged use of corticosteroids may suppress the host response and thus increase the hazard of secondary ocular infections. In acute purulent conditions of the eye, steroids may mask infection or enhance existing infection. If signs and symptoms fail to improve after 2 days, the patient should be re-evaluated.

5.5 Viral Infections

Employment of a corticosteroid medication in the treatment of patients with a history of herpes simplex requires great caution. Use of ocular steroids may prolong the course and may exacerbate the severity of many viral infections of the eye (including herpes simplex).

5.6 Fungal Infections

Fungal infections of the cornea are particularly prone to develop coincidentally with long-term local steroid application. Fungus invasion must be considered in any persistent corneal ulceration where a steroid has been used or is in use. Fungal cultures should be taken when appropriate.

5.7 Aminoglycoside Hypersensitivity

Sensitivity to topically applied aminoglycosides may occur in some patients. If hypersensitivity develops with this product, discontinue use and institute appropriate therapy.

ADVERSE REACTIONS

Adverse reactions have occurred with steroid/anti-infective combination drugs which can be attributed to the steroid component, the anti-infective component, or the combination.

Zylet:

In a 42 day safety study comparing Zylet to placebo, ocular adverse reactions included injection (approximately 20%) and superficial punctate keratitis (approximately 15%). Increased intraocular pressure was reported in 10% (Zylet) and 4% (placebo) of subjects. Nine percent (9%) of Zylet subjects reported burning and stinging upon instillation.

Ocular reactions reported with an incidence less than 4% include vision disorders, discharge, itching, lacrimation disorder, photophobia, corneal deposits, ocular discomfort, eyelid disorder, and other unspecified eye disorders.

The incidence of non-ocular reactions reported in approximately 14% of subjects was headache; all other non-ocular reactions had an incidence of less than 5%.

Loteprednol etabonate ophthalmic suspension 0.2% - 0.5%:

Reactions associated with ophthalmic steroids include elevated intraocular pressure, which may be associated with infrequent optic nerve damage, visual acuity and field defects, posterior subcapsular cataract formation, delayed wound healing and secondary ocular infection from pathogens including herpes simplex, and perforation of the globe where there is thinning of the cornea or sclera.

In a summation of controlled, randomized studies of individuals treated for 28 days or longer with loteprednol etabonate, the incidence of significant elevation of intraocular pressure (≥10 mm Hg) was 2% (15/901) among patients receiving loteprednol etabonate, 7% (11/164) among patients receiving 1% prednisolone acetate and 0.5% (3/583) among patients receiving placebo.

Tobramycin ophthalmic solution 0.3%:

The most frequent adverse reactions to topical tobramycin are hypersensitivity and localized ocular toxicity, including lid itching and swelling and conjunctival erythema. These reactions occur in less than 4% of patients. Similar reactions may occur with the topical use of other aminoglycoside antibiotics.

Secondary Infection:

The development of secondary infection has occurred after use of combinations containing steroids and antimicrobials. Fungal infections of the cornea are particularly prone to develop coincidentally with long-term applications of steroids.

The possibility of fungal invasion must be considered in any persistent corneal ulceration where steroid treatment has been used.

Secondary bacterial ocular infection following suppression of host responses also occurs.

USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic effects: Loteprednol etabonate has been shown to be embryotoxic (delayed ossification) and teratogenic (increased incidence of meningocele, abnormal left common carotid artery, and limb fixtures) when administered orally to rabbits during organogenesis at a dose of 3 mg/kg/day (35 times the maximum daily clinical dose), a dose which caused no maternal toxicity. The no-observed-effect-level (NOEL) for these effects was 0.5 mg/kg/day (6 times the maximum daily clinical dose). Oral treatment of rats during organogenesis resulted in teratogenicity (absent innominate artery at ≥5 mg/kg/day doses, and cleft palate and umbilical hernia at ≥50 mg/kg/day) and embryotoxicity (increased post-implantation losses at 100 mg/kg/day and decreased fetal body weight and skeletal ossification with ≥50 mg/kg/day). Treatment of rats at 0.5 mg/kg/day (6 times the maximum daily clinical dose) during organogenesis did not result in any reproductive toxicity. Loteprednol etabonate was maternally toxic (significantly reduced body weight gain during treatment) when administered to pregnant rats during organogenesis at doses of ≥5 mg/kg/day.

Oral exposure of female rats to 50 mg/kg/day of loteprednol etabonate from the start of the fetal period through the end of lactation, a maternally toxic treatment regimen (significantly decreased body weight gain), gave rise to decreased growth and survival and retarded development in the offspring during lactation; the NOEL for these effects was 5 mg/kg/day. Loteprednol etabonate had no effect on the duration of gestation or parturition when administered orally to pregnant rats at doses up to 50 mg/kg/day during the fetal period.

Reproductive studies have been performed in rats and rabbits with tobramycin at doses up to 100 mg/kg/day parenterally and have revealed no evidence of impaired fertility or harm to the fetus. There are no adequate and well controlled studies in pregnant women. Zylet should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

8.3 Nursing Mothers

It is not known whether topical ophthalmic administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in human milk. Systemic steroids that appear in human milk could suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects. Caution should be exercised when Zylet is administered to a nursing woman.

8.4 Pediatric Use

Two trials were conducted to evaluate the safety and efficacy of Zylet® (loteprednol etabonate and tobramycin ophthalmic suspension) in pediatric subjects age zero to six years; one was in subjects with lid inflammation and the other was in subjects with blepharoconjunctivitis.

In the lid inflammation trial, Zylet with warm compresses did not demonstrate efficacy compared to vehicle with warm compresses. Patients received warm compress lid treatment plus Zylet or vehicle for 14 days. The majority of patients in both treatment groups showed reduced lid inflammation.

In the blepharoconjunctivitis trial, Zylet did not demonstrate efficacy compared to vehicle, loteprednol etabonate ophthalmic suspension, or tobramycin ophthalmic solution. There was no difference between treatment groups in mean change from baseline blepharoconjunctivitis score at Day 15.

There were no differences in safety assessments between the treatment groups in either trial.

8.5 Geriatric Use

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

NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term animal studies have not been conducted to evaluate the carcinogenic potential of loteprednol etabonate or tobramycin.

Loteprednol etabonate was not genotoxic *in vitro* in the Ames test, the mouse lymphoma TK assay, a chromosome aberration test in human lymphocytes, or in an *in vivo* mouse micronucleus assay.

Oral treatment of male and female rats at 50 mg/kg/day and 25 mg/kg/day of loteprednol etabonate, respectively, (500 and 250 times the maximum clinical dose, respectively) prior to and during mating did not impair fertility in either gender. No impairment of fertility was noted in studies of subcutaneous tobramycin in rats at 100 mg/kg/day (1700 times the maximum daily clinical dose).

PATIENT COUNSELING INFORMATION

This product is sterile when packaged. Patients should be advised not to allow the dropper tip to touch any surface, as this may contaminate the suspension. If pain develops, redness, itching or inflammation becomes aggravated, the patient should be advised to consult a physician. As with all ophthalmic preparations containing benzalkonium chloride, patients should be advised not to wear soft contact lenses when using Zylet.

MANUFACTURER INFORMATION

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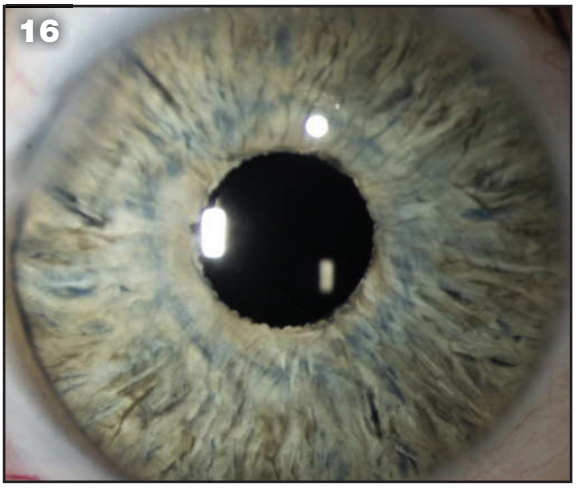

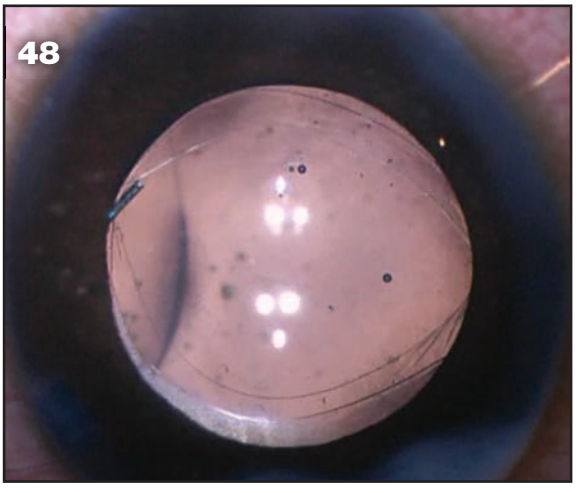

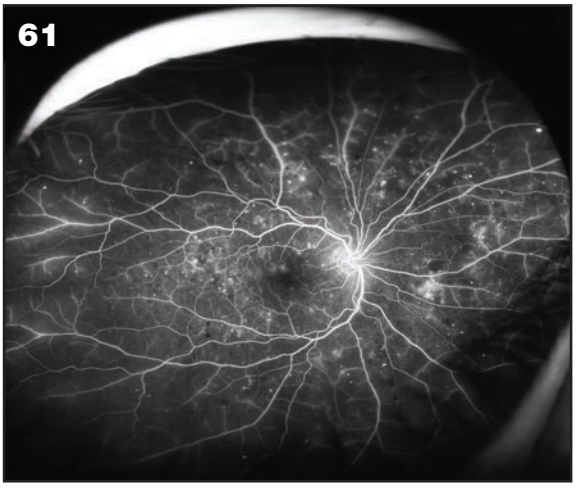

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IMPORTANT SAFETY INFORMATION

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.

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Shedding (Less) Light on Aniridia: Device Update

A report from the U.S. regulatory path, which may lead to a device approval in the near future.

Kristine Brennan, Senior Associate Editor

Whether present at birth or resulting from trauma, surgery or illness, aniridia can be visually and socially debilitating. Without a healthy iris acting as the eye's diaphragm to regulate incoming light, patients can suffer from painful glare and light sensitivity. Comorbidities include, but aren't limited to, problems with depth of field, cataract, glaucoma and retinal detachment. When an iris defect is too big to suture or the entire iris is missing, prosthetic iris devices can alleviate light sensitivity and may assist with visual acuity and cosmesis.

Iris prosthetics manufacturers include Ophtec BV (Groningen, The Netherlands), maker of the 311 Aniridia Lens II, the Iris Prosthetic System, the Artisan pupil occluder and Artisan Iris Reconstruction IOL; Morcher GmbH (Stuttgart, Germany), maker of black polyethyl methacrylate acrylic (PEMA) devices, including modified capsular tension rings with occluder fins to cover segments of missing iris tissue and iris prosthetics designed to be dialed into the eye for larger defects; and HumanOptics AG (formerly Dr. Schmidt Intraocularlinsen; Erlangen, Germany), whose flexible, silicone CustomFlex artificial iris (also known as the Artificial*Iris)* comprises a lifelike, hand-painted silicone replica of the patient's fellow iris encapsulated in clear silicone. Russian manufacturer Reper-NN (Nizhny, Novgorod) also makes an artificial iris.

Morcher aniridia rings are made to be dialed into the capsular bag, one ring on top of the other, so that the occluders interlock.

Not one of these devices is FDA approved, however. Having served as an investigator for Ophtec BV, Morcher GmbH and HumanOptics AG, Kevin M. Miller, MD, professor of clinical ophthalmology, David Geffen School of Medicine at UCLA, is well positioned to describe the regulatory journey of iris prosthetics in the United States to date. While unrelenting effort is a unifying theme running through endeavors to get devices from all three manufacturers to market, it has not yet paid off. He outlines his experiences with the Ophtec 311 Aniridia Lens (*See sidebar, p. 17.*), Morcher aniridia implants, and the HumanOptics CustomFlex artificial iris.

Morcher Devices

Morcher makes a variety of black PEMA devices for aniridia, partial iris defects and colobomas. "Internationally, Morcher's probably the number-one manufacturer," says Dr. Miller. "Morcher makes two types of aniridia devices: intracapsular tension rings with paddles on them, intended for implantation into the capsular bag, and some sulcus devices. But most of them are meant for the capsular bag. Their other product line is iris-reconstruction lenses. These are combination artificial iris devices and lenses, and the optics come in various diameters," he says. Dr. Miller's experience with iris-reconstruction lenses is exclusively with Morcher's 67B model (a 12.5-mm aniridia implant with a 3-mm optic meant for sulcus place-

Ophtec's Model 311: What Happened?

Ophtec BV's 311 Aniridia Lens II (as it is now known) is a rigid one-piece implant with a 9-mm body, made of clear and colored PMMA to correct aniridia and iris coloboma. The colored outer zone and haptics come in brown, blue or green, but the colors are light, bright and lacking in variegation. (Ophtec makes a variety of aniridia implants, none of which have FDA approval.)

Although Dr. Miller believes that the Ophtec artificial iris has a rightful place in the aniridia armamentarium, he describes its prospects of becoming available in the United States as "probably dead in the water." He participated in a three-year device trial. "The data looked good—as good as these eyes can look," he recalls. Preliminary Phase I results indicated that the model 311 could improve uncorrected visual acuity, glare and photophobia for patients with iris defects and aniridia.[4]

Submission of the formal PMA application to the FDA exposed a technical glitch that doomed the 311 Aniridia Lens, however: The FDA wanted to inspect the facility that made raw materials for the device, but Ophtec informed the FDA that the facility had been shuttered for years. "They had a warehouse full of this material, but they couldn't inspect the plant because the plant no longer existed. The FDA's response was, 'No inspection, no approval,'" Dr. Miller recalls. "They wanted to be able to check the manufacturing process, but we had data that was way better than anything they could get out of inspecting the manufacturing facility, and that was the device itself sitting in people's eyes."

—K.B.

ment or scleral suturing). Regarding the company's modified capsular tension rings, "I have the most experience with the 50F (a 10-mm aniridia ring with occluder panels all the way around, meant to be dialed into the capsular bag against another one) and the 96F (an 11-mm partial aniridia ring with an occluder paddle that covers up to three clock hours), although I have limited experience with some of the others," he says.

Dr. Miller notes that modified intracapsular tension rings are well suited for dimming colobomas or traumatic iris defects that can be covered by the occluder fins on the devices. "I occasionally get patients sent to me who had cataract surgery, and the iris prolapsed out of the incision and then was pushed back in during the surgery," he says "Those patients present with significant sectoral iris trauma and transillumination defects where the temporal side of their iris is chewed up and light pours in through that damaged iris as well as going into the pupil. For that particular patient, the ideal implant would be a Morcher 96F device, where you can put the black occluder panel inside the capsular bag. You orient the paddle underneath the damaged iris, and it will block the light coming in through there." Morcher's iris reconstruction devices are relatively inexpensive, he notes, but cosmetic outcomes are limited by their lack of color options. "For very dark-colored irises, it doesn't really matter if you use a black implant because you're not going to see discrete pupil, per se, but in a blue, blue-green or hazel iris, the option of color is really helpful because the big black defect of those eyes carries with it cosmetic consequences for those patients, in addition to light and glare-sensitivity problems," he says.

The CustomFlex artificial iris is made of soft, foldable silicone, so its implantation requires a smaller incision than is needed for rigid artificial irises.

"I'm the only U.S. ophthalmologist that has permission to implant Morcher devices," Dr. Miller adds. But this is a privilege he had to become a clinical investigator to get, and one he is not exercising at this time: Instead, Dr. Miller wants to bring these devices to the American market so that other surgeons might also use them.

"I actually have my own independent Morcher device trial (*Trial Identifier NCT00812708*), which I've been running for almost 15 years now," he explains. "In the early 2000's, I learned how to file for a compassionate-use device exemption. It took a mountain of time and effort to figure it out." Vowing to never put himself through that process again, Dr. Miller contacted CEO Olaf K. Morcher directly to ask if the company was planning to run a formal device trial in the United States. When Morcher demurred, citing the costs involved, Dr. Miller got his blessing to apply for an IDE and run his own American clinical trial. Dr. Miller and colleagues have investigated compassionate use of several different iris diaphragms,[1] the 96F capsular tension ring with a single black occluder panel[2] and the 50F iris diaphragm,[3] and found them to improve median CDVA and median subjective day and nighttime glare symptom scores.

"Initially, they allowed me to implant 20 devices, and then they allowed me to expand the trial to 70 devices. I used up my allotment several years ago," he continues. "All I'd have to do is ask the FDA to allow me to implant more, and I'm sure they would, but I want to close this study. If I keep asking for more I'll constantly be studying these things. It's hard to enroll these patients: I was enrolling four to five patients a year, so it took years and years to reach 70," he says.

"Since then I've been doing follow-up and data analysis and producing

papers on these devices," he adds. Dr. Miller reports that he's currently working on his final paper, and focusing his next effort on three papers from his Morcher trial that analyze the devices he implanted most. "My plan is to take that data, after formal analysis, to the FDA and see if I can get these devices on the market under some sort of humanitarian device permission, or maybe even a PMA if they'll allow me to do that with single-site, single-investigator data," he says.

CustomFlex Artificial Iris

While Dr. Miller is trying to get Morcher aniridia devices to market, he reports more cause for optimism regarding the CustomFlex artificial iris (HumanOptics AG). "The clinical trial ended a year ago and the regulatory group that's running the trial out of Cincinnati is preparing to file a PMA application within the next several weeks," he reports.

The Customflex is the only artificial iris currently available in the United States—albeit on a strictly limited basis. "It's available for patients who don't mind entering into a continuing-access clinical trial," Dr. Miller explains. "The company petitioned the FDA to allow the device to be implanted in patients after the clinical trial, following the same protocol as the trial. There are about 12 investigators from the original clinical trial that are still implanting the device, including me." The clinical sites are scattered throughout the country, and the protocol requires postop follow-up visits.

At a cost of $5,000 per device, the implant is still out of reach for many patients even without travel-related expenses. "Odds are, there are no investigators anywhere close to you," says Dr. Miller. "So you're going to be hopping on a plane for the initial consultation, for the study enrollment visit, the preoperative visit, the surgery and all the subsequent postoperative visits. It's a big, big hardship."

While clinical-trial participation is seldom easy for patients or investigators, the CustomFlex has some attributes that make implantation less physically traumatic—an important consideration in these eyes. The CustomFlex's soft silicon body can be rolled and then laid flat after insertion, allowing for smaller incisions than those required by some Morcher devices.

> *"The untold story in all of this is that many patients with light-colored irises not only have light and glare sensitivity problems; they also have the emotional baggage that comes along with everybody staring at them, trying to figure out what's wrong with their eye."*
> *— Kevin M. Miller, MD*

The CustomFlex can also be trephined to fit individual patients, or cut to cover smaller segmental iris defects. The CustomFlex comes in a standard diameter of 12.2 mm, but as Dr. Miller notes, "Nobody has a really foolproof way of measuring sulcus diameter. A diameter of 12.2 mm fits quite nicely in average eyes. But for the smaller eyes, you need to trephine the device to fit. The most obvious way of doing that is to put the device in and if it looks too big, take it out, trephinate it and stick it back in," he says. "But implanting these devices is fairly traumatic. You don't want to place them twice. So most of us that are doing this are sort of guessing as to the sizes we need. I have personally built a trephine set that allows me to cut these devices down in 0.2-mm diameter increments. We don't really know how to best size these things. There's room for improvement there."

Although he thinks the CustomFlex gets a great deal right when it comes to color matching, Dr. Miller also sees room for improvement in that area. The manufacturer sends the surgeon a hand-painted CustomFlex iris, plus a spare, based upon an index photograph of the patient's fellow eye. They can paint any natural eye color requested in cases of bilateral aniridia. "Some of them turn out to be too light in color: If they're going to be off, they'll be off in the too-light direction, rather than too dark," notes Dr. Miller. "When you place them under the cornea, they appear a couple of shades lighter in the eye, so if you target for exactly the same color as in the photograph of the iris, the implant is going to wind up being several shades lighter than the fellow eye that we photographed. Another thing that makes them 'pop' more is that the iris in the injured eye is almost always darker in color than the iris in the normal eye, so we also have a contrast between whatever residual iris is still in the injured eye and the lighter color of the artificial iris. So even if the artificial iris is perfectly matched under the cornea to the color of the good eye, you're going to see a contrast between the artificial iris and the residual native iris tissue in the eye. There's no perfect solution."

