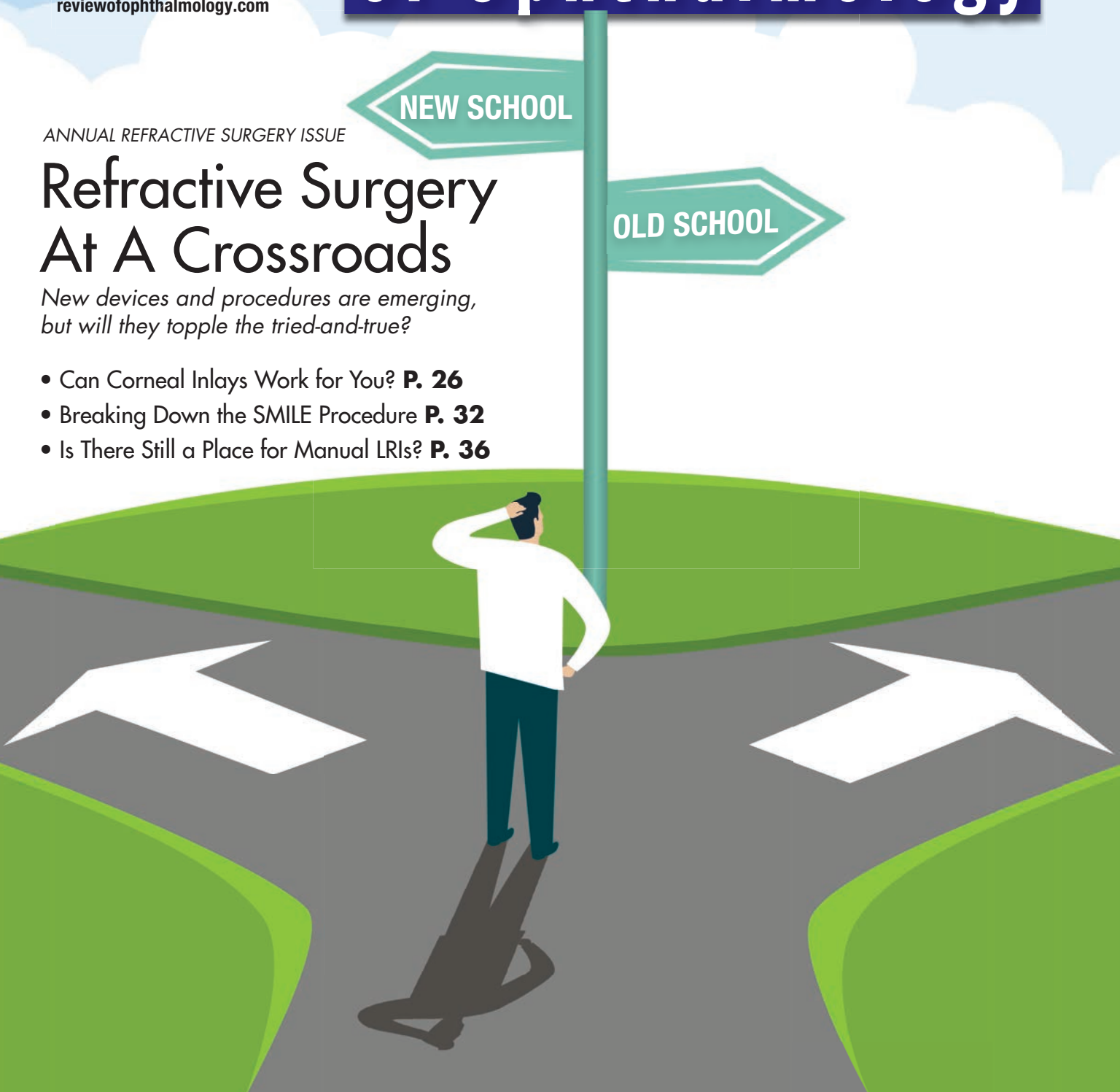
REVIEW® of Ophthalmology

February 2018