Imperfections aside, the lifelike detail of the CustomFlex does more than improve glare sensitivity and photophobia in aniridic patients,

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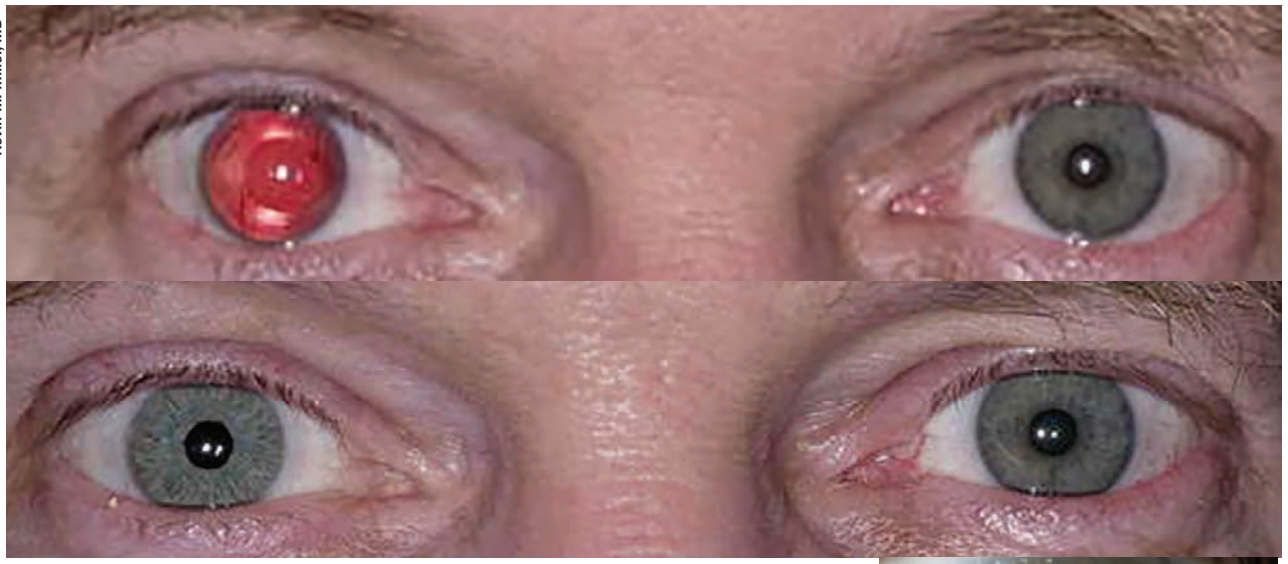

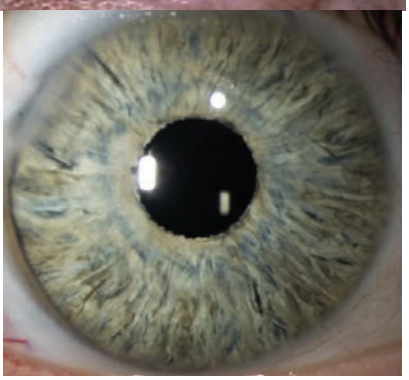

Top: Traumatic aniridia OD, resulting from a flag-football injury, before surgery. Center: The same patient post implantation of a CustomFlex artificial iris, a customized device fabricated to match the fellow eye. Bottom right: A close-up view of the CustomFlex in the postoperative eye. The CustomFlex device is hand-painted to match an index photo of the patient's healthy fellow eye. In bilateral aniridia, the patient can select a naturally-occurring color or use an index photo of another person's iris that they wish to replicate. Manufacturer Humanoptics AG says that in addition to their cosmetic benefits, CustomFlex artificial irises improve glare symptoms and depth-of-field and contrast-sensitivity deficits. This procedure took place in 2010; patients may enter a continued-access trial to receive the implant at this time, but the associated costs are substantial. A future FDA approval may do little to broaden access to the CustomFlex, however, unless insurers will cover its use and a number of surgeons become proficient with it.

according to Dr. Miller. "In the end, except for dark, dark brown irises where you can't see anything, the cosmetic effects of these devices are actually really important to these patients; the lighter the iris color, the more important they become. The untold story in all of this is that many patients with light-colored irises not only have light and glare sensitivity problems; they also have the emotional baggage that comes along with everybody staring at them, trying to figure out what's wrong with their eye. They get treated like they're on drugs or like there's something else wrong with them. They get told they look weird. Kids stare at them in the grocery store checkout line. These patients carry a lot of emotional trauma from that. They've lived with that for a long time," Dr. Miller says.

Continued Hurdles

Aniridia devices have a difficult road to FDA approval for a number of reasons, including the inherent difficulty of designing studies and quantifying improvements in eyes that tend to have many comorbidities. "These are sick eyes," notes Dr. Miller. "So we're taking care of their iris problem in the context of lots of other diseases of the eye. This makes these eyes very hard to study, because the FDA wants to ask, 'How do they see?' Well, if they have congenital aniridia, then the best they're ever going to see is 20/200. But the FDA wants to see a result of 20/20. You can't get 20/20 out of a 20/200 eye. You can't get 20/20 out of an eye that's had three retinal detachment repairs and submacular fibrosis. But those are pretty much average eyes in these studies. So when you compare these device trials to a straightforward lens-implant study where the eyes all end up 20/20, these devices seem terrible. But those are the cards that we're dealt," he says.

Efficacy in the CustomFlex trial was measured by reduction of light and glare symptoms via questionnaire responses. Safety was measured by loss of CDVA, by adverse events and secondary surgical interventions (*Trial Identifier: NCT01860612*).

Prior to the clinical trial, Dr. Miller and colleagues needed to file for compassionate-use exemptions from the FDA to implant the CustomFlex—a process he says requires submitting at least 11 different documents, followed by an IRB application. In early 2017, after the trial for the CustomFlex in the PMA cohort concluded, the manufacturer was allowed to run the continued-access study, which Dr.

Miller anticipates will continue for another year or so. "Now all the reports are being generated to file with the FDA to get a formal approval on the clinical trial," he says.

Eventual FDA approvals will mean little if patients can't afford the CustomFlex or Morcher devices, Dr. Miller cautions. "Once we get the first device approved, the next problem is going to be getting insurance companies to pay for these things—especially the CustomFlex at $5,000 a pop," he notes. "You can imagine the pushback we're going to see from insurers.

"In addition to getting insurance companies to foot the bill for the surgery and the cost of the device, another problem in rolling these devices out is going to be that of training surgeons to use them and avoid all the potential pitfalls," Dr. Miller continues. "All the surgeons in the clinical trial are really world-class surgeons; they've had something of a near-fellowship in the use of these implants. Teaching surgeons how to use the iris devices properly is going to be the final mountain to overcome."

To that end, Dr. Miller and colleagues offer artificial iris device implantation courses at international meetings for surgeons who want to get ready for the coming technology. "I run one at the ASCRS, Academy, and ESCRS meetings. We get the word out," he says. REVIEW

Dr. Miller is an investigator for Morcher GmbH and HumanOptics AG, and has served as an investigator for Ophtec BV. He has not received remuneration in any of these roles.

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Paul M. Larson, MBA, MMSc, COMT, COE, CPC, CPMA

What's an SMRC and Why Should I Care?

A quick look at the SMRC, and how to ensure claims payment.

Many practices get chart requests. There are a few entities that are not as well-known as others, but one of them is currently active in the eye-care world now.

Let's examine some things about the new kid on the block: the Supplemental Medical Review/Specialty Contractor.

Q What is the SMRC program?

A The Centers for Medicare & Medicaid Services does many things to ensure proper claims payment. Sometimes it hires outside entities to assist with this effort. The SMRC program is one such entity. Though they're similar to the Recovery Auditors we hear so much about, SMRCs have a national scope and aren't restricted to one region, specialty or service type. CMS notes that an SMRC will "provide support for a variety of tasks aimed at lowering the improper payment rates and increasing efficiencies of the medical review functions of the Medicare and Medicaid programs." CMS also states that the "focus of the reviews may include, but is not limited to, vulnerabilities identified by CMS internal data analysis, the Comprehensive Error Rate Testing program, professional organizations and Federal oversight agencies … [and that] providers/suppliers must provide documentation upon request."

Q Who is the current SMRC organization?

A In September 2012, CMS selected StrategicHealthSolutions, based in Omaha, Nebraska, as an SMRC. StrategicHealthSolutions lays out its tasks on its website: "[One] of the primary tasks will be conducting nationwide medical review as directed by CMS. The medical review will be performed on Part A, Part B, and DME providers and suppliers to determine whether Medicare claims were billed in compliance with coverage, coding, payment and billing practices. The selection of topics and time frames to be reviewed is determined by and at the direction of CMS. The SMRC is assigned each project through Technical Direction Letters (TDL) issued by CMS." It notes that one of its advantages over recovery auditors is that it conducts "medical review based on the analysis of national claims data versus that limited to a specific jurisdiction."

Q How does the SMRC select who is the subject of a review, and how will I know if I am under review by StrategicHealthSolutions?

A While CMS must direct the topics, some reviews are truly random—others are data-driven. The notice of a review will come in the form of a letter addressed to the provider/practice, and StrategicHealthSolutions is careful to note its authority to do so. The letter tells the practice what the SMRC is, what the practice must do and gives the time frame within which to respond. It also notes that there is not to be any reimbursement for supplying the records to the SMRC. Practices are solely responsible for the costs, even if that practice uses a copying service.

Q Once I turn in the records, how long will I have to wait for a response?

A Generally, responses from the SMRC take about three months. The results letter identifies for the provider whatever does not pass muster. If a practice has claims that have no issues, the SMRC letter notes that "no further action is needed" or something similar for those particular records.

Q What topics is the SMRC currently reviewing?

A There are currently two active SMRC "projects":

- Project Y3P0225 – Blepharoplasty and other related facial procedures.
- Project Y3P0239 – Ophthalmology Services.

The Blepharoplasty project is focused on medical support for functional eyelid surgery. Ptosis surgery is included. The Ophthalmology Services project has a wide scope and includes support for cataract surgery, eye exams, diagnostic testing and a few others. There is a third project related to Lucentis, but it is wrapping up.

Q What happens if I sent in documentation that didn't pass?

A The SMRC gives a provider an " … opportunity for a Discussion/Education Period … The Review Results Letter will inform providers if the project is eligible for a Discussion/Education Period [which] is intended to allow for the review of specific claim denials, deliver rationale and education for the determination(s), and provide information on how the denial can be avoided in the future. Additionally, if a provider determines there is additional information and/or documentation relevant to supporting payment of the denied claim(s), the provider may submit the additional information and/or documentation. All Discussion/Education Period requests must be in writing."[2] If you're allowed this opportunity for discussion, you have 30 days from the date of the letter to respond. One of the options is to have a teleconference, but that's not always required.

It's possible that the SMRC might alter its decision based on additional information you send during this period. If the SMRC still feels you have not met the required standard, CMS states that "StrategicHealthSolutions, LLC has a responsibility to notify CMS of any identified improper payments and noncompliance with documentation requests." CMS does this most often by notifying your Medicare Administrative Contractor. The MAC may initiate claim adjustments and/or overpayment recoupment actions through the standard overpayment recovery process.

Q What happens if I miss the deadline?

A Don't! Anything received after 30 days is considered invalid by the SMRC, so be sure and send via an appropriate method with delivery tracking of some sort.

Q What else should I be aware of?

A Be sure the person opening the mail in your office knows what StrategicHealthSolutions is and how important it is to get the letter to you right away. Also, don't assume the person reviewing your documents for the SMRC will know, for example, that optical coherence tomography images are in color if you send them in black-and-white. You don't know who the reviewer will be or their sophistication relating to eye care. Make your best effort the first time, which includes sending a written summary in addition to your records if you feel this will help give the reviewer a better clinical picture. REVIEW

Mr. Larson is a senior consultant at the Corcoran Consulting Group. Contact him at plarson@corcoranccg.com.

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2. https://strategichs.com/smrc/discussion-period-or-education-session/. Accessed 17 August, 2017.

Three New Algorithms For Treating Dry Eye

Christopher Kent, Senior Editor

New guidelines aim to help clinicians make sense of today's dry-eye management options.

Once upon a time, dry eye was treated as a simple, straightforward problem—one that wasn't terribly important—and it was addressed with a few predictable treatment options. Today, a growing body of knowledge about the causes of dry eye signs and symptoms, along with an ever-increasing number of diagnostic tests and treatment options, has made effective management of dry eye a much more complex challenge. At the same time, ophthalmologists have realized that dry eye can have far-reaching impacts on vision—not to mention altering the outcome of other interventions such as refractive surgery.

As the complexity of managing dry eye has grown, so too has clinicians' need for help in navigating the sea of diagnostic and treatment options. This year, that focus has culminated in the appearance of three new algorithms intended to make dry-eye management easier for the clinician. Here, three surgeons who helped to develop these algorithms explain how the algoriths were created, the intended thrust of each algorithm and how they differ from one another.

TFOS DEWS II

One of this year's three new dry-eye treatment algorithms is part of the Tear Film and Ocular Surface Society Dry Eye Workshop II report, better known as TFOS DEWS II. TFOS DEWS II was recently published as a series of focused reports in the July 2017 issue of *The Ocular Surface*; the series includes a Management and Therapy Report that discusses the new treatment algorithm. (TFOS DEWS II also offers updates of the definition, classification and diagnosis of dry-eye disease, as well as an assessment of its etiology, mechanism, distribution and impact.)

The intention of the authors was to make the TFOS DEWS II report evidence-based. Accordingly, the members of the management and therapy subcommittee reviewed the literature concerning current treatment options of all types, including treatments for tear insufficiency and lid abnormalities, anti-inflammatory medications, surgical approaches, dietary and environmental modifications and complementary therapies, to determine what concrete evidence currently exists to support each option.

"In this report we discuss almost every treatment that's ever been described, even options such as using honey in the eye," notes J. Daniel Nelson, MD, FACS, FARVO, professor of ophthalmology at the University

TFOS DEWS II Dry-eye Treatment Algorithm

Step 1:
- Education regarding the condition, its management, treatment and prognosis
- Modification of local environment
- Education regarding potential dietary modifications (including oral essential fatty acid supplementation)
- Identification and potential modification/elimination of offending systemic and topical medications
- Ocular lubricants of various types (if MGD is present, then consider lipid-containing supplements)
- Lid hygiene and warm compresses of various types

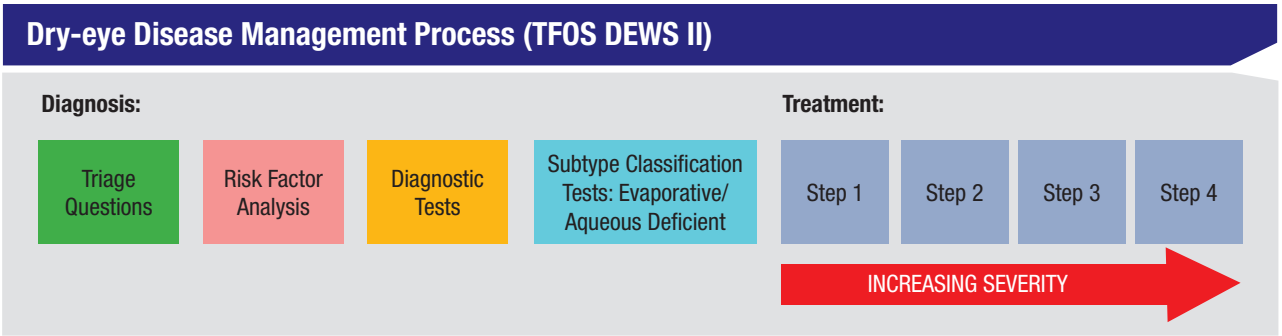
Step 2: If the above options are inadequate, consider:
- Nonpreserved ocular lubricants to minimize preservative-induced toxicity
- Tea tree oil treatment for Demodex (if present)
- Tear conservation
  - — Punctal occlusion
  - — Moisture chamber spectacles/goggles
- Overnight treatments (such as ointment or moisture chamber devices)
- In-office, physical heating and expression of the meibomian glands (including device-assisted therapies, such as LipiFlow)
- In-office intense pulsed light therapy for MGD
- Prescription drugs to manage DED *[Note: The use of prescription drugs needs to be considered in the context of the individual patient presentation, and the relative level of evidence supporting their use for that specific indication, as this group of agents differs widely in mechanism of action.]*
  - — Topical antibiotic or antibiotic/steroid combination applied to the lid margins for anterior blepharitis (if present)
  - — Topical corticosteroid (limited duration)
  - — Topical secretagogues
  - — Topical nonglucocorticoid immunomodulatory drugs such as cyclosporine
  - — Topical LFA-1 antagonist drugs (such as lifitegrast)
  - — Oral macrolide or tetracycline antibiotics

Step 3: If the above options are inadequate, consider:
- Oral secretagogues
- Autologous/allogeneic serum eye drops
- Therapeutic contact lens options
  - — Soft bandage lenses
  - — Rigid scleral lenses

Step 4: If the above options are inadequate, consider:
- Topical corticosteroid for a longer duration
- Amniotic membrane grafts
- Surgical punctal occlusion
- Other surgical approaches (e.g., tarsorrhaphy, salivary gland transplantation)

The authors of the TFOS DEWS II treatment algorithm note that when patients do not respond to a given level of management or exhibit more severe dry-eye disease, the next level of management is recommended; in some cases, the previous therapy may be continued. Options within a category are not ranked according to importance and may be equally valid. Management options chosen should be dictated by the severity and etiology of the DED state. (For more information, see Jones, Downie, Korb et al, 2017.[1])

of Minnesota and an ophthalmologist in the HealthPartners Medical Group in Bloomington, Minn. (Dr. Nelson was chair of the TFOS DEWS II report project.) "However, the focus is on the literature: Which treatments can be recommended based on the evidence? What's the pathophysiological justification for a given approach? Of course, we do understand that very new treatment options may not have a lot of support in the literature yet, and



The TFOS DEWS II report proposes following a process like the one pictured above when initiating dry-eye treatment. The authors note that this is not a rigid, stepwise approach, but an organizational tool. They also note that when diagnosing and deciding on a treatment there is a broad spectrum of disease that may encompass both evaporative and aqueous-deficient dry eye.[1]

that this is not necessarily a reflection on the validity of that treatment."

Dr. Nelson says a big part of choosing an appropriate treatment still comes down to determining whether the problem is primarily evaporative or aqueous-deficient, or a combination of both. "One of the big challenges of the report was how to define the subtypes of dry eye," he says. "We opted to define it in terms of aqueous-deficient and evaporative disease. These classifications have been used for many years; everybody understands them, and in general they are probably the closest you're going to get to the right terms. However, it's clear that there's a huge overlap between evaporative and aqueous-deficient dry eye. In fact, the report emphasizes that the lipid layer is not solely responsible for preventing evaporation; the entire tear film is involved. So even in an aqueous-deficient eye, you're going to end up having an evaporative component."

Severity-based Treatment

The recommendations in the TFOS DEWS II treatment algorithm are based on four levels of disease severity. Dr. Nelson explains the four stages and how they've been modified since the first TFOS DEWS report. "The new algorithm can be thought of as taking things from the least interventional—and in some cases the least expensive and least risky—up to more significant interventions with greater cost and perhaps more risk," he says. "Stage one is largely focused on education, topical lubricants and physical therapy—meaning lid hygiene and warm compresses. At this stage you're identifying whether the patient has any systemic conditions such as Sjögren's; you might need to treat the patient systemically for that disease. The options at this level are mostly the traditional treatment options, although we've added dietary modifications such as the addition of omega-3 fatty acid supplements.

"Stage two is partly concerned with the presence of inflammation," he continues. "It adds in new treatment alternatives designed to counteract inflammation, including prescription drugs such as topical antibiotics, corticosteroids, secretagogues, cyclosporine A, lifitegrast, nonglucocorticoid immunomodulatory drugs and oral macrolides like azithromycin. It also includes tea tree oil to treat Demodex, and intense pulsed light therapy.

"If those treatments are not adequate, stage three is more interventional, both with nonprescription medications and interventions such as punctal occlusion," he says. "This stage involves more aggressive approaches, including oral medications such as secretagogues, as well as autologous serum and therapeutic contact lenses. Finally, stage four includes options such as using topical corticosteroids for a longer duration, and amniotic membranes. Also, if you're at this level and punctal plugs aren't staying in place, you might want to resort to surgical punctal occlusion and/or tarsorrhaphy."

In the management report, the authors state that their treatment algorithm should not be seen as a rigid, stepwise approach, but as an organizational tool to aid treatment decisions. They believe the heterogeneity of this patient population precludes an overly formulaic approach, so treatment should be individualized based on each patient's signs, symptoms and situation. "As all clinicians treating dry eye know, you often have to customize your treatment to the patient," Dr. Nelson says. "You may start with steps one and two; or you might jump to step three. If a patient comes in with Sjögren's and severe dry-eye symptoms, I'll be using treatments from stages one, two and three all at the same time. Based on experience, I know that this patient will require more than just the topical interventions; the patient will need topical anti-inflammatories, and I may have to treat with systemic medications. So dry-eye treatment is not really linear. Our algorithm can be seen as a list of options that we suggest you try."

Dr. Nelson notes that the choice of which treatment options to pursue may be partly risk-based. "If a patient's dry-eye problem is clearly not an im-

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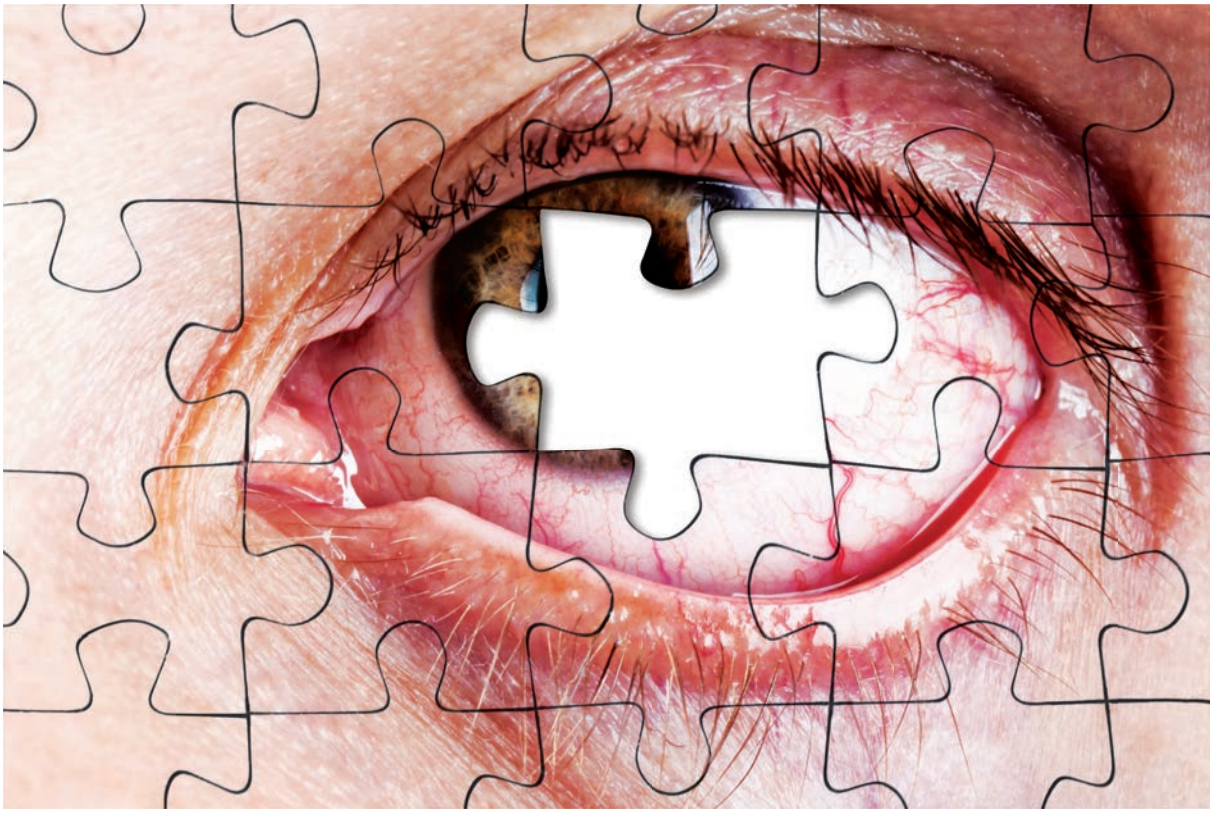

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mediate threat to her cornea or vision, you know you've got more time to try alternatives than when somebody comes in with a lot of corneal staining, perhaps a big epithelial defect, filaments, and so forth," he says. "In the latter situation you know you'll have to be more aggressive or you might put the eye at risk."

Dr. Nelson says he believes that new alternatives that appear in coming years will still fit into one of these four treatment stages. "If the world's greatest artificial tear comes along and solves everybody's problems, that would still probably be a stage-one treatment," he says. "On the other hand, if we came up with a great surgical treatment, that would still likely be stage four because it wouldn't be the first thing you'd jump to."

The CEDARS Algorithm

Another dry-eye treatment algorithm was published earlier this year by the Cornea External Disease and Refractive Society, or CEDARS.[2] It takes a different approach to dry-eye disease treatment than the TFOS DEWS II report.

A driving force behind the CEDARS algorithm was Mark S. Milner, MD, FACS, associate clinical professor at Yale University School of Medicine and co-founder and co-medical director of the Precision LASIK Group in New Haven, Conn. "I've had a niche dry-eye practice for 15 or 20 years now," he explains. "I give many lectures every year on dry-eye disease and related clinical studies, and I've noted that most dry-eye treatment algorithms are based on severity," he says. "They suggest treating mild dry eye differently than moderate or severe dry eye.

"Although this approach is commonly accepted and considered to be standard-of-care, I thought the focus of such an algorithm should be on the diagnosis rather than the severity," he continues. "I've always felt that it didn't make sense to treat mild aqueous deficiency the same as you'd treat mild blepharitis. So for the past 15 years or so I've been teaching a different way of approaching dry-eye disease, and that approach culminated in the CEDARS treatment algorithm that we recently published."

> *"If you separate your dry-eye patients into four categories instead of two, you could have a much more directed treatment."*
> *— Mark S. Milner, MD*

Dr. Milner notes that most doctors treating dry eye separate patients into two categories: aqueous deficiency and evaporative disease. "The problem is, evaporative disease is a very big category," he says. "I realized that if you separate your dry-eye patients into four categories instead of two, you could have a much more directed treatment. Aqueous deficiency is one category, but you can break up evaporative dry eye into three separate categories. The first is evaporative based on goblet cell or mucin deficiency. The second category is blepharitis, although it is possible to have blepharitis without necessarily having an evaporative problem. The third evaporative category is exposure-related dry eye. These patients have an evaporative problem because their eyes are not closing all the way."

Eventually, Dr. Milner took this line of reasoning one step further. "In 2009, after giving a lecture at the New England Ophthalmic Society, I realized that we needed a fifth category, which is what I call the co-conspirators," he says. "The co-conspirators are those diseases that masquerade as dry eye or exacerbate it. Masqueraders include Thygeson's superficial punctate keratopathy; superior limbic keratoconjunctivitis; medication toxicity or medicamentosa; mucous fishing syndrome; conjunctivochalasis; allergic/atopic keratoconjunctivits; and chemical toxicity. A lot of these are often misdiagnosed as dry eye. If a patient has one of these problems, you may be spinning your wheels trying to treat the patient for dry eye, and not have much success.

"We look at the CEDARS algorithm as a better approach to treating dry eye," he continues. "Now, when patients walk in with keratitis signs and symptoms, we can separate them into the four categories: aqueous deficiency; evaporative based on goblet cell and mucin deficiency; blepharitis; and exposure. Then our algorithm provides a first-, second- and third-line treatment you can use in each situation, based on the diagnosis—not necessarily based on severity. If none of these diagnoses makes sense, then we look for the co-conspirators."

Maximizing Options

In addition to the CEDARS algorithm's focus on multiple diagnostic categories rather than severity, it also includes a broad range of treatment suggestions. The published report[2] discusses each treatment in detail and provides references with clinical evidence supporting its use—if any exists. "I use a lot of esoteric treatments for dry eye, things that many clinicians don't commonly use," explains Dr. Milner. "In addition to options such as topical hormones and autologous serum, I sometimes treat with albumin or medroxyprogesterone or DHEA drops. Many of these options are off-label and compounded, so they're not commercially available.

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CEDARS Recommended Treatment Options for Dysfunctional Tear Syndrome*

Treatment option	Aqueous tear deficiency	Blepharitis/meibomian gland dysfunction (evaporative or nonevaporative)	Goblet-cell deficiency/ mucin deficiency	Exposure-related DTS
First line	• Tear supplements and lubricants (i.e., drops, gels, ointments, sprays and lubricating inserts) • Nutritional supplements • Topical cyclosporine • Topical lifitegrast • Topical steroids • Topical secretagogues • Moisture chamber eyewear	• Tear supplements and lubricants (i.e., drops, gels, ointments, sprays and lubricating inserts) • Lid hygiene and lid scrubs (i.e., cleansers, warm compresses, and massage) • Nutritional supplements • Topical cyclosporine • Topical lifitegrast • Topical erythromycin/ bacitracin • Topical azithromycin • Topical steroids or antibiotic/ steroids	• Tear supplements and lubricants (i.e., drops, gels, ointments, sprays, and lubricating inserts) • Topical cyclosporine • Topical lifitegrast • Vitamin A ointment – retinoic acid (compounded) • Moisture chamber eyewear • Topical secretagogues	• Tear supplements and lubricants (i.e., drops, gels, ointments, sprays, and lubricating inserts) • Taping of the eyelid • Moisture chamber eyewear
Second line	• Oral secretagogues • Topical hormones (compounded) • Autologous serum (compounded) • Albumin (compounded) • Bandage contact lenses/ scleral lenses • Topical dapsone (compounded) • Topical tacrolimus (compounded) • Topical *N*-acetylcysteine	• Oral doxycycline/tetracycline • Tea tree oil • Topical metronidazole ointment or drops (compounded) • Topical doxycycline (compounded) • Topical clindamycin (compounded) • Topical dehydroepian-drosterone (compounded) • Topical dapsone (compounded) • Topical N-acetylcysteine	• Scleral lenses	• Scleral lenses
Procedures	• Punctal plugs • Cautery occlusion • Amniotic membrane transplantation	• In-office thermal pulsation and/or lid massage • Debridement of the lid margin • Intense pulsed light • Meibomian gland probing		• Eyelid surgery (i.e., correction of lid malposition and tarsorrhaphy)

* The order of treatment in each category is left to the clinical judgment of the clinician and the preference of the patient.

The CEDARS treatment algorithm is arranged by diagnostic category rather than disease severity. It was intended to cover a comprehensive list of treatments, including many that are off-label and compounded, as well as many that are not widely known in the ophthalmic community. It provides first-, second- and third-line treatments that can be used in each situation—though not necessarily based on the severity of the patient's disease. (For more information, see the complete published report.[2])

"For example," he continues, "I often use topical metronidazole ointment to treat blepharitis. It's a very efficacious treatment that most doctors are aware of as a treatment for rosacea dermatitis, but few are using for blepharitis. Metrogel is a commercially available treatment for rosacea dermatitis on the face, but some compounding pharmacies will make it into an ophthalmic preparation that's great for posterior blepharitis secondary to rosacea. I've used it for 20 years. It's safe and easy to use and works well.

"Several of my colleagues in the Cornea Society were discussing dry-eye algorithms, and we decided that this particular approach was worth publishing," he recalls. "This was what initially led to the idea of creating an algorithm refined by a CEDARS panel. So about two years ago with the help of Ken Beckman, MD, and Jodi Luchs, MD, co-authors on the paper, we started the process of forming a CEDARS dry-eye panel, and earlier this year we published the algorithm."

Dr. Milner points out that the report also returns to the use of the briefly popular term "dysfunctional tear syndrome." "I believe it makes sense to go back to this because the term 'dry-eye disease' seems to imply to the

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patient and doctor that the problem is just a lack of tear production," he explains. "Calling it dysfunctional tear syndrome does a better job of conveying that it's not just about tear quantity—it's about tear quality as well. The reality is, we need to treat both the abnormal quality and quantity of the tear film."

But Will They Use It?

A key issue with any algorithm is whether clinicians will actually find it useful. "For the past 10 years, I've taught this diagnosis-based approach," Dr. Milner says. "The feedback from doctors has been very positive. Dry eye is a very complex disease, for many reasons, and for years we've had very few good treatments. Now we have two commercially available drugs, and although this has helped, doctors are still frustrated. Doctors say that they love Restasis and Xiidra, but ask what else they can do when they need to add additional treatments. The CEDARS algorithm lists a lot of esoteric treatments, as well as a nice road map on how to add them to a treatment regimen, based on what they find and what the patients are saying. I think it's a more directed approach to solving a lot of our dry-eye treatment problems."

Dr. Milner notes that many doctors don't think of dry eye as a multitreatment disease. "In my experience, that's a mistake," he says. "Dry eye, like glaucoma, is often a multitreatment disease, especially if the disease is more severe. Patients may need cyclosporine and lifitegrast and plugs and maybe a topical antibiotic. Our algorithm helps provide numerous treatment alternatives to try in those situations."

The ASCRS Algorithm

A third dry-eye management algorithm is being developed by the American Society of Cataract and Refractive Surgery's corneal committee. (The ASCRS algorithm should be published before the end of 2017.) Francis Mah, MD, who specializes in cornea, external disease and refractive surgery at Scripps Health System in San Diego, is a member of that committee; he explains the thrust of their approach and how it differs from the other two algorithms already published.

> *"[The ASCRS algorithm] is a much more specific type of algorithm. We go into detail about what to do, and what order to do it in: If you find this, then do that. It's almost like a recipe."*
> *— Francis Mah, MD*

"Christopher E. Starr, MD, FACS, a cornea specialist at Weill Cornell Medicine in New York, has been leading the charge in this endeavor," notes Dr. Mah. "At this point, the algorithm has been approved by all of the committee members. In fact, we've already put it into use in the clinic, and we're preparing to publish a second paper talking about how the algorithm works in real clinical practice."

Dr. Mah notes several differences between the ASCRS algorithm and the others. "The CEDARS algorithm is extremely inclusive," he says. "It incorporates a lot of different tests and therapies, many of which are not FDA-approved. I see it less as an algorithm than an encyclopedic list of everything relating to treating the ocular surface.

"The TFOS DEWS II algorithm is very scientific; they reference the medical literature extensively," he continues. "However, it's a very simple algorithm that leaves a lot up to the clinician. I think it's more a source of suggestions and guidelines than a specific description of how to proceed. For example, in each stage they list some treatment options, but they don't go into great detail as far as the specific order in which to use them. The same thing is true of their diagnostic recommendations.

"Ours is a much more specific type of algorithm," he notes. "We go into detail about what to do, and what order to do it in: If you find this, then do that. It's almost like a recipe. We also go into great detail about conditions besides dry eye and blepharitis, such as allergic conjunctivitis, infectious, viral or bacterial conjunctivitis, and anterior basement membrane dystrophy, many of which can masquerade as dry eye or blepharitis. In general, our algorithm is a lot more specific, provides a lot more direction, and is a lot more inclusive in terms of diagnoses and some of the masqueraders."

Dr. Mah says that the ASCRS committee has been very conscious of the other groups' efforts. "We started this process a couple of years ago, about the same time as the DEWS II group," he explains. "We have members who are part of the same committees and groups as DEWS II and CEDARS. So of course we wanted to make sure we were not duplicating or taking information from the other groups. We wanted to make sure ours would be a unique algorithm. In fact, we delayed our algorithm so that we could ensure that we weren't duplicating what the Tear Film and Ocular Surface group was doing."

Laying It Out, Step by Step

Dr. Mah notes that it's common practice to divide treatment

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algorithms by levels of severity. "I'm co-chair of the committee working on AAO's revised Preferred Practice Pattern for cornea, and we do divide our recommendations into mild, moderate and severe disease," he says. "However, the ASCRS algorithm for dry-eye management is divided by diagnosis first. Omitting this from the treatment algorithm assumes the clinician is making the correct diagnosis, which may not be the case, given all of the diagnostic challenges involved in managing dry eye.

"As in our treatment algorithm," he continues, "our recommendations for diagnosis are laid out in a step-by-step manner. If this test is positive and that test is negative, that means that the diagnosis is in this direction; and with this diagnosis, the next step is testing for X, Y or Z. In fact, we've designed the diagnostic algorithm so that it can be hung up in an eye specialist's exam lane."

Dr. Mah says the committee has worked to incorporate all of the tests that are currently available into their diagnostic algorithm. "We want to help clinicians make sense of all of the different point-of-care tests that are out there, and provide guidance on how to incorporate them logically and inclusively," he says. "For example, the algorithm includes using a questionnaire; testing for osmolarity and/or inflammation—specifically MMP-9—and looking at tear-film interferometry. So it's not a question of 'Should I buy this or that test?' It's, 'If I have access to two or three tests, how do I incorporate them to make sense of the information I'm getting to try to come up with a cogent thought process as far as the diagnosis?'

"Ultimately, we hope this will become an online algorithm that will allow you to input whatever testing information you have, whether you're using one test, multiple tests or no tests," he says. "The online algorithm will then provide a tentative list of diagnoses. Such an online system could be similar to the current ASCRS refractive surgery website, where you put in the information that you have and whatever calculations you've completed, and it comes up with some options for you. Obviously this would grow and develop to incorporate new tests as they appear, and to reflect the latest medical literature.

"Once you have a diagnosis, then our treatment algorithm takes over," he adds. "Depending on the diagnosis, we describe various treatments that can be used to manage, for example, meibomian gland dysfunction or aqueous deficiency, or a combination of the two, or bacterial conjunctivitis, or adenoviral conjunctivitis or allergic conjunctivitis."

Keeping Things in Perspective

Dr. Mah stresses that the committee's goal was to make its algorithm(s) clinically useful. "All the dry-eye management algorithms have benefits," he says. "I think this is currently a very confusing area, because we have a lot of information, but there's still a lot of information that's lacking. Ocular surface disease is a huge, diverse area, yet we're trying to narrow everything down to one diagnosis.

"I believe that as we get more information things will be better elucidated, but in the meantime, anything we can do to make things better for clinicians and their patients is a step in the right direction," he continues. "Our focus was on making sure that our algorithm is clinically useful in the everyday interaction between clinicians and patients. However, I think there's merit and value to all three algorithms. I don't think there's supposed to be a winner or loser, or one that gets discarded. They should all be helpful to clinicians."

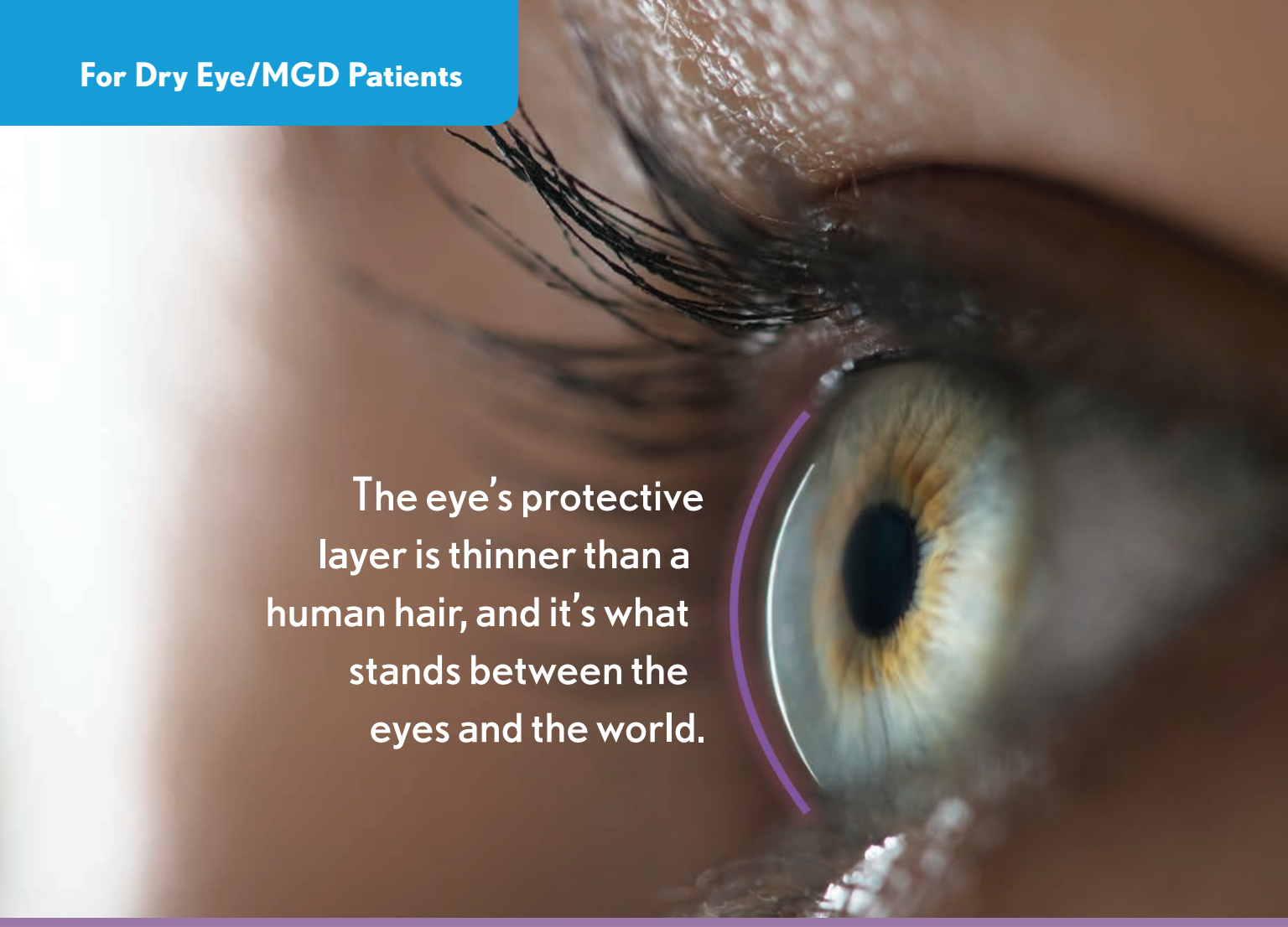
Looking at dry-eye management from a historical perspective, Dr. Mah says we're still early on in the grand scheme of things. "The traditional ways of approaching dry eye still have value," he says. "It's still important to look at conjunctival and corneal staining with fluorescein and lissamine green; it's still very important to do tear-film breakup time; it's still important to look at the meniscus and the meibum that's being expressed from the meibomian glands. None of the new tests or treatment approaches are so groundbreaking that we should discard what we've been doing all along.

"I hope that this year's focus on dry-eye management algorithms will help to increase clinicians' awareness and stimulate discussion," he concludes. "Dry eyes and ocular surface disease impact the majority of our patients. If these algorithms increase awareness and help clinicians understand dry-eye disease better, that will translate into better patient care. Even with all of the information about dry eye that's been disseminated over the past couple of years, there are still many doctors who aren't really thinking about it. If we can get everybody to look at it and not dismiss it as something just for the cornea specialist or dry-eye specialist, that will be a big step forward." REVIEW

Dr. Milner has financial interests with Allergan, Shire, Bausch + Lomb, TearScience, Aldeyra Therapeutics, Eleven Biotherapeutics, Kala Pharmaceuticals, and Refocus Group. He's a speaker and consultant for Allergan, Shire, TearScience and Sun Pharmaceuticals and owns stock in RPS (Rapid Pathogen Screening). Dr. Mah is a consultant for TearLab, Allergan and Shire. Dr. Nelson is conducting research for Santen Pharmaceuticals and is on the medical advisory board for TearSolutions.

1. Jones L, Downie LE, Korb D, et al. TFOS DEWS II management and therapy report. The Ocular Surface 2017;15;3;575-628.
2. Milner MS, Beckman KA, Luchs JI, et al. Dysfunctional tear syndrome: Dry eye disease and associated tear film disorders - new strategies for diagnosis and treatment. Curr Opin Ophthalmol 2017;27:Suppl 1:3-47.

For Dry Eye/MGD Patients



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[1]Blackie CA et al. Cornea 2009 (v0.1) p.1.

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Blepharitis: Know What to Look For

Liam Jordan, Associate Editor

Experts provide tips on how to recognize and eliminate bouts of blepharitis ranging from mild to acute.

American psychologist Abraham Maslow once said, "I suppose it is tempting, if the only tool you have is a hammer, to treat everything as if it were a nail." Ophthalmologists often have the opposite problem; they have plenty of hammers, but may be unsure about the nature of the nail.

A disease like blepharitis is a classic example. There are several types of blepharitis and multiple causes, and your armamentarium can be rendered ineffective if you don't accurately identify the precise nature of the problem. Only by understanding the disease can a physician effectively diagnosis and treat it. Thus, deciphering and identifying the unique signs and symptoms of blepharitis pave the way for effective treatment.

The Blepharitis Basics

Blepharitis is an inflammatory condition associated with redness, itchiness and flaking and crusting of the eyelids, found in both children and adults. Classifications of the disease range from chronic to acute, and anterior vs. posterior. Anterior blepharitis is typically the result of Demodex mite infestations, or bacteria found on the eyelid. Seborrheic blepharitis is one type of anterior disease in which patients often find flaking in their eyebrows or lashes. The more typical type of blepharitis is posterior, known as meibomian gland disease or dysfunction.

As well as causing general discomfort and inflammation for patients, blepharitis can also affect the outcomes of cataract and refractive surgery, so it's important for physicians to remain vigilant for this often-overlooked condition.

Symptoms

In a study looking at the symptoms and causes of dry-eye disease, researchers noted that up to 20 percent of adults over the age of 45 reported some discomfort from blepharitis and meibomian gland dysfunction.[1] From there, the reported cases of blepharitis increase to the point where it's present in 68 percent of patients over the age of 60.[2] Because of the prevalence of the disease, physicians need to be on the lookout for symptoms that indicate either acute or chronic blepharitis.

Some of the most common symptoms and signs of blepharitis are:

- lid-margin inflammation or redness;
- collarettes around the base of each eyelash;

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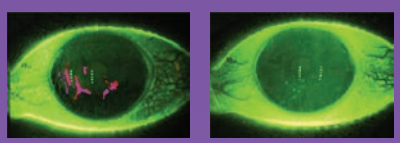

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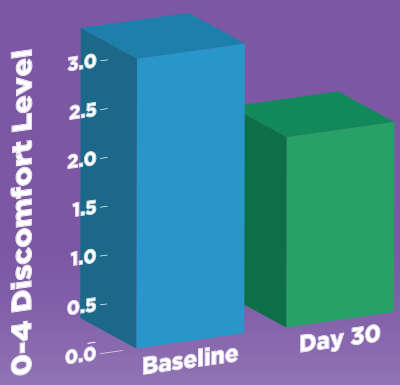
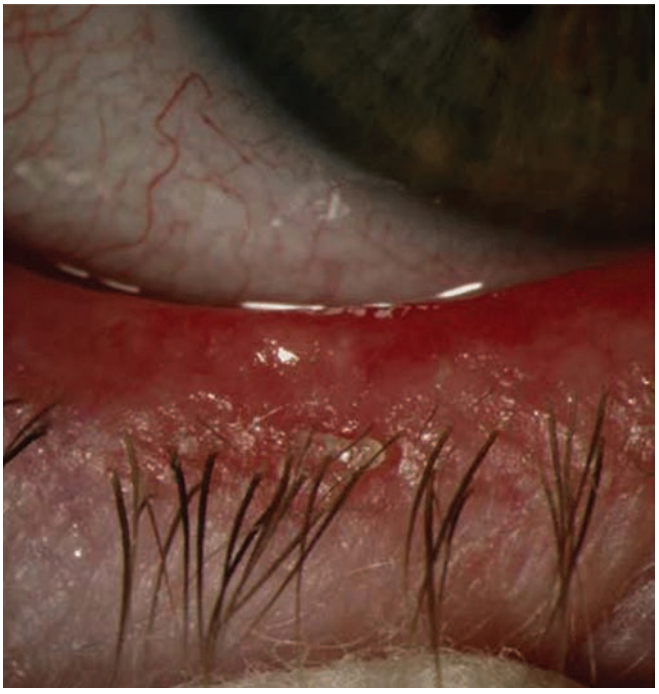


- the thickening and cloudiness of the clear oil of the meibomian glands;
- lash loss;
- complaints of itching or a tickling sensation around or on the eyelids; and
- the presence of Demodex mites.



A case of blepharitis displaying eyelid inflamation and collarettes around the base of the lashes.

Telltale Causes

Demodex mites. A Demodex mite infestation can incite blepharitis. In a 2010 study on the role of Demodex mites in blepharitis, researchers found that the incidence of Demodex infestations increases with age, affecting 84 percent of the population at age 60 and 100 percent of those older than 70 years.[3]

The two species of Demodex found to cause blepharitis are *Demodex folliculorum* (anterior blepharitis, with issues associated with the eyelashes) and *Demodex brevis* (posterior blepharitis, with issues related to the meibomian gland and keratoconjunctivitis).

Staphylococcal infection. "This type of anterior blepharitis is a result of a bacterial infection," Meraf Wolle, MD, an assistant professor of ophthalmology at Johns Hopkins University, says. "You'll typically see some gold crusting on the lid margins. As long as there are no resistant bacteria, an antibiotic will usually clear this up."

Seborrheic. "Patients with seborrheic blepharitis usually complain of eyelash flaking, along with the redness and irritation you typically see with other types of blepharitis," Dr. Wolle says. Due to these symptoms, it's often mistaken for other common skin conditions such as eczema, so it may be overlooked.

Rosacea. Due to the nature of rosacea, this skin condition also affects the eyes of patients, paving the way for blepharitis to take root, so the two often present hand-in-hand.

Meibomian gland dysfunction. Because the meibomian glands don't secrete enough oil into the tears, they evaporate too quickly, which can result in dry eye. "This one is tricky, because blepharitis can either be the cause or the result of meibomian gland dysfunction," says Dr. Wolle. "MGD is usually identified by tear-duct obstruction and changes in glandular secretion, which will lead to the irritation you usually see with blepharitis."

Diagnostic Issues

Because so many patients present with some sort of untreated blepharitis, identifying and diagnosing the disease can be a tricky issue. Robert Noecker, MD, an ophthalmologist based in Fairfield, Conn., discusses the challenges of identifying blepharitis before it gets into its acute stages. "It's a double-edged sword. In some ways, diagnosis is relatively straightforward, but on the other hand, blepharitis flies under the radar a lot because it usually comes in the context of other things," he says. "Other types of dry-eye issues or ocular surface diseases and such can sometimes come packaged with blepharitis. Patients taking glaucoma medication probably all have some degree of blepharitis. So if a doctor isn't careful, and looking for Demodex mites or crusting on the lids and lashes, the symptoms of blepharitis might be dismissed as those of dry eye or some other issue."

Dr. Wolle highlights the important role that the patient's age plays in her diagnosis and personalized treatment. "Usually it's present in elderly women, but you can find it in the whole gamut," she says. "However, because our older patients are usually suffering from some other eye disorder (typically dry eye and/or glaucoma), and are on medications for said disorder, we have to be careful about administering another medications that may interact with what they're already prescribed."

Dr. Noecker also discusses the importance of demographics and how they can affect the severity of the disease. "Immune problems like cirrhosis also exhibit symptoms and cases of blepharitis. Blepharitis tracks into the portions of the population that typically have eye concerns (dry-eye patients, glaucoma), so once you get into the later stages of your life,

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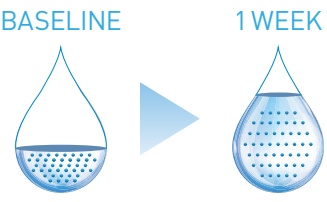

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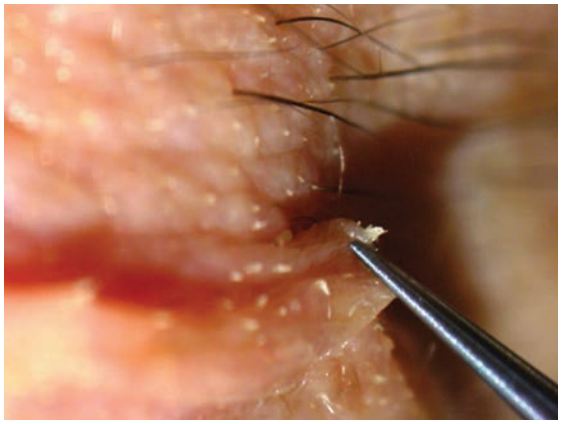
you're more likely to have it," he says. "But it can happen to anyone. Allergy season can contribute to flare-ups. Treatment just comes down to the chronicity of it."

Dr. Noecker continues, providing some advice for a quick and accurate diagnosis. "It's like everything else. The more you look for it, the more you'll find it. In an exam, sometimes you have the tendency to just go for the cornea, and not look at the lids or the meibomian glands. This contributes to the ocular surface dysfunction," he says. "Following patients' questionnaires is important, too. You have to look at what they write and pay close attention to both signs and symptoms. Just performing a quick external examination before they pop their head into the slit lamp makes a big difference, too. The due diligence can get away from you sometimes.

"It's just saying, 'Okay, I'm going to take these five seconds of the exam and pay attention to the eyelid margin,' and actively doing that," Dr. Noecker adds. "We have to mentally check the list we have in our heads as we step through the exam. It's about awareness and making it a part of your typical clinical exam. Once you're aware of it, the treatment is determined by whatever you think the underlying cause is, and whether it's anterior or posterior blepharitis."

Dr. Wolle also provides some advice for identifying blepharitis. "The eye exam really starts with looking at the lids, and that's where we sometimes don't focus. Or maybe it's not as extreme as one expects. Maybe there are just a few collarettes hanging on the base of the lids, so they are overlooked," she says. "Those types of blepharitis are more extreme because of the mites. Sometimes you don't see the crusting or the mucus on the lashes, so one should really focus on the lashes as well as the lid margin. Paying close attention to the lashes and lids will allow you to catch most of the cases."



In this case, a patient presented with both rosacea and Demodex mites.

"It's like everything else. The more you look for it, the more you'll find it. In an exam, sometimes you have the tendency to just go for the cornea, and not look at the lids or the meibomian glands. This contributes to the ocular surface dysfunction."
— Robert Noecker, MD

Treatment Options

Because of the different types of the disease, the treatments (or, rather, management) vary. Underlying causes and conditions should be addressed first (dry eye, etc.) so that recurring bouts of blepharitis are minimized. Once underlying causes are taken care of, symptoms can be tackled, experts say.

Dr. Wolle highlights the different approaches to treating this problematic disease. "For the chronic treatment of blepharitis, the main therapy is going to be warm compresses for at least five minutes, followed by lid massages or scrubs twice a day to get rid of recurring bouts," she says. "If it's more than a mild bout, the patient can apply some topical antibiotic ointment to the eyelids during or after the warm compresses to help manage it." While these lid scrubs and compresses aren't cures for the condition, they can provide relief, while eliminating lid-margin debris and bacteria.

"Now for acute blepharitis, you have a few options," she says. "Typically, you can administer an antibiotic either orally or topically. You may also consider using a weak steroid if it's a really bad bout. You'll quiet it down, but you wouldn't want to use a steroid for more than a few weeks because it could damage the eye." She adds that one must also be careful in administering these steroids since their long-term use could be problematic in their interaction with other medications, leading to other complications outside of blepharitis. As of today, the most common treatment is a combination of corticosteroid therapy with antibiotics to alleviate the symptoms of blepharitis. The persistence of blepharitis requires several repeat visits to effectively treat the disease, as treatment/management will likely be ongoing.

"When Demodex mites are identified as being present, the treatment is straightforward. However, because of the nature of the mites, they can multiply at a rapid pace, so they must all be removed," Dr.

Wolle says. "The best way to go about this is through lid scrubs and tea tree oil, which cleans the dandruff from the lash root and irritates the mites enough for them to move out of the skin. Like anything else, maintaining proper hygiene is essential."

Getting Ahead of the Curve

In order to manage and prevent bouts of blepharitis, patient education is essential. Dr. Wolle discusses how to best prevent the development of blepharitis before you step into the exam room. "Let your patients know what to look for. Tell them to be good about their eyelid hygiene. Even if they don't have an issue with blepharitis, they should be washing their eyelids in general to prevent any issues of colonization," she says. "For women especially, they should be careful about their makeup. They tend to reuse their makeup or don't change it for a period of time, and from that you can get organisms that can end up causing blepharitis. Suggest that they try to be as hygienic as they would be with their teeth and their faces." Dr. Wolle does, however, note, "Some of it isn't that preventable. There are genetic issues that people have which are hard to get around, but that's a whole different category."

With proper hygiene and lid scrubs, most patients with blepharitis can have their symptoms alleviated. Proper physician diligence can help patients get ahead of a chronic flare-up and avoid the nuisance of a corticosteroid and antibiotic regimen. However, it must be noted that even if the symptoms are gone, there is always the possibility of a recurring problem, so diligence with eyelid care is essential to avoideng and overcoming persistent bouts of blepharitis. REVIEW

Drs. Wolle and Noecker have no financial interest in any product discussed in the article.

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The DED Pipeline Isn't Drying Up

By Kristine Brennan, Senior Associate Editor

The possible causes are many and prescription treatments few, but new and potential dry-eye therapeutics keep coming.

This past summer, the Dry Eye Workshop's TFOS DEWS II report defined dry-eye disease as follows:

"Dry eye is a multifactorial disease of the ocular surface characterized by a loss of homeostasis of the tear film, and accompanied by ocular symptoms, in which tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play etiological roles."[1]

The update reflects the most current understanding of dry-eye disease as a disruption in homeostasis and emphasizes the importance of hyperosmolarity in dry-eye tears and the role of inflammation in DED. Inflammatory mediators are frequent therapeutic targets. As things stand, Restasis and Xiidra (Allergan and Shire, respectively) are the only prescription eye drops approved by the Food and Drug Administration for the treatment of dry-eye disease. Both medications are thought to inhibit T cells by different mechanisms of action. The heterogeneous nature of dry-eye disease is one of the things confounding new drug development: Drug makers have multiple potential molecular and tissue targets to consider and DED is notorious for a lack of overlap between signs and symptoms.[2] With an estimated global prevalence ranging from 5 to 50 percent[3] and the potential for corneal surface damage and diminished quality of life absent good treatment, DED's therapeutic pipeline is unlikely to run dry anytime soon.

Four dry-eye treatments at various stages follow: a freshly FDA-approved medical device; a drug in the middle of the investigational stage; a patented topical solution/gel formulation; and a protein-fragment-based drop beginning a human trial.

TrueTear

Approved by the Food and Drug Administration in the spring of 2017, Allergan's TrueTear Intranasal Tear Neurostimulator device relies on an old idea—nerve stimulation—to address the problem of dry eye. Oculeve, the startup that invented the device before being purchased by Allergan, based TrueTear on technology used in TENS units and for the treatment of movement disorders. The True-

The TrueTear is an intranasal device that uses neurostimulation.

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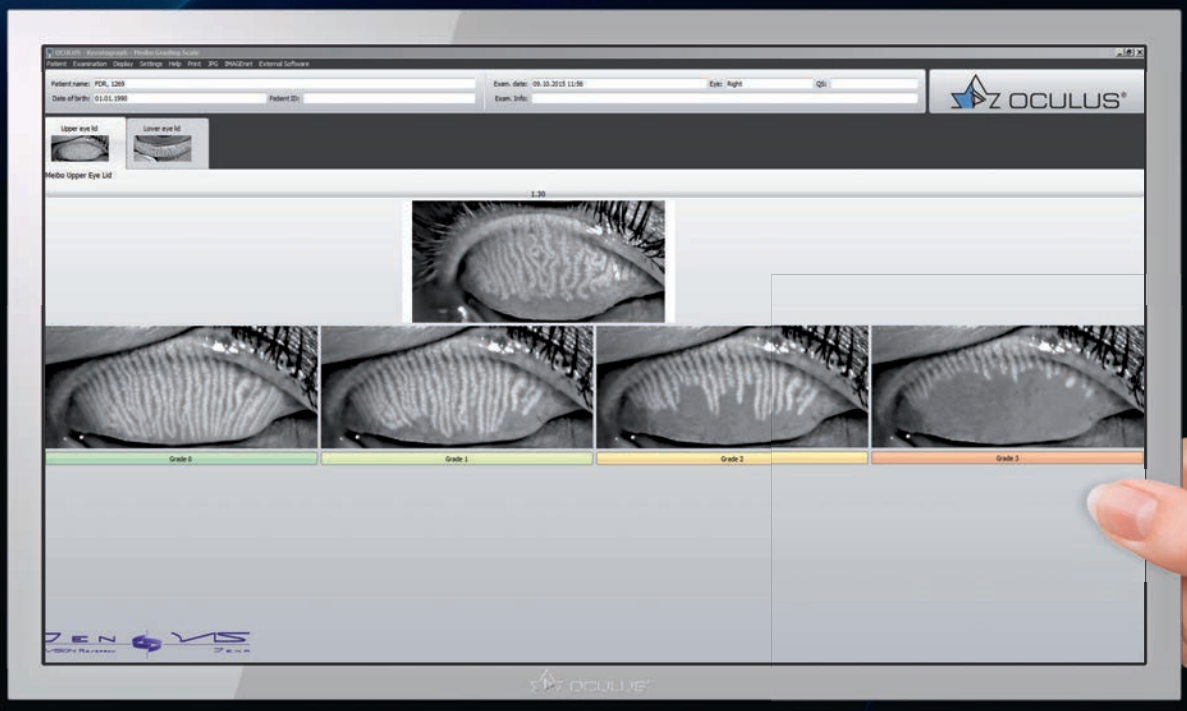

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Tear stimulates the trigeminal nerve and, in turn, the seventh cranial nerve with small electrical pulses that ultimately trigger the lacrimal gland to produce tears.

To reach the ophthalmic branch of the trigeminal nerve, this small handheld device has two prongs covered in disposable hydrogel tips that go up the patient's nostrils. Patients can choose from five levels to control the intensity of electrical stimulation. According to patient information for the TrueTear,[4] patients should aim to use the device at least twice a day for no more than three minutes per session; the TrueTear automatically shuts off after 30 minutes of use in a 24-hour period. Allergan lists a tendency for nosebleeds, a history of clotting disorders, the use of pacemakers or wearable defibrillators, as well as the presence of metallic or electronic implants in the head or neck as contraindications to TrueTear use. The device is currently approved for patients 22 years of age and older.

Supportive data released by Allergan[4] consist of two studies: OCUN-009, a look at one-day correct use of the device versus one-day sham control treatments, and OCUN-010, a six-month trial comparing tear production at six months to baseline. Forty-eight dry-eye patients at two sites underwent three applications of neurostimulation in OCUN-009: correctly applied intranasal stimulation treatment with an active TrueTear; intranasal application of an inactive TrueTear; or extranasal (incorrect) application of an active TrueTear. The average Schirmer's score for the treatment group was 25 mm during treatment, versus 9 mm for both sham groups. OCUN-010 was an interventional open-label study looking at tear production in 97 dry-eye patients at treatment days one, seven, 30, 90 and 180. Patients were told to use the TrueTear anywhere from two to 10 times per day for a maximum of three minutes per session. At each follow-up visit, Schirmer's testing without stimulation was compared to scores with stimulation; tear production was consistently significantly greater with active TrueTear stimulation than without. The effect appeared to decrease from the first-day results but then plateaued over time (still remaining higher than without stimulation). The average differences in Schirmer's scores (with stimulation versus without) were 18 mm on day one, 13.1 mm at seven days, 8.1 mm at 30 days, 8.3 mm at 90 days and 9.4 mm at 180 days. In both studies, adverse events were minor and included nasal complaints such as irritation.

"Crazy," is how John Berhdahl, MD, of Vance Thompson Vision in Sioux Falls, S.D., sums up his first impression of the TrueTear upon getting the chance to try it out a couple of years ago. "But I love outside-the-box ideas, and as I thought about it more deeply, it made sense," he says. "We know that reflex tearing can occur when you stimulate nerves, and it's not so different from other electrotherapies that we use to stimulate nerves in other parts of the body. I believed that it would be safe, so I thought, 'Let's try it. Let's see if this crazy idea turns out to be legit,'" he recalls.

So far, Dr. Berdahl reports that patients are having "a very good response" to the TrueTear since it has become generally available. "I like that we're using concepts outside of ophthalmology like electrostimulation and applying them to ophthalmology to see if we can control the pathophysiology of the eye: I think that's great," he says. He thinks that the high degree of control over treatment that the device affords patients is one factor in its success to date. "One of the things that's really nice about it is that we allow them to try it in the office so that they can experience the increased tearing," he notes. "Then they can try it for a month, and if it's not working for them, it can be returned. Those two steps allow people to climb the learning curve in a noncommittal way."

Dr. Berdahl also values the safety and flexibility of the TrueTear, since it fits well into comprehensive treatment plans that include other modalities. "I believe in treating severe dry eye by hitting it really, really hard to get it under control and then backing off the things that you no longer need, or that the patient likes the least," he says. Using the TrueTear is part of that treatment philosophy for dozens of patients in his practice.

Surgeons say that the base price of the TrueTear is $750 and a month's supply of disposable tips costs $250, although Allergan does offer some rebates to help defray costs.

In addition to stimulating the lacrimal gland in aqueous-deficient dry eye, Dr. Berdahl says that there is evidence that using TrueTear improves the tear film in dry eye as well. "They have done some work to show that it improves meibum secretion, so it would improve tear-film quality," he says. A small study[5] suggests that use of the neurostimulator can promote degranulation of conjunctival goblet cells in both dry and healthy control eyes.

CyclASol

Since its launch in 2003, Restasis (0.05% cyclosporine A emulsion), has been a dry-eye treatment mainstay, thought to inhibit the action of inflammatory T-cell mediators. Cyclosporine eye drops, however, present the same roadblocks to efficacy and compliance as other topical drops: Many patients have difficulty getting them into the eye without blinking as soon as they reach the cornea, which results in spillover and drainage into the lacrimal system before the drug can provide much therapeutic benefit.

Novaliq GmbH (Heidelberg, Germany) has combined cyclosporine A with its Eyesol drug-delivery platform,

which is made up of semifluorinated alkanes, in a bid to create a more bioavailable and user-friendly alternative to aqueous drops.

Semifluorinated alkanes aren't new to ophthalmology because they possess characteristics that make them suitable tamponades in vitreoretinal surgery, including good solubility in silicone oils, perfluorocarbon and hydrofluorocarbon liquids; a refractive index of 1.3; and a specific gravity of 1.35 g/mL.[6] Those attributes also make semifluorinated alkanes good for mixing with cyclosporine A—a drug with poor water solubility—to make a slick, clear, preservative-free solution with low surface tension that spreads rapidly over the ocular surface.

One drop of a 0.05% aqueous emulsion has a volume of 40 to 50 µL: a drop of that size triggers reflexive blinking in many patients when it contacts the eye. To create a cyclosporine A drop that will more successfully reside on the cornea, Novaliq has developed CyclASol, a preservative-free cyclosporine A solution with Eyesol. Novaliq says that a drop of CyclASol is only about 10 µL in volume, so it doesn't trigger a blink reflex and accompanying spillover in the eye, and its low surface tension allows the drop to spread over the cornea more quickly and evenly than aqueous eye drops. Alternate dry-eye treatments include gels and ointments, but these are often limited to nighttime use because they blur and distort vision, even though they reside on the cornea better than aqueous drops. The company claims that CyclASol's refractive index is very close to that of the crystalline lens, so it will not blur or distort vision.

A Phase II study (*Trial Identifier: NCT02617667*) comparing two dose levels of CyclASol (0.05% and 0.1%) solution with cyclosporine A 0.05% emulsion and a placebo followed 207 randomized patients with moderate-to-severe dry-eye disease for four months. Novaliq released topline data from this study in early 2017.[7] Although patients in all treatment arms showed reduced corneal fluorescein staining, patients enrolled in both CyclASol groups showed significantly more disease-sign improvement than patients in the vehicle (placebo) group. Novaliq says that its data also demonstrated that CyclASol patients began showing reduced corneal and conjuctival staining as early as 14 days into treatment. It reports that the drops were well tolerated with no serious adverse events. Novaliq added that improvement was most marked in the central area of the cornea and noted that area's importance to good visual functioning.

Upon release of the topline data, a company press release[7] quoted Claus Cursiefen, MD, PhD, FEBO, professor and chair of the ophthalmology department at University of Cologne, Germany, and member of Novaliq's scientific advisory board, on the therapeutic benefits of

CyclASol: "Consistent improvements in several measures of ocular inflammation of dry-eye disease, particularly the improvement in central corneal staining, is a very important feature of the formulation because it positively influences visual function. This, combined with the early onset of action and an excellent tolerability profile, represents a highly relevant improvement over currently available therapies."

Klarity

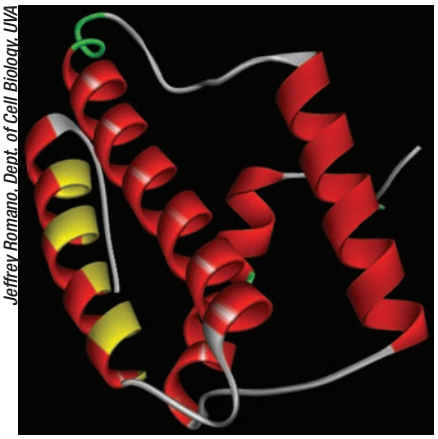
In the spring of 2017, Imprimis Pharmaceuticals (San Diego) announced that it had purchased the exclusive worldwide rights to Klarity, a patented topical ophthalmic solution created by Richard L. Lindstrom, MD, to protect and heal the ocular surface in moderate-to-severe DED. Klarity is also intended for dry eye and corneal irregularities arising from intraocular surgery or contact lens wear.

The preservative-free Klarity solution contains chondroitin sulfate, thought to have protective and healing effects on the corneal epithelium,[8] and established as safe for intraocular use in viscosurgery. It also contains dextran and glycerol. Imprimis says that the solution can be formulated to vary in viscosity, making it suitable as a topical drop, a gel or even a dispersive OVD.

The company plans to make Klarity part of its emerging dry-eye program. According to the Imprimis website, another upcoming addition is the compounding of autologous serum tears at the company's 503A PCAB-accredited pharmacies.

Lacripep

Lacripep (TearSolutions, Inc.) is a synthetic protein fragment incubated in the Laurie Cell Biology Laboratory at the University of Virginia in Charlottesville. Its inventor, Gordon W. Laurie, PhD, professor of cell biology, biomedical engineering and ophthalmology at UVA and co-founder and CSO of TearSolutions, and colleagues say that Lacripep is potentially the first therapeutic agent capable of improving dry-eye disease regardless of etiology.



Jeffrey Romano, Dept. of Cell Biology, UVA

A molecular model of lacritin, a protein that is selectively deficient in dry-eye tears. Lacripep is a synthetic lacritin fragment.

"Lacripep is a synthetically generated 19-amino-acid fragment of lacritin," Dr. Laurie explains. "Lacritin is a naturally occurring protein in tears, first identified in 2001 by the Laurie Cell Biology Lab out of an unbiased discovery screen for factors that regulate basal tearing." He notes that Lacripep-like lacritin fragments occur naturally in tears secreted by healthy eyes—and that they are deficient (as is lacritin) in dry-eye tears. "Lacripep and lacritin have been studied in several dry-eye animal and human cell-culture models, and have been found to restore ocular surface health by: promoting tear protein release and tearing, even under conditions of inflammation; transiently stimulating a cellular lysosomal pathway known as autophagy to rid cells of damaged proteins and organelles that accumulate under conditions of stress; and restoring mitochondrial oxidative phosphorylation. In unpublished data, both also appear to stimulate and benefit sensory nerves at the ocular surface that in dry eye are disrupted and diminished," he says.

This neural stimulation may bring relief for both aqueous-deficient and evaporative dry-eye patients. "By apparently targeting corneal sensory nerves that in turn regulate all glandular and secretory elements of the ocular surface, Lacripep is expected to benefit both evaporative and aqueous-deficient dry eye," Dr. Laurie explains.

With support from the National Eye Institute, Dr. Laurie and colleagues focused on the causes of dry eye rather than the effects of the disease. "With NEI R01 support, we were the first to explore the cell biological basis of dry eye using an unbiased biochemical screen. This differs from others who have largely employed a candidate approach, in most cases focused on downstream inflammation," says Dr. Laurie. "It took years, but we succeeded in identifying a natural tear activity, encapsulated in Lacripep, that appears to be fundamental for the maintenance and restoration of ocular surface homeostasis. Yet, dry-eye tears are selectively deficient in lacritin and natural Lacripep-like fragments. This draws a parallel to type I diabetes and insulin, and offers a new way to think about dry eye with Lacripep as a replacement therapy, that based on the biology, could be a game changer."

"A shout-out to the National Eye Institute for their many years of support, without which this discovery would not have been possible," says Dr. Laurie. "We also wish to acknowledge the Lacritin Consortium of labs in the U.S. and outside, who have contributed fundamentally to our understanding of Lacritin," he says.

Dr. Laurie, Marc G. Odrich, MD, associate professor of ophthalmology at University of Virginia and medical director of TearSolutions, Inc., and colleagues have recently begun an attempt to transition from the laboratory to the marketplace with a double-masked, randomized, placebo-controlled Phase

II study of topical Lacripep in more than 200 patients with Sjögren's-associated dry-eye disease at 27 U.S. sites (*Trial Identifier: NCT03226444*). Enrolled patients receive one of two concentrations of Lacripep eye drops or a placebo three times a day for four weeks. Improvement in fluorescein corneal staining is the primary endpoint.

Dr. Odrich says that they selected Sjögren's patients for the first study because primary dry eye associated with the disorder "is the most homogenous form of dry-eye disease, with diagnosis aided by blood tests and salivary gland biopsy." He adds, "Second, lacritin deficiency in Sjögren's syndrome correlates with reduced corneal nerve fiber density and length, tear insufficiency, increased ocular staining and reduced corneal sensitivity. Third, in two different mouse models of Sjögren's syndrome, lacritin promoted rapid resolution of corneal staining and/or tearing. Fourth, Sjögren's syndrome patients are highly motivated."

Dr. Odrich estimates that data will become available in the first half of 2018. Should Lacripep garner FDA approval in the future, he believes that patients could titrate the number of daily doses down from three once their condition stabilizes. "There appears to be a lasting effect with repeated dosing," Dr. Odrich says of his team's studies in rabbits that were dosed three times daily for two weeks. "Basal tearing steadily increased and remained elevated one week after washout. The molecular basis is under study. At least two different mechanisms are likely involved," he says.

The dry-eye pipeline is tricky for a variety of reasons: the heterogeneity of the target disease; the lack of overlap between signs and symptoms; and the costly path to FDA approval, to name a few. As the most prevalent ocular surface disease globally, however, DED will never be without therapeutic contenders.

"Dry eye is a disease that has real unmet needs because we can't get everybody better right now," Dr. Berdahl observes. "So I'm excited about all of it, but it remains to be seen which things will be the most clinically useful." REVIEW

Dr. Berdahl is a consultant to Allergan. As mentioned in the article, Drs. Laurie and Odrich are the CSO and medical director, respectively, of TearSolutions, Inc.

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How to Think Outside the Capsule

A novel approach to cataract surgery and lens replacement offers some benefits, but its adoption rate may be slow.

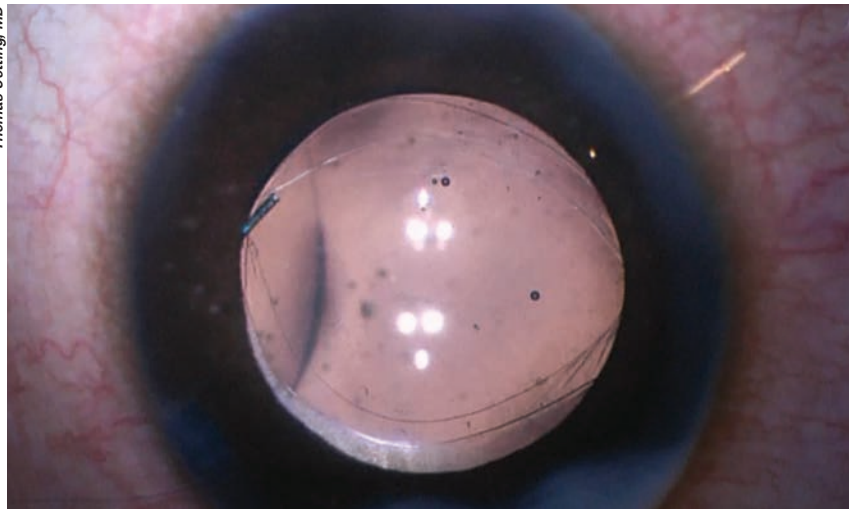
Walter Bethke, Editor in Chief

Everyone's familiar with the old aphorism, "An ounce of prevention's worth a pound of cure," especially cataract surgeons, who try their best to perform as flawless a procedure as possible in order to minimize the risk of any postop complications. After studying various surgeons' techniques, professor and researcher Lisa Brothers Arbisser, MD, thinks she's hit upon an approach to cataract surgery and intraocular lens implantation that combines these surgeons' methods and which could possibly eliminate one or more common complications. Now she just has to convince her colleagues that it's worth doing.

Scleral Bi-Capsulotomy Capture

Dr. Arbisser, an adjunct associate professor at the University of Utah's Moran Eye Center, calls her approach scleral bi-capsulotomy capture, and though it involves maneuvers that may take some getting used to, she thinks surgeons would benefit from SBCC in the long run.

After studying the unique techniques of Canadian surgeon Howard Gimbel, MD, Austria's Rupert Menapace, MD, and France's Marie Tassignon, MD, Dr. Arbisser says she was struck with an idea. "It occurred to me that all bag/lens subluxations have one thing in common: a capsulorhexis," she says. "We never saw bag/lens subluxations in the days of the can-opener capsulotomy, and you very rarely see a pseudoexfoliation patient subluxate his normal crystalline lens. I then reasoned that if I could stent the anterior capsule by capturing the optic in there, and place the haptics in the sulcus—which is partially defined by the zonules—there would be no movement, pressure or weight on the bag. So, in a sense, the bag would support the lens and the lens would support the bag, with the most important part being that the lens is captured to prevent phymosis. It occurred to me: Why not combine these two techniques into



Thomas Oetting, MD

Scleral bi-capsulotomy capture consists of capturing the optic with both anterior and posterior capsulotomies and placing the haptics in the sulcus. It could potentially eliminate the incidence of posterior capsular opacification, but it comes with a learning curve.

one routine procedure? In the procedure, scleral bi-capsulotomy capture, you've got a three-piece lens placed in the sulcus and captured through both the anterior and posterior capsules."

Possible Advantages

Dr. Arbisser says eliminating posterior capsule problems is a big reason to perform SBCC.

"The advantage of mastering and not being afraid of the posterior capsule is huge," she says. "We know from Dr. Menapace and his extensive studies of fellow eyes that the anterior hyaloid is really the barrier between the front and the back of the eye. The posterior capsule is redundant. Because of Wieger's ligament and the anterior hyaloid, if you leave that complex intact, you can very safely open the posterior capsule and there's no increase in cystoid macular edema, no increase in IOP, no untoward problems and, theoretically, according to Robert Stegmann and others, if we don't release vitreal elements to the trabecular meshwork, there's a lower rate of postop glaucoma. This last benefit is due to the fact that we know we have pressure rises when we do a YAG capsulotomy, a procedure which wouldn't be necessary after SBCC since it eliminates posterior capsular opacification."

Dr. Arbisser says there's a second, more-immediate reason to pursue this technique. "Those cases with posterior plaques will get an immediate visual rehabilitation," she avers. "So, too, will posterior polar cataract cases in which there's a very weak and very unreliable posterior capsule. In such cases, you open the posterior capsule in a controlled fashion with SBCC, rather than allowing it to break in an uncontrolled way.

"The advantages of optic capture are huge," Dr. Arbisser continues. "Number one: We know there's no PCO. To this a surgeon might say, 'A YAG laser's no big deal.' We have studies that show, however, that even in a case of a 'clear' 20/20 Snellen acuity, the posterior capsule causes straylight abnormalities. The vision is actually clearer, more reliable and simply better without a posterior capsule, with the lens in Berger's space, than with a posterior capsule. Therefore, you get better vision to start with in SBCC. Number two: There's no second period of visual degredation until you finally decide that the vision is bad enough and meets Medicare's requirements for a secondary [YAG] procedure. This could be crucial in the developing world, where it might be impossible to come back for a YAG. Number three: When we do a YAG laser posterior capsulotomy, we almost invariably rupture the anterior hyaloid. That's why we have an increased incidence of retinal tears and detachments afterward, particularly in high myopes. Number four: There's an increase in IOP after a YAG, and often glaucoma patients

have glaucoma that's more difficult to control thereafter. So, besides avoiding the visual disability of PCO and the need for a second procedure—not to mention the cost of that procedure—the primary advantage is that SBCC stabilizes our anterior and posterior segment separation forever. I think this will impact not only the rate of retinal detachment, but the progression of diabetic retinopathy, the incidence of CME—particularly in patients with uveitis—and will block the prostaglandins from the anterior chamber to the posterior."

Possible Disadvantages

Dr. Arbisser says the potential downsides of the procedure include the learning curve, the ramifications of a future IOL exchange and economics.

• ***Learning curve.*** "Dr. Menapace declared the learning curve to be about 150 cases," Dr. Arbisser says. "Before I retired from patient care, I did about 80 and felt very comfortable with it. I had two complications. One complication occurred in a pediatric intumescent cataract in which I inadvertently opened the anterior hyaloid along with the anterior capsule. I believe there was no Berger's space—even potentially—there. In response, I performed an anterior vitrectomy, which would be done routinely in such a case, and put the lens in the sulcus and performed anterior optic capture. The other complication occurred as I was trying to optic capture through the posterior capsulorhexis. I had made the capsulorhexis a little too small. I was using a different lens and was hoping to emulate what Dr. Menapace was doing and unfortunately broke the edge of the posterior capsulorhexis. The haptics remained in the bag and I captured the optic above the anterior capsulotomy. There was no vitreous prolapse.

"A femtosecond laser might be a way to make the learning curve easier," Dr. Arbisser adds. "With the femto, it's possible to make a posterior capsulorhexis that's hyaloid-sparing. For example, Burkhard Dick has found that 72 percent of adults can have their anterior hyaloid and posterior capsule visualized, and a posterior capsulotomy done easily, with the Catalys laser.[1] Interestingly, this can be done in 100 percent of patients with axial lengths over 25 mm, who might be the people who need it most. Dr. Dick found that every capsule scrolled out of the way by day one postop, and there was no vitreous prolapse in his series."

"A femtosecond laser might be a way to make the learning curve easier. With a femtosecond laser, it's possible to make a posterior capsulorhexis that's hyaloid-sparing."
— Lisa Arbisser, MD

Alexandria, La., surgeon R. Bruce Wallace says that some steps of the procedure could risk complications. "When you make a posterior capsulotomy, there's the possibility you'll disturb the vitreous face," he says. "That would mean that it's possible for some strands to get into the anterior chamber as you pull the needle out. This wouldn't be a common situation, though. Also, as postop capsular contraction occurs, there may be a risk of IOL optic decentration."

• ***Anterior vitrectomy.*** If SBCC were performed and a lens exchange was subsequently required, Dr. Arbisser says an anterior vitrectomy, something surgeons obviously usually try to avoid whenever possible, "would be a sure thing."

"I think we'd do a one-port, pars plana, limited anterior vitrectomy," she explains. "And, using the vitrector, we'd poke the lens back and then immediately place OVD to cover any of the area of the open capsule so there'd be no vitreous prolapse. We could then go about the exchange."

Dr. Wallace doesn't think this would be common, but is something to consider. "Exchanges don't happen frequently," he says. "And, in the world of cataract surgery, with a lot of people paying out-of-pocket for premium procedures, many patients can have LASIK to correct postop power problems. But, on occasion, LASIK isn't an option, such as in situations in which the patient had LASIK previously or needs a significant power change. In those cases, you'd have the vitreous to worry about."

• ***Economic factors***. Not to put too fine a point on it: Almost half of cataract-surgery patients need a YAG capsulotomy, which is an extra reimbursement stream for the surgeon. SBCC does away with the need for YAG. "Though the world in general and any socialized medicine scheme in particular stand to benefit greatly by eliminating millions of secondary procedures," says Dr. Arbisser, "we as ophthalmologists enjoy and count on the secondary reimbusement, so it's very difficult to convince ophthalmologists in the United States to do this."

For surgeons interested in learning more about SBCC, Dr. Arbisser will be a co-instructor at a course on it during Monday's session at this year's Academy meeting in New Orleans. REVIEW

Drs. Arbisser and Wallace have no financial interest in any of the products mentioned in the article.

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Optimizing the Efficacy of Topical Medications

A number of simple strategies can go a long way toward making sure your patients benefit from their eye drops.

Thomas D. Patrianakos, DO, Chicago

As ophthalmologists managing glaucoma, we have some excellent topical medications that do a very good job of lowering IOP. However, in order for those medications to have maximum efficacy, they have to surmount numerous barriers. Those barriers include patients not understanding the value of taking the drops; patients not being good at getting them onto the eye; the drops not remaining on the eye long enough to work; and the drugs being partially blocked by the cornea's natural defenses. (For example, when most drops are placed on the eye, only 5 percent of the medication actually penetrates the cornea, and of that, only 1 percent actually reaches the aqueous humor.) Factors such as systemic medications the patient is taking can also reduce the impact of topical drops.

All of these barriers, however, can be surmounted if you accomplish five things:

- educate your patients about glaucoma;
- teach proper instillation;
- increase the time the medication remains on the eye;
- improve drug penetration; and
- choose the most efficacious regimen for each patient.

Here, I'd like to share 14 specific steps you can take that will help ensure that your patients get the most out of their topical medications. (Note: In this day and age, when we're being asked to take care of more patients with fewer resources, it may not be easy to personally execute all of the strategies listed below with your patients. However, well-trained technicians should be able to do much of this for you.)

1. *Educate the patient.* As everyone knows, lack of patient adherence to a prescribed protocol is a prime cause of reduced efficacy. One reason for lack of adherence is that many patients don't really understand the value of the medication, especially since glaucoma is usually painless and doesn't elicit symptoms until a lot of damage has already been done. At the end of the day, a patient who fully understands the disease and the importance of taking the drops is far more likely to follow instructions. Studies have confirmed this.[1,2]

For patient education to be effective, you need to:

- Maintain a good doctor-patient relationship. Without this, the patient will be far less interested in taking your advice.
- Make sure the patient understands what glaucoma is and how it affects vision. As noted, patients often have a poor grasp of the reasons they need to be concerned.
- Educate the patient about the medication, including how it works, how it will benefit the patient when taken properly and any side effects it may have. The last item is important because if you give someone a medication that has a side effect without mentioning it, the patient may simply stop using the drop when he encounters the side effect.

It may help to provide the patient with pamphlets and brochures containing much of this information. However, this approach may be best when used to supplement face-to-face education in the office.

2. *Ask patients open-ended questions about their medication use.* This will often get them to

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reveal problems they're having that are affecting their compliance. For instance, you might ask, "How often do you miss taking your medications?" Or, "Are you having any problems with your medications?" The patient is more likely to admit problems if you take the time to ask.

3. *Show patients evidence of their disease severity and/or progression.* Showing patients how their nerve fiber layer has changed on optical coherence tomography since the previous visit, for example, can go a long way toward getting them to take the disease seriously. You might say, "You came in in 2014 and your nerve fiber layer was this thick. Now it's 2017 and it's this thick. If you don't use your medications, it will continue to get thinner and thinner and you'll start to lose your vision." This can be a powerful motivator.

4. *Watch the patient instill a drop.* Many ophthalmologists don't take the time to do this, but it may be the crux of the matter. You'll almost always find several things that patients are not doing optimally to make the medication work. For instance, some patients actually apply the drops to the outside of the eye! By watching the patient instill a drop, you may catch a problem and be able to address it right up front, preventing all of your efforts from being wasted.

5. *Show the patient proper instillation technique*. This is the other half of getting patients to show you their instillation technique: teaching them to do it right. Showing them your technique of choice while they're in the office is ideal, but you can also refer patients to videos on YouTube. There are thousands of videos showing how to instill drops; you can find one that matches your technique and ask patients to watch it several times at home. Better yet, get them to watch it in the office (so you can be sure they've seen it).

Manual punctal occlusion increases the amount of drug getting into the eye and decreases systemic absorption.

After they've seen the video, of course, you should check to see what the patient actually ends up doing. If you stay on the case until the patient learns to correctly instill the drops, you'll go a long way towards eliminating a major cause of treatment failure.

6. *Teach patients to avoid the washout effect.* Even if a patient's technique is successfully getting drops onto the eye, when more than one drop is being used, the washout effect potentially caused by the second drop can undo the potential value of the first drop.[3] I tell patients that when they instill a topical medication in the eye, they should wait at least five minutes before instilling the second drop so that they don't wash out the first medication.

7. *Consider prescribing a combination medication.* Combining two medications into one bottle is an excellent way to avoid the potential problems caused by having to manage multiple medications—including the problem of a second drop washing out the first.[4]

8. *Teach the patient to perform manual punctal occlusion.* Punctal plugs prevent a drug placed on the eye from draining down into the throat as quickly, thus increasing the residence time, penetration and efficacy of the drug.[5] Fortunately, patients can duplicate this effect in a temporary manner by blocking the lower puncta with the fingers (usually the index finger and thumb, on either side of the nose—see image, left), which has also been shown to be effective.[6] Furthermore, blocking the flow of medication into the throat decreases the systemic side effects of the medication.

Closing the eye after instilling the medication is another technique that's also recommended by many doctors, but I believe that manual punctal occlusion is the most effective strategy. (In any case, the patient may want to close his or her eyes whenever fingers are placed that close to the eye.)

9. *Consider prescribing a gel.* Doctors sometimes forget that many medications are available in gel form. Increased viscosity leads to increased time on the cornea, more sustained released and improved bioavailability, allowing the drug to be more effective.[7]

A second benefit in some cases is that the gel version of a drug may need to be used less often. For example, the drop version of timolol is generally used twice a day, whereas the gel version only needs a single application per day. The downside of using a gel, of course, is that there's some transient blurriness associated with it. Many patients, however, won't find this objectionable, especially if it reduces the number of applications per day.

10. *Teach the patient to induce a temporary dry-eye state.* As noted earlier, the tear film is one of the eye's natural barriers, helping to prevent unwanted substances from getting inside the eye. But in the case of a glaucoma medication, we want to get past as many barriers as possible to ensure that the medication has a chance to help the patient. As it turns

out, there's a simple way to temporarily minimize the tear-film barrier and let more medication through.

If your patient resists the urge to blink—perhaps by engaging in a staring contest for 10 seconds—this creates a temporary dry-eye state. It causes a decrease in the quantity and quality of the tear film and an increase in tear-film breakup time, minimizing the tear-film barrier. If a drop is applied with the tear-film barrier reduced, more drug is absorbed into the cornea. This was demonstrated in one study in which researchers created a dry-eye state in one eye while allowing the other eye to blink normally, as a control. They then instilled either pilocarpine or phenylephrine into both eyes and measured how long it took for the pupils to constrict or dilate. They found that the medications entered into the cornea significantly faster in the eye that had the dry-eye state.[8]

11. *When possible, prescribe prodrugs.* The other barrier that keeps unwanted chemicals out of the eye is the cornea itself. One reason the cornea is so effective as a barrier is that it's made up of a lipophilic epithelium and a hydrophilic stroma. That makes it very difficult for any medications to penetrate all the way through the cornea, whether the medication is hydrophilic or lipophilic; if one layer doesn't block the drug, the other layer will.

Nevertheless, some drugs are able to make it past this obstacle by changing form as they go through the cornea. These are referred to as prodrugs. These molecules have a lipophilic segment that initially allows them to penetrate into the epithelium. Then, as they go into the stroma, they undergo hydrolysis by esterases, which causes them to become hydrophilic and allows them to get through the stroma. This results in the slow release of significant concentrations into the aqueous humor.[9,10]

All of the prostaglandins except for Lumigan—including Travatan and Xalatan—are prodrugs.

12. *Choose a second medication wisely.* If it's necessary to add a second drop to the patient's regimen, it's important to choose one that will be most effective in conjunction with the first drop. If I'm adding a second-line agent to the patient's regimen, I generally choose a drop that works via a different mechanism. Prostaglandins, for example, work by increasing uveoscleral outflow. Therefore, if I've started with a prostaglandin and the patient had a good response but the pressure still isn't low enough, my second-line agent would be something that decreases aqueous humor production, such as a carbonic anhydrase inhibitor or a beta-blocker. The combination of two different mechanisms tends to be more effective.

In addition, studies have demonstrated that some of these drugs do better than others as a second-line agent, in terms of the percentage of patients that show a ≥10 percent extra pressure reduction when the second drug is added. One study found that 84 percent achieved this reduction when a CAI was added; 61 percent achieved this when a beta blocker was added; and 44 percent achieved this when an alpha agonist was added.[11] For that reason, I favor CAIs as my go-to second-line agent.

13. *Check for systemic drugs being used by the patient.* Patients on systemic equivalents to a topical drop may not respond as well to the drops.[12] For example, if the patient is on a systemic beta blocker for a heart condition or blood pressure problem, he might not have as much of an IOP response to a topical beta blocker. Similarly, systemic CAIs are sometimes used for blood pressure control or conditions such as pseudotumor cerebri to lower intracranial pressure; the same principle applies.

14. *Remember that you can increase the effect of some medications by increasing the frequency of the drops.* Although there's nothing to gain from increasing the frequency of drugs such as prostaglandins or beta blockers, studies have shown that if you increase your CAI or alpha agonist dosage from two times a day to three times a day, you may get another point or two of IOP lowering.[13] This also works with a combination drop such as Simbrinza (brinzolamide/brimonidine tartrate ophthalmic suspension). REVIEW

Dr. Patrianakos is chair of ophthalmology for the Cook County Health and Hospitals System. He has no financial interest in any product mentioned in this article.

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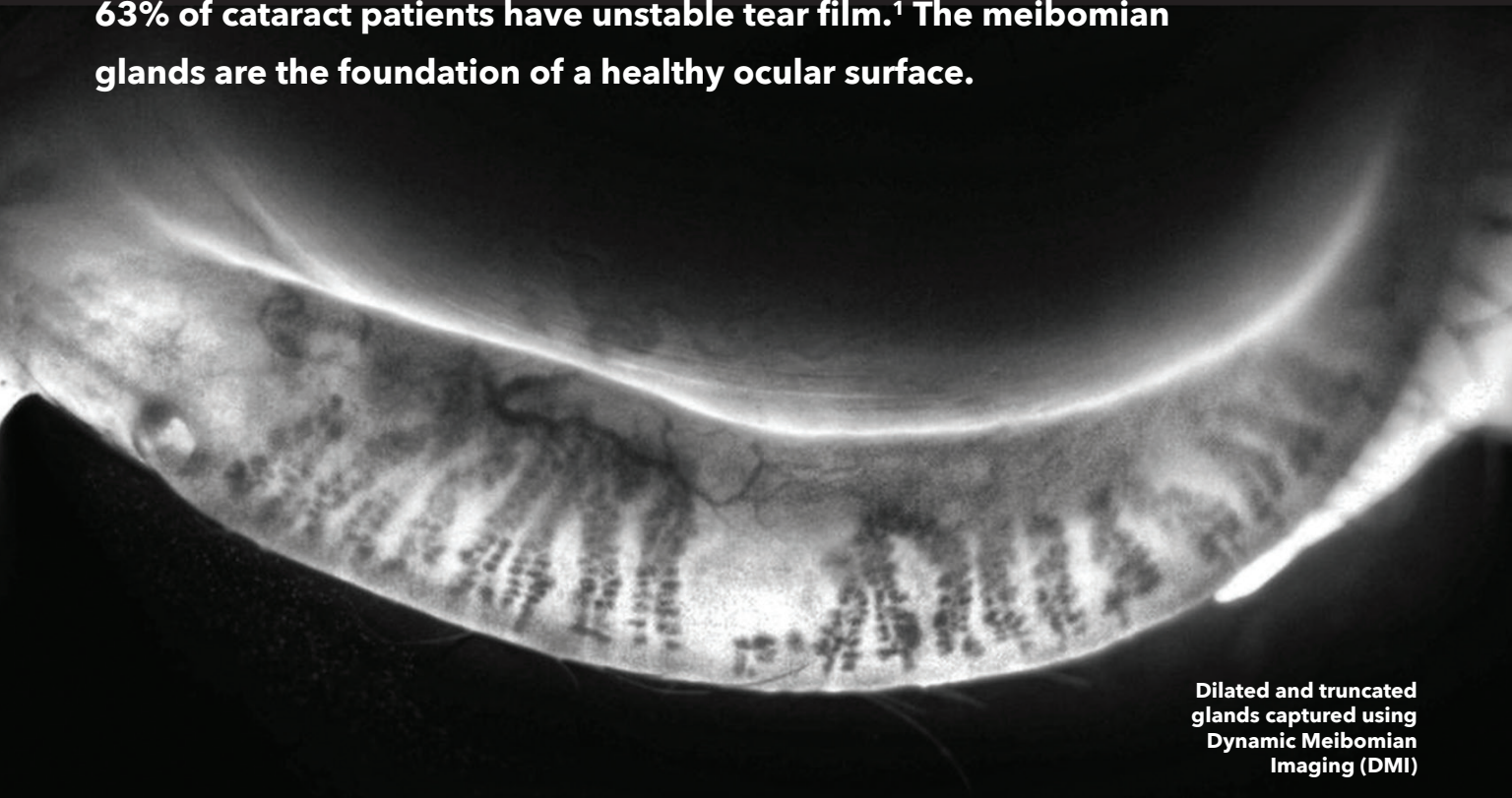

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One or Two More Pearls ...

After 23 years, Therapeutic Topics comes to an end with an installment filled with several decades' worth of wisdom.

Mark B. Abelson, MD, CM, DSc, FRCSC, FARVO
Andover, Mass.

In "Finnegan's Wake," the cycle of life and regeneration is explored by James Joyce. In his poem "Hundred Year Old Shay," physician Oliver Wendell Holmes parodies the reality that we don't age all at once. Somerset Maugham wrote "The Summing Up" as a recap of his literary career. Proust's "In Search of Lost Time" takes us, in detail and in 6,000 pages, through his own life from first to almost last memories...maybe finding that lost time in the minutiae of daily existence. In common, they all dealt with the relentless effects of time on our psyche, on our body, on our avocation. It is hard not to think of these literary codas when reaching the end of my scientific writing odyssey in these pages after 23 years and more than 280 columns.

In this column, my goal has always been to speak to my friends and colleagues about the incredible gift and opportunity we have as ophthalmologists to recognize disease and its underlying causes and sometimes be able to use this understanding to intervene therapeutically. After all these years I am still in awe of our collective ability to treat disease with our current knowledge, while exploring the unknown for better interventions. As a clinician, I strive to combine the critical observation skills described by Sir William Osler as, "Listen carefully to the patient, he is trying to tell you his diagnosis," and the integrative effort highlighted by Arthur Conan Doyle who, as it turns out, was also a physician. The deductive reasoning exemplified by the fictional Sherlock Holmes has guided me in looking for the clinical pearls I tried to imbed in these columns. With this, my final column, I'll share some parting tips.

Looking Back

The expanding scope of our knowledge, of biochemical pathways, cellular biology and genetic modulation, has continued to accelerate over the years, and I must admit I have used the monthly deadlines and selected topics to keep myself, as well my readers, abreast. I will continue to read a wide range of scientific literature and hope you will too. But it is at these times I start to reel off all that is still left unsaid ...

Please consider debriding corneal ulcers, the removal of fibrin and bacterial load and necrotic tissue will enhance antibiotic kinetics. Debridement and *ubi pus*, *ibi evacuo* have stood the test of time, back to the Romans. Then a drop of peroxide; don't forget the value of disinfectants in this era of uncertain antibiotic sensitivity. I've also noted that frequent use of topical aminoglycosides such as gentamicin dramatically decreases melt in scleromalacia. I have no idea why. I was always waiting for a larger series to report this.

When I approached him about it, corneal expert Claes Dohlman, MD, PhD, agreed that the only way for a researcher to understand the role of inflammatory mediators and byproducts in the human eye was to use the drugs himself, but suggested offering only one eye for science. I did that—in fact, I've tested most known inflammatory mediators and byproducts in my right eye for the past 30 years. (The presence of unilateral open-angle glaucoma and asymmetric early lens changes in this eye may be the result of this multi-year, multi-agent experiment.) Along the way, insight into the action of leukotrienes, prostaglandins, antihistamines, tryptase, bradykinin,

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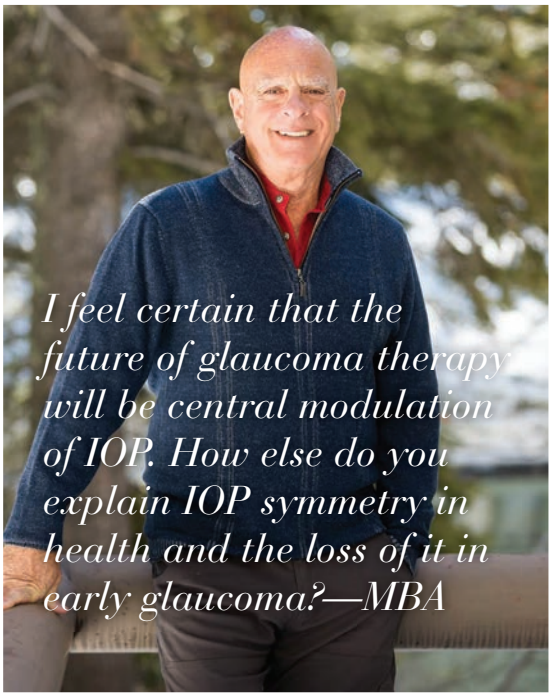
platelet activating factor and dozens of other agents helped guide our lab and the ophthalmic pharma groups that I consulted with over these decades. Of course, "one eye for science" requires prior animal testing and incremental titration: Don't try this at home!

My use of topical leukotriene beta 4 produced a prolonged migraine and a massive white blood cell infiltration into conjunctiva—fortunately without degranulation stimulus. Even this adverse reaction provided a kernel of wisdom: Isn't it reasonable to suggest that a migraine associated with throbbing pain over one eye without visual disturbance, identified and slightly relieved by pressure on a pulsating temporal artery, might be related to pollen entering the eye in a predisposed (allergic) subject? Under this premise, allergic neutrophil infiltration results in local degranulation, release of histamine and other vasoactive amines, and pathologic vasoconstriction. Histamine had already been identified in Horton's cluster headaches. So, in hindsight, after putting the most powerful neutrophil chemotactic factor, LTB4, in my right eye, it was no wonder I developed a severe migraine for more than a week. At that point, I thought that I had done myself in! The use of beta-blocker drops and topical high-strength ketotifen eye drops provided significant relief and became staples among our type-one personality, migraine-sensitive scientists.

At this time we still don't fully understand the cause of open-angle glaucoma and the full mechanism of treatments like alpha-agonists. Parasympathetic agents, beta blockers and prostanoid therapies point to a large number of possible etiologies. But I feel certain that the future will be central modulation of IOP. How else do you explain IOP symmetry in health and the loss of it in early glaucoma? All other paired organs in the body are under central control. When I put either a beta blocker or an alpha agonist in my nose (just one nostril), the IOP drops in both eyes: with this N of 1, I can rest my case. Those of us working on arachidonic acid knew prostaglandins could reduce pressure in inflammation; we called it hypotony and thought it would lead to phthisis bulbi. Even though I put these agents in my eye, it took a non-ophthalmologist to see its potential use in glaucoma.



I cannot help wondering what we might learn by looking at other ultrafiltration-producing organs, the semicircular canal fluid, cerebral spinal fluid and perhaps aspects of the glomerulus. Secretion of an acellular, protein-free fluid is not unique to the aqueous humor. Certainly the ciliary body and choroid plexus share some physiology and pathology.

Team Efforts

I have learned much with Paul Gomes (Vice President for Allergy at the ophthalmology consulting firm Ora Inc.) throughout decades of challenging tens of thousands of eyes with pollen. Twenty FDA drug approvals aside, many questions remain unanswered, particularly as they relate to chronic or panseasonal ocular allergy. Representing perhaps one-third of all ocular allergy patients, they don't respond well, if at all, to current antihistamine or mast-cell stabilization therapy. There's a need to understand how these patients differ immunologically from others with histamine-dependent allergy. Of course, ongoing research will point the way and clinical trials will continue. I have no doubt there will be another generation of anti-allergy eye drops.

Vernal keratoconjunctivitis has been of great interest to me. The dramatic effect of aspirin, particularly in contrast to the negligible effect of other NSAIDs in this disease, suggests additional ocular anti-inflammatory effects of this ancient, tree-bark-derived agent. In a human arachidonic acid ocular challenge model it proved to be far superior to NSAIDs. Asprin is difficult to formulate for topical use, but new nanotechnology formulations may change that. Another key aspect of VKC is that it proved to be a great model for understanding the role of histamine in the eye; the absence of histaminase appears to be a primary underlying etiology of VKC.[1] This implies a metabolic disease with delayed development of this enzyme (as VKC patients invariably outgrow the disease) allowing an allergic reaction to run wild. The path for therapeutic development seems clear and I hope someone takes this route.

More Connections

Dry eye is undoubtedly a wide

range of conditions and diseases still grouped together and, in my opinion, not driven by subtle changes in osmolality. New therapies in the past two years show a role for treating inflammation and neural lethargy, and we at Ora have been pleased to be part of these and other, up-and-coming dry-eye treatments. Meibomian gland "disease" must be separated from dramatic gland dropout in normal aging and the life cycle of individual holocrine glands that puts them through an inspiration phase. We have enough diseases without creating more.

We have not made dramatic progress on anti-inflammatory therapy since the advent of steroids in the eye in the mid-1950s. "Soft steroids" was marketing hype for "weak steroids," and have still not broken the anti-inflammation and intraocular pressure effect connection. Cyclooxygenase-1 inhibitors have helped in the margins. Topical aspirin could hold some benefit if formulation difficulties can be addressed, and the splenic tyrosine kinase inhibitors that target the immunoglobin-receptor pathways hold great promise for the future.[2]

As for wet age-related macular degeneration, I once told my colleague Judah Folkman, MD, "Anti-VEGF will not work and will only produce necrosis." I was wrong. Had he lived, he would have been a Nobel Laureate.

The next great frontier is dry AMD, which is currently the center of much attention. The recognition that form follows function is leading to exciting preliminary results in psychophysical tests for early identification of dry AMD at the reversible stage.[3] I confess to being focused on this disease with my own research group at Ora, as we aim to develop new models for screening.

Although the chimeric antigen receptor therapy revolution is upon us, changes in drug reimbursement do not bode well for the continued investment in research needed for the next generation.[4,5] In ophthalmology, there is no longer interest in incremental drug development, which has been at the core of our historic progress, thanks to the economic benefits accruing to the six sisters, the large pharmacy chains and their benefit managers. These nefarious managers control drug availabilities even after Food and Drug Administration approval of new agents with demonstrated superiority to existing agents, in order to preserve a multi-billion dollar rebate scam that resembles the payola debacle in the music industry 50 years ago. In time, this will get the legislative attention it deserves and then, hopefully, the drug development that has increased the length and quality of our lives will continue apace.

The routine eye exam is now quite clearly capable of being fully automated, with any initial abnormality tagged for referral. This will most certainly shift ophthalmic practice to a pathology-enriched environment and enhance early detection of disease and visual dysfunction; the compiling, organizing, sequencing and miniaturizing of appropriate equipment are well under way. Computerized recognition of retinal and corneal abnormalities is now excellent and having had the chance to help in their clinical regulatory progression, I find them impressive. I suspect these kiosks will be placed in pharmacies and dispense prescriptions for glasses and contacts with minimal or no charge for testing.

Artificial intelligence is much in the news today and its application to clinical history is burgeoning. In an early version smart form, 25 years ago, we developed a questionnaire/algorithm for differentiating peripheral immune infiltrates from early infectious corneal ulcers, which proved important in the early years of continuous-wear contact lenses. This form then proved in thousands of cases to be more accurate than any one of us over time. The prolonged nature of that endeavor for one situation can be obviated by self-learning questionnaires and their associated algorithms, leading ultimately to timely diagnosis online from a mobile device. The Kardia smartphone application (AliveCor, Mountain View, Calif.) allows for a remote electrocardiogram completed through a small touch pad connected via Bluetooth to a user's smartphone, then to a computer for analysis. Abnormalities are sent to a live cardiologist, for further examination. At Ora, we have already validated and used (in FDA trials) a smartphone camera with an adapted eye cone to control quality, and an alarm-prompted, smartphone-based treatment diary. Embrace the future!

Finally, my thanks to many colleagues, particularly Mathea Allansmith, Wiley Chambers, Claes Dohlman, Joan Miller, Jerry Cagle, Art Neufeld and the late Sean Murphy and David Maurice. Your guidance, support and friendship over half a century have been much appreciated. I conclude as I have in many lectures, in many countries, over many years, with one of my favorite pearls: If it itches, it's allergy; if it burns, it's dry eye; and if it sticks in the morning, it's bacterial. REVIEW

Dr. Abelson is a clinical professor of ophthalmology at Harvard Medical School and Emeritus Surgeon and Trustee at the Massachusetts Eye and Ear Infirmary. He is the founder of the ophthalmic consulting firm, Ora.

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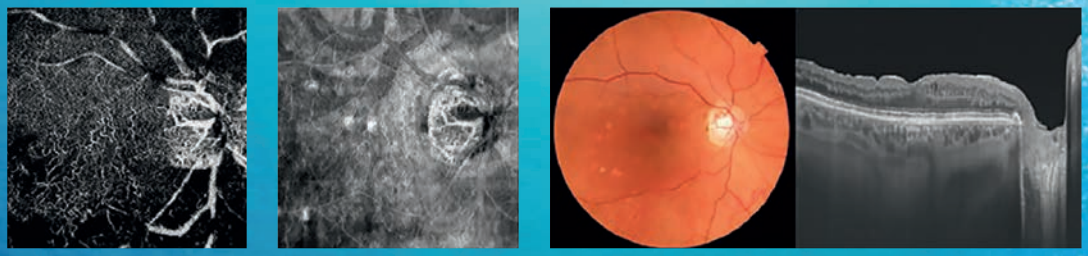

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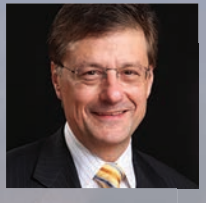

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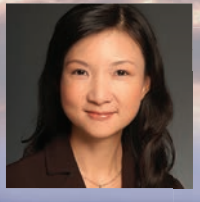

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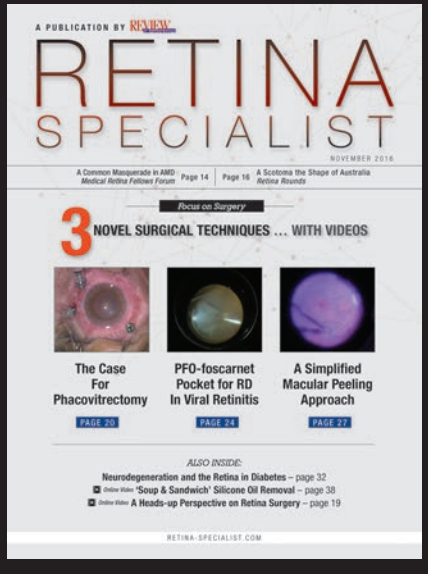

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Using VEGF Inhibitors For Diabetic Retinopathy

Though these remarkably helpful drugs are mainstays for AMD and DME, they're also showing efficacy in DR.

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Diana V. Do, MD, Palo Alto, Calif.

Several large multicenter studies have firmly established anti-vascular endothelial growth factor drugs as first-line treatment for diabetic macular edema. In addition to their efficacy at treating DME, anti-VEGF drugs have been shown in a number of studies to have promise for halting and reversing diabetic retinopathy. In this article, we'll review the current data supporting the use of anti-VEGF medications for the treatment of diabetic retinopathy.

Ranibizumab

In April 2017, ranibizumab was approved by the FDA for treatment of all forms of diabetic retinopathy. Before that point, however, several studies began showing the drug's treatment potential.

RISE and RIDE were large multicenter trials evaluating the use of ranibizumab (Lucentis, Genentech; South San Francisco, Calif.) for DME.[1] Patients were randomized to receive 0.3-mg or 0.5-mg ranibizumab or sham injections. In addition to showing ranibizumab's efficacy for treatment of DME, a secondary analysis showed a ≥3-step improvement in Diabetic Retinopathy Severity Scale (DRSS) in 15 percent and 13.2 percent of patients receiving monthly 0.3-mg or 0.5-mg injections, respectively, at 36 months, compared to only 3.3 percent of patients in the sham group.[1] The probability of progression to proliferative diabetic retinopathy was 39 percent in the sham group, compared to 18.3 percent and 17.1 percent in the 0.3-mg and 0.5-mg

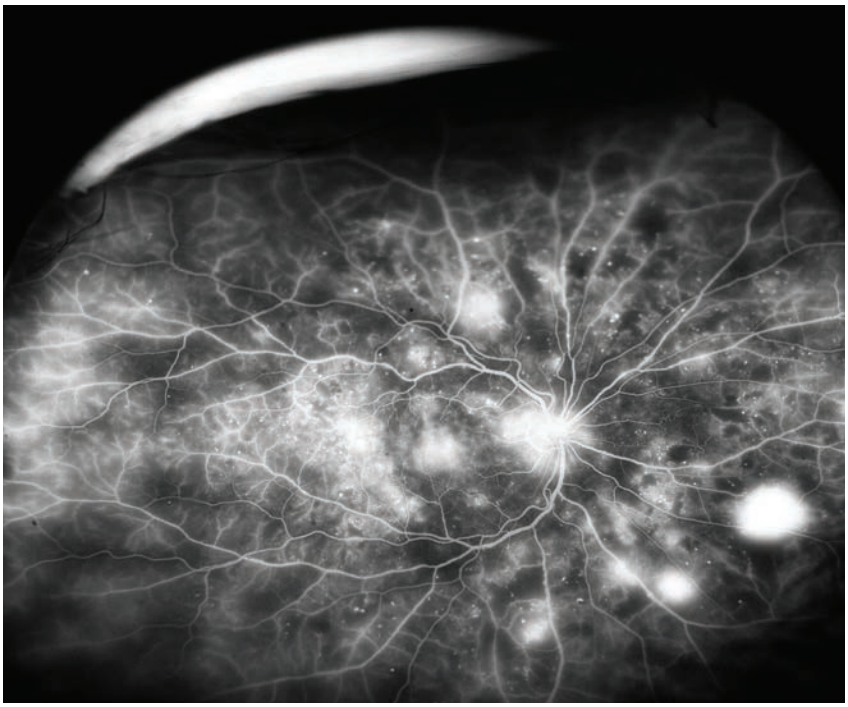

Figure 1. Fluorescein angiography showing areas of retinal neovascularization consistent with proliferative diabetic retinopathy.

This article has no commercial sponsorship.

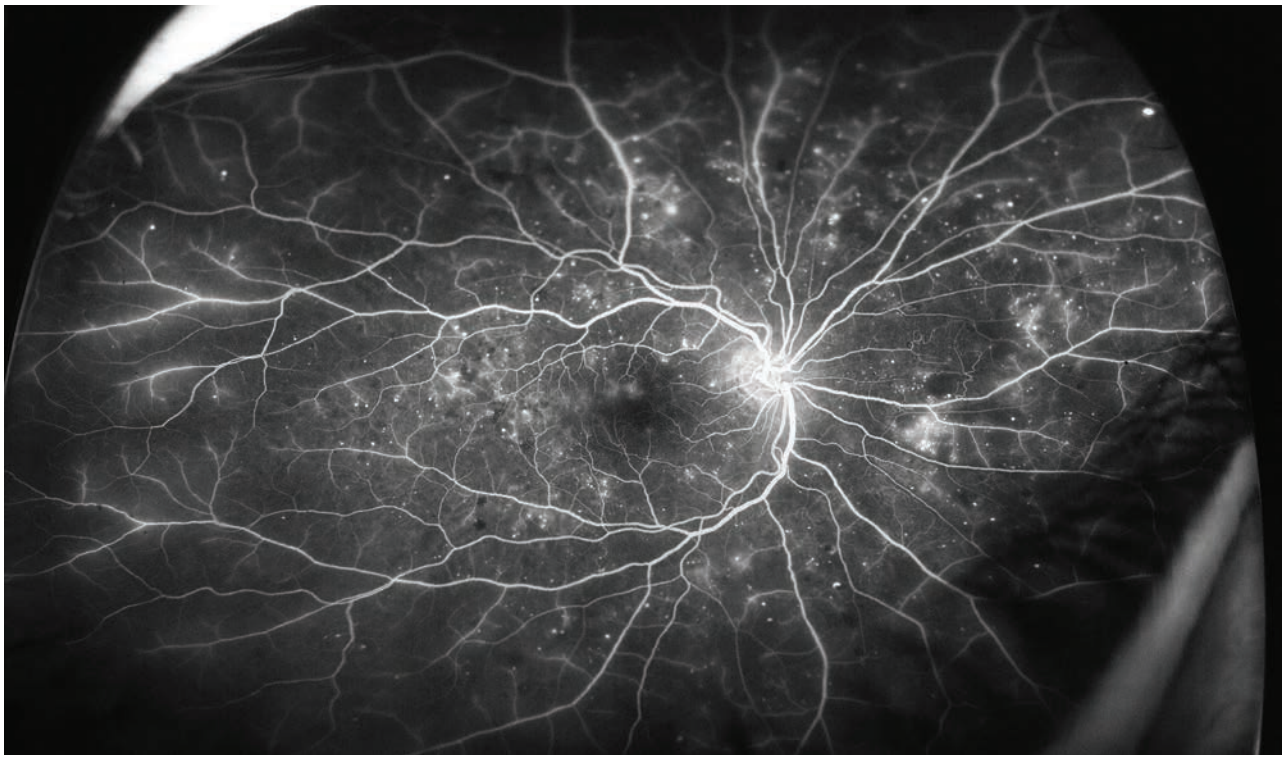

Figure 2. Fluorescein angiography of the same eye shown in Figure 1, following intravitreal bevacizumab injections, demonstrating regression of neovascularization.

groups, respectively.

An open-label extension of RISE and RIDE enrolled 500 patients who had completed the original 36-month randomized studies.[2] Patients were offered ranibizumab 0.5 mg as needed based on predefined criteria, and outcomes at 48 months were examined. At 48 months, 11.2 percent and 7.6 percent of patients in the 0.3-mg and 0.5-mg groups achieved a ≥3-step DRSS improvement, respectively, compared to 4.8 percent of patients in the sham-with-crossover group. Only 2.5 percent of patients receiving ranibizumab had a ≥2-step worsening, compared to 11.3 percent of sham patients. Patients originally randomized to ranibizumab had an overall lower risk of PDR development than the sham group, and this finding persisted to month 54.[2]

Diabetic Retinopathy Clinical Research Protocol I was a randomized trial comparing focal laser (L), triamcinolone plus focal laser (T+L), ranibizumab plus prompt focal laser (R+pL), and ranibizumab plus deferred laser (R+dL) for DME.[3] An additional analysis was performed to evaluate the effects of intravitreal ranibizumab and triamcinolone on worsening of diabetic retinopathy in this study.[4] For patients without PDR, at 36 months, retinopathy worsened in: 7 percent in R+dL; 18 percent in R+pL; 23 percent in sham+L; and 37 percent in T+L.

Among patients with PDR, at 36 months, 18 percent, 21 percent, 40 percent and 12 percent had worsening of retinopathy among the same respective groups. Patients who received ranibizumab or triamcinolone had lower rates of vitreous hemorrhage and were less likely to require panretinal photocoagulation laser treatment.

DRCR Protocol S compared ranibizumab to PRP for high risk PDR.[5] Patients with PDR were randomized to six ranibizumab injections every four weeks followed by as-needed retreatment at follow-up or PRP. The study demonstrated that ranibizumab treatment was non-inferior to PRP with regard to visual acuity outcomes. Additionally, patients with PDR treated with ranibizumab progressed less than patients treated with PRP, had less-affected peripheral vision, had more improvement in terms of central macular thickness and were less likely to go on to vitrectomy than patients who received PRP.[5]

Aflibercept

Aflibercept is FDA-approved for diabetic retinopathy in the setting of DME. A discussion of the following major studies explains its potential treatment benefit.

VIVID and VISTA were large multicenter studies comparing intravit-

real aflibercept (Eylea, Regeneron; Tarrytown, N.Y.) to focal laser for the treatment of DME.[6] Patients were randomized to receive focal laser, 2 mg of intravitreal aflibercept every four weeks or 2 mg of intravitreal aflibercept every eight weeks after five monthly loading doses. Patients who received aflibercept had better visual acuity improvement than those who received focal laser, and also were more likely to have ≥2-step improvement in DRSS score. Patients in both aflibercept groups were three times more likely to achieve ≥2-step DRSS improvement than patients in the laser group.

DRCR Protocol T was a randomized clinical trial comparing aflibercept 2 mg, bevacizumab 1.25 mg and ranibizumab 0.3 mg for the treatment of DME.[7] A secondary analysis was performed to evaluate the effects on DRSS with these agents.[8] At one year, in patients with NPDR, improvement in diabetic retinopathy severity was seen in 31.2 percent with aflibercept, 22.1 percent with bevacizumab and 37.7 percent with ranibizumab. In patients with PDR, improvement in diabetic retinopathy severity was seen in 75.9 percent for aflibercept, 31.4 percent for bevacizumab and 55.2 percent for ranibizumab. These effects persisted at two years. These findings demonstrate less improvement with bevacizumab than with the other two agents in terms of DRSS, and show that aflibercept was associated with more improvement in patients with PDR.

Bevacizumab

The intravitreal bevacizumab or laser therapy in the management of diabetic macular edema (BOLT) study compared bevacizumab (Avastin, Genentech; South San Francisco, Calif.) to focal laser for DME.[9] Patients in the bevacizumab group had significant BCVA improvement and improvement in central macular thickness compared to patients in the laser group. DRSS scores were also assessed, and patients receiving bevacizumab trended towards DR reduction, but this effect was not statistically significant, possibly due to the small size of the study.

As mentioned above, DRCR Protocol T compared bevacizumab with ranibizumab and aflibercept for diabetic macular edema, and found that all three agents reduce DR severity through two years of follow-up, although patients treated with bevacizumab had less improvement than aflibercept or ranibizumab.[8]

Bevacizumab is frequently used off-label for the treatment of DME and is a cost-effective alternative to ranibi-

zumab or aflibercept. Because bevacizumab blocks VEGF, it likely will improve diabetic retinopathy. However, further investigation is needed to fully evaluate the effects of bevacizumab on DR.

Discussion

Secondary analyses of several large clinical trials have demonstrated the benefit of anti-VEGF treatment, specifically ranibizumab and aflibercept, at halting—and in some cases reversing—DR. The clinical importance of these improvements in DRSS score with the administration of intravitreal anti-VEGF was evaluated by the Doheny Eye Institute's Michael Ip, MD, and his colleagues.[10] Based on a post-hoc analysis of data from RISE and RIDE, BCVA improvement of ≥15 letters was 51.9 percent and 44.6 percent in patients who had a two- or three-step improvement in DRSS, respectively. In contrast, ≥15 letter improvement in patients with either a one-step DRSS improvement, no change, or worsening of DRSS, was 37.9 percent, 39.6 percent and 26.7 percent, respectively. In addition, a loss of ≥15 letters was seen in 13.3 percent of patients with DRSS worsening compared to zero to 2.8 percent in patients with stable or improved DRSS. Patients with DRSS improvement were also more likely to achieve resolution of macular edema than those with stable or worsening DRSS. Thus, improvements in DRSS with ranibizumab treatment were also associated with better vision and better DME response to treatment. Lower rates of transitioning from NPDR to PDR mean less vitreous hemorrhage and less need for PRP.

Protocol S demonstrated noninferiority of intravitreal ranibizumab compared to PRP for treatment of PDR, and the data suggest some potential benefits of ranibizumab over laser in terms of less effect on peripheral vision, better central macular thickness, and lower rates of vitrectomy, as mentioned above. These findings may lead to a paradigm shift in the treatment of PDR, although the frequency of injections and long-term follow-up intervals have yet to be established. PRP laser will remain an important treatment modality for PDR due to concerns about the burden of injections and those patients unable to return for frequent follow-up.

Bevacizumab is frequently used off-label for DME. Because it blocks VEGF, it likely will improve diabetic retinopathy. However, further investigation is needed to fully evaluate the effects of bevacizumab on diabetic retinopathy.

At our institutions, we treat patients with DME and concomitant DR with intravitreal anti-VEGF injections. We don't routinely treat patients with NPDR without macular edema with intravitreal anti-VEGF injections. For our patients with PDR, we have a frank discussion regarding the results of Protocol S, and discuss the options of intravitreal anti-VEGF or PRP or combining both, deciding with the patient which treatment to pursue. For the majority of patients with PDR, we recommend initial treatment with anti-VEGF injections and then consider adding PRP laser at a subsequent visit if the burden of visits and injections is too difficult for the patient. Ultimately, we provide the patient with an individualized treatment plan based on the available medical evidence, in order to prevent progression of their proliferative diabetic retinopathy.

Looking towards the future, the treatment intervals and follow-up required to maintain improvements in diabetic retinopathy and proliferative DR will need to be determined, but long-acting anti-VEGF agents and delivery methods have the potential to transform the diabetic retinopathy treatment landscape. REVIEW

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Researchers Investigate Induced Astigmatism

In a retrospective study of patients who underwent LASIK surgery between 2005 and 2014, researchers from Holon, Israel, wanted to compare the astigmatism induced surgically by spherical hyperopic LASIK versus myopic LASIK in nonastigmatic eyes. The researchers calculated the mean absolute SIA and performed risk-factor analysis for induced astigmatism. Differences between H-LASIK and M-LASIK were analyzed.

The study analyzed eyes of 3,877 patients who underwent M-LASIK and 549 patients who underwent H-LASIK, and who were non-astigmatic preoperatively and received a non-astigmatic treatment. Three months after surgery, hyperopic treatment induced more astigmatism (0.49 ±0.48 D) than did myopic treatment (0.36 ±0.4 D) (p<0.001). In the H-LASIK group, the risk factors for induced astigmatism greater than 0.5 D were a higher preoperative refractive error (p=0.003) and larger optical zone (7 vs. 6 mm).

In the M-LASIK group, eyes with SIA greater than 0.5 D tended to have steeper corneas preoperatively (43.8 ±1.5 vs 43.6 ±1.4 D; p=0.001), a higher spherical equivalent (-3.43 ±1.53 vs. -3.07 ±1.45; p<0.001), and smaller treatment zones (6 vs 7 mm). In H-LASIK, the mean induced astigmatic axis was 74.6 degrees.

Based on the results of this retrospective study, researchers concluded that there was a consistent trend toward more SIA in H-LASIK and in higher refractive error correction. In H-LASIK, larger optical zones induced more SIA, while in M-LASIK smaller ones caused it.

Cornea 2017;36:1040-1043
Karmona L, Mimouni M, Vainer I, et al.

Visual and Refractive Outcomes of SMILE

Researchers from Hong Kong investigated the effect of the learning curve on small-incision lenticule extraction during surgeons' first two years of experience.

SMILE was performed using the 500-kHz VisuMax femtosecond laser by the same surgeon. The initial 100 patients after the surgeon started operating independently were Group 1; the most recent 100 patients were Group 2. The same laser settings and technique were used. The visual and refractive outcomes were compared between groups at postoperative week one and at six months. Vector analysis was performed for eyes with astigmatic correction.

Two hundred right eyes of 200 patients were included. Age, preoperative corrected visual acuity, manifest refraction and central corneal thickness were similar between groups (p≤0.154). Postoperatively, the efficacy index at one week was better in Group 2 (Group 1: 0.85 ±0.16 vs. Group 2: 0.91 ±0.10; p=0.019) but was similar between groups at six months (Group 1: 0.91 ±0.14 vs. Group 2: 0.94 ±0.08; p=0.181). The safety index was higher in Group 2 at one week (Group 1: 0.93 ±0.10 vs. Group 2: 0.95 ±0.08; p=0.045) and six months postoperatively (Group 1: 0.97 ±0.07 vs Group 2: 0.99 ±0.03; p=0.011). Vector analysis showed that postoperative residual astigmatism and misalignment of astigmatic correction were lower in Group 2 than in Group 1 (p≤0.039) at one week and six months. The duration of docking and duration of lenticule extraction were shorter in Group 2 (p≤0.034).

Researchers concluded that the study showed that faster visual recovery, a better safety profile and more accurate astigmatic correction could be attained with increasing surgical experience.

Cornea 2017;36:1044-1050
Chan T, Ng A, Cheng G, et al.

Access to YAGs: Optometrists vs. Ophthalmologists

Researchers from the Mayo Clinic in Rochester, Minn., wanted to quantify Medicare beneficiary proximity to his or her YAG-capsulotomy-providing ophthalmologist or optometrist in Oklahoma by calculating driving distances and times.

The cross-sectional cohort study used 2014 Oklahoma Medicare 100-percent and 5-percent data sets and Google Maps distance and travel-

time application programming interfaces. These data sets were obtained to identify the office street addresses of Oklahoma ophthalmologists and optometrists who submitted claims to Medicare for a YAG laser capsulotomy, and the county addresses of the corresponding Medicare beneficiaries who received the laser capsulotomies. The shortest travel distances and travel times between the beneficiary and the laser provider were calculated by using Google Maps distance and travel time interfaces.

In 2014, 90 (57 percent) of 157 Oklahoma ophthalmologists and 65 (13 percent) of 506 Oklahoma optometrists submitted a total of 7,521 and 3,751 YAG laser capsulotomy claims to Medicare, respectively. By using the Medicare Limited 5-percent dataset, there was no difference in driving distance between beneficiaries who received a laser capsulotomy from an ophthalmologist (median: 39 miles; interquartile range: 13 to 113 miles) compared with an optometrist (median: 46 miles; IQR: 13 to 125 miles; p=0.93) or in driving time to an ophthalmologist (median: 47 minutes; IQR: 19 to 110 minutes) compared with an optometrist (median: 50 minutes; IQR: 17 to 117 minutes; p=0.76).

Based on these results, researchers stated that, for Medicare beneficiaries, there was no difference in geographic access to YAG laser capsulotomy whether performed by an Oklahoma ophthalmologist or optometrist as determined by calculated driving distances and times.

Ophthalmology 2017;124:1290-1295
Mahr M, Erie J

Brolucizumab vs. Aflibercept For Neovascular AMD

In a prospective, randomized, double-masked, multicenter, two-arm, Phase II study, researchers compared the efficacy and safety of brolucizumab with aflibercept to treat neovascular age-related macular degeneration.

The study examined 89 treatment-naïve participants, aged 50 and above, with active choroidal neovascularization secondary to AMD. The eligible participants were randomized 1:1 to intravitreal brolucizumab (6 mg/50 µl) or aflibercept (2 mg/50 µl). Both groups received three monthly loading doses and were then treated every eight weeks (q8) with assessment up to week 40. In the brolucizumab group, the final q8 cycle was extended to enable two cycles of treatment every 12 weeks (q12; to week 56); participants on aflibercept continued on q8. Unscheduled treatments were allowed at the investigator's discretion. The primary and secondary hypotheses were noninferiority (margin: five letters at a one-sided alpha level 0.1) in best-corrected visual acuity change from baseline of brolucizumab versus aflibercept at weeks 12 and 16, respectively. BCVA, central subfield thickness and morphologic features were assessed throughout the study.

The mean BCVA change from baseline (letters) with brolucizumab was noninferior to aflibercept at week 12 (5.75 and 6.89, respectively [80 percent confidence interval for treatment difference: -4.19 to 1.93]) and week 16 (6.04 and 6.62 [-3.72 to 2.56]), with no notable differences up to week 40. Outcomes exploring disease activity during the q8 treatment cycles suggest greater stability of the brolucizumab participants, supported by receipt of fewer unscheduled treatments versus aflibercept (six vs. 15) and more stable CSFT reductions. In addition, from post hoc analysis, a greater proportion of brolucizumab-treated eyes had resolved intraretinal and subretinal fluid compared with aflibercept-treated eyes. Approximately half of the brolucizumab-treated eyes had stable BCVA during the q12 cycles. Brolucizumab and aflibercept adverse events were comparable.

During the matched q8 phase, the BCVA in brolucizumab-treated eyes appeared comparable to aflibercept-treated eyes, with more stable CSFT reductions, receipt of fewer unscheduled treatments and higher rates of fluid resolution. The brolucizumab safety profile was similar to aflibercept over 56 weeks of treatment. Researchers claim that a 12-week treatment cycle for brolucizumab may be viable in a relevant proportion of eyes.

Ophthalmology 2017;124:1296-1304
Dugel P, Jaffe G, Sallstig P, et al.

Macular Degeneration and Aspirin Use

Researchers from Glendale, Calif., reviewed current literature on the benefits that aspirin provides for patients' cardiovascular health compared with the risk of worsening age-related macular degeneration. They performed a review and critically analyzed six cardiovascular and four ophthalmological trials regarding risks and benefits of aspirin use. The prospective, randomized cardiovascular trials comprised 167,580 subjects, while the three smaller ophthalmological data sets had 12,015 subjects.

The meta-analysis of the literature demonstrated a statistically significant 32-percent reduction in the risk of nonfatal stroke with regular aspirin users. The study also documented that aspirin users decreased the risk of fatal vascular deaths by 15 percent. Of the three ophthalmological studies highlighting the adverse affects of aspirin associated with AMD, all suggested an exacerbation of AMD without statistical significance or broad confidence bands.

Overall, the researchers say the number, size and quality of the cardiovascular studies recommending aspirin use are far superior to the fewer, smaller and conflicting studies suggesting a possible adverse effect of aspirin use in relation to AMD. The benefits of aspirin usage include preserving the duration and quality of life by decreasing stroke and heart-at-

tack risk, according to the results. Researchers say that these benefits seem to far outweigh the theoretical risks of possibly exacerbating wet AMD, which can be reasonably controlled with anti-VEGF therapy.

Retina 2017;37:1630-1635
Small K, Garabetian C, Shaya F

Gamma-Irradiated Corneal Patch Graft Thickness

This cross-sectional study of graft thickness using anterior segment optic coherence tomography was conducted at Johns Hopkins Hospital to measure gamma-irradiated sterile cornea patch graft thickness as a function of time after surgery, estimate the rate of graft thinning, and determine risk factors for graft thinning. They examined 107 patients (120 eyes, 120 ADDs) 18 years or older who underwent aqueous drainage device surgery at Johns Hopkins with GISC patch graft between July 1, 2010, and October 31, 2016.

Of the 107 patients included in the analysis, the mean age was 64 ±16.2 years. The mean time of measurement after surgery was 1.7 years (range: one day to six years). Thinner grafts were observed as the time after surgery lengthened (regression coefficient, -60 µm per year since surgery; 95% CI: -80 to -40 µm). The odds ratio of undetectable grafts per year after ADD surgery was 2.1 (95% CI: 1.5-3.0; $p<0.001$). Age, sex, race, type of ADD, quadrant of ADD placement, diagnosis of uveitis or dry eye, and prior conjunctival surgery weren't correlated with the presence or absence of the graft.

This study showed that on average, the longer the time after surgery, the thinner the graft. These findings suggest that placement of a GISC patch graft is no guarantee against tube exposure, and that better strategies are needed for preventing this complication.

JAMA Ophthalmol 2017;135:941-946
Moledina A, Wang J, Jampel H, et al.

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An elderly patient with a history of diabetes presents with vision problems in his right eye.

Daniel J. Ozzello, MD, and James P. Dunn, MD

Presentation

An 87-year-old Caucasian male presented to the Retina Department at Wills Eye Hospital with one month of visual distortion and floaters in the right eye. There were no flashes or pain. Ocular history was significant for bilateral pseudophakia and moderate bilateral non-proliferative diabetic retinopathy, with macular edema worse in the right eye than the left. Previous treatment by an outside physician for the diabetic macular edema OD had consisted of five intravitreal injections of bevacizumab with little response, three injections of intravitreal triamcinolone with moderate response and nine injections of dexamethasone intravitreal implants with more sustained improvement in edema and visual symptoms.

Medical History

Medical history was significant for poorly controlled insulin-dependent diabetes mellitus with a hemoglobin-A1C value often above 10 percent, though most recently at 7.8 percent. He also reported hypertension, coronary artery disease and valvular heart disease treated with coumadin. He was a former smoker and denied alcohol or illicit drug use.

Examination

Visual acuity was 20/60 in the right eye with no pinhole improvement and 20/30 in the left eye. The right pupil was surgically irregular and was poorly reactive, but there was no relative afferent pupillary defect. The left pupil was round and reactive. Intraocular pressure was 13 mmHg OU, motility was normal and confrontational visual fields were full OU. External and eyelid examination were normal bilaterally. On the right, corneal examination revealed small- to medium-sized keratic precipitates. The anterior chamber was deep with 3+ cell. The iris was irregular with patches of atrophy, and there was a posterior chamber intraocular lens. Anterior examination on the left was normal except for a posterior chamber intraocular lens with mild posterior capsular opacity.

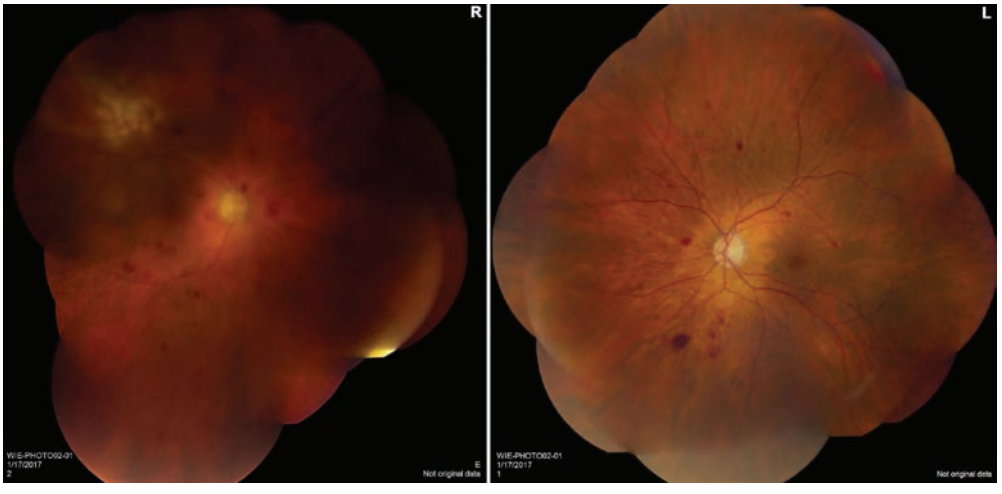

Figure 1. Montage fundus photographs of the right and left eyes demonstrating severe non-proliferative diabetic retinopathy. There is an area of retinal whitening with associated hemorrhages superotemporally in the right eye.

Dilated fundus examination of the right eye demonstrated vitreous haze with 1+ vitreous cells. The right optic nerve appeared normal without edema or neovascularization. The macula appeared thickened, and there were scattered intraretinal hemorrhages in the macula and throughout the periphery. There was a patch of retinal whitening in the supero-

temporal mid-periphery with irregular borders and a few associated retinal hemorrhages *(See Figure 1)*. The retinal vessels appeared mildly attenuated throughout, with a focal area of vasculitis associated with the area of retinal whitening. Dilated fundus examination on the left showed clear vitreous and a normal-appearing optic nerve. There was no macular edema, but intraretinal hemorrhages were noted to be scattered throughout the macula and periphery.

What is your differential diagnosis? What further workup would you pursue? The diagnosis appears below.

Workup, Diagnosis and Treatment

At presentation, the patient had already undergone an initial serologic evaluation for several forms of infectious retinitis by an outside ophthalmologist. HIV testing was negative, QuantiFERON-TB Gold was negative for tuberculosis and RPR/FTA-ABS tests for syphilis were nonreactive. Serum IgG testing returned positive for HSV-1, CMV and VZV, but IgM testing was negative for all three. Both IgG and IgM testing were negative for HSV-2. Complete blood count, basic metabolic panel and liver function tests were unremarkable.

Fundus photographs and OCT of the macula OU were taken in the office, and can be seen in Figures 1 and 2, respectively. Anterior chamber paracentesis with removal of 0.1 ml of aqueous fluid was performed on the right eye and sent for viral PCR studies. The patient was started empirically on oral valganciclovir 900 mg twice per day due to concern for cytomegalovirus retinitis.

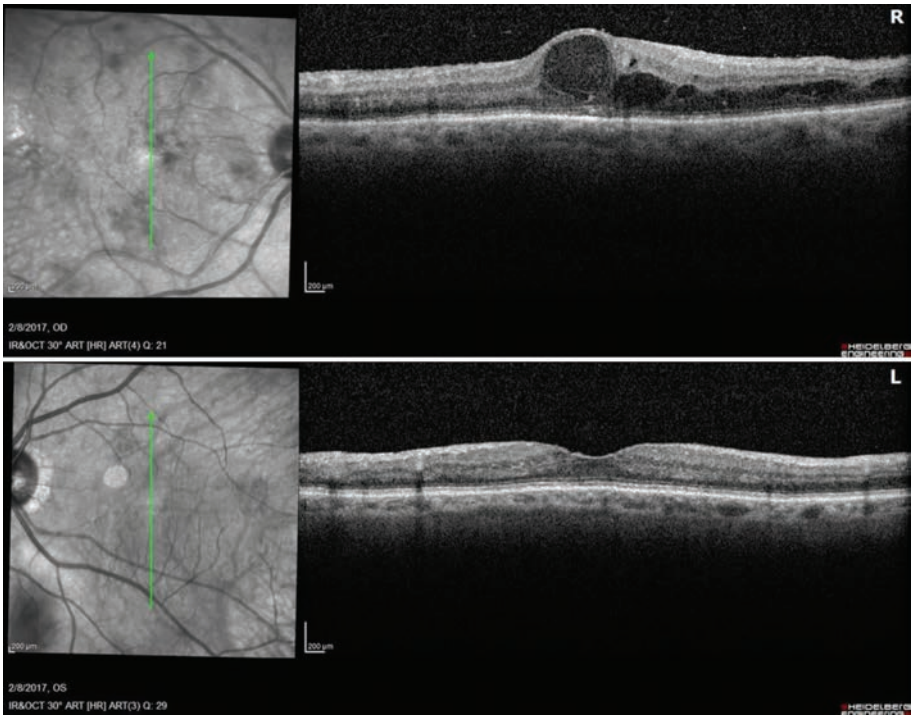

Figure 2. OCT macula of the right and left eyes demonstrating macular thickening and edema on the right.

The patient returned two weeks later with slight subjective improvement in his vision and fewer floaters. Visual acuity had improved to 20/50 in the right eye. The anterior chamber reaction was improved. Repeat dilated fundus examination revealed less vitreous haze and stability in the area of retinitis OD *(See Figure 3)*. PCR from the anterior chamber sample returned positive for CMV (377,000 copies/ml) and negative for HSV-1 and -2, VZV and *Toxoplasma gondii*.

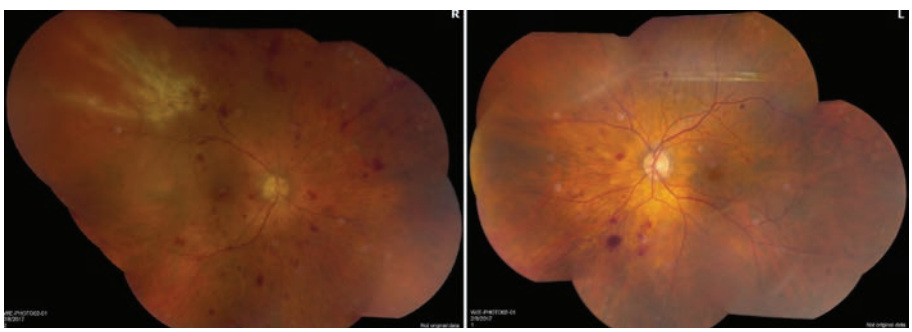

Figure 3. Repeat montage fundus photographs of both eyes showing less vitreous haze and stability of the retinitis OD after two weeks of oral valganciclovir therapy for CMV retinitis.

Discussion

Diabetes mellitus leads to a state of relative immune compromise through complex mechanisms, including dysfunction of host immune cells and increased virulence of pathogenic organisms in a high-glucose environment.[1-3] Although cytomegalovirus (CMV) retinitis is classically associated with acquired immune deficiency syndrome (AIDS) with CD4 counts below 50 cells/ul,[4] it has been reported in a variety of other conditions of immune dysfunction. A recent review identified 208 HIV-negative patients who developed CMV retinitis in one or both eyes. Nearly 80 percent of the patients included in the review had a clear cause for immune dysfunction such as malignancy, severe autoimmune condition requiring immunosuppression or a history of bone marrow or solid organ transplantation requiring long-term immunosuppressive therapy.[5] However, in 6.1 percent of patients, the only identified cause of immune dysfunction was diabetes. A total of 10.1 percent of patients developed CMV retinitis after injection of intraocular or periocular corticosteroids. Intraocular corticosteroids are a therapeutic option for diabetic macular edema, but they also lead to local immunosuppression within the eye. The patient presented here received multiple intraocular injections of corticosteroids that may have contributed to a degree of local immunosuppression sufficient for the development of CMV retinitis.

Cystoid macular edema is a frequent cause of decreased vision among patients with diabetes, but it is rarely encountered in patients with AIDS-related CMV retinitis.[6-9] Diabetes likely contributed to the macular edema seen in this case, but it may not have been the only causative factor. In contrast to AIDS-related CMV retinitis, HIV-negative patients with CMV retinitis may develop CME. HIV-negative patients with CMV retinitis develop more pronounced intraocular inflammation in response to the infection, and it is theorized that this inflammation may lead to the development of macular edema.[9] With treatment of the CMV retinitis, the CME seen in this case improved, though it did not completely resolve.

While medications active against vascular endothelial growth factor (VEGF) have become the first-line intravitreal pharmacologic agent in the treatment of diabetic macular edema based on the results of several large trials demonstrating their efficacy,[10-12] as previously stated, intravitreal corticosteroid agents are another therapeutic option. Investigations have shown that visual acuity gains in pseudophakic patients with DME treated with intravitreal triamcinolone may be similar to those treated with intravitreal ranibizumab, though the risk of intraocular pressure elevation is greater in those receiving corticosteroid injections.[10] Therefore, intravitreal steroid injection may be considered in patients with DME who have shown poor treatment response to injection of an anti-VEGF agent, as was the case with the patient presented above. Though these medications provide extended local anti-inflammatory action that is helpful in improving edema, they also cause extended local immunosuppression that can lead to intraocular infection. A large retrospective cohort study comparing the rates of development of bacterial endophthalmitis following intravitreal injection of a corticosteroid versus an anti-VEGF agent found a significantly increased odds ratio (6.92) among patients receiving a corticosteroid.[13] While the reasons for this increase are likely multifactorial, the study's authors felt that local immunosuppression played an important role.

In the patient presented, relative systemic immune compromise from diabetes as well as local immune suppression from intravitreal corticosteroid injections likely contributed to the development of CMV retinitis. CMV retinitis should be kept in the differential diagnosis when the typical funduscopic findings of the infection are seen, even among patients without HIV who are traditionally described as immunocompetent. The risk of intraocular infection should be considered in patients receiving repeated intravitreal corticosteroid injections. REVIEW

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xiidra® (lifitegrast ophthalmic solution) 5%

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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

Manufactured for: Shire US Inc., 300 Shire Way, Lexington, MA 02421.

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.
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Reference: 1. FDA approves new medication for dry eye disease. FDA News Release. July 2016. *http://www.fda.gov/newsevents/newsroom/pressannouncements/ucm510720.htm*. Accessed July 12, 2016.

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 on the adjacent page and Full Prescribing Information on Xiidra-ECP.com.

Shire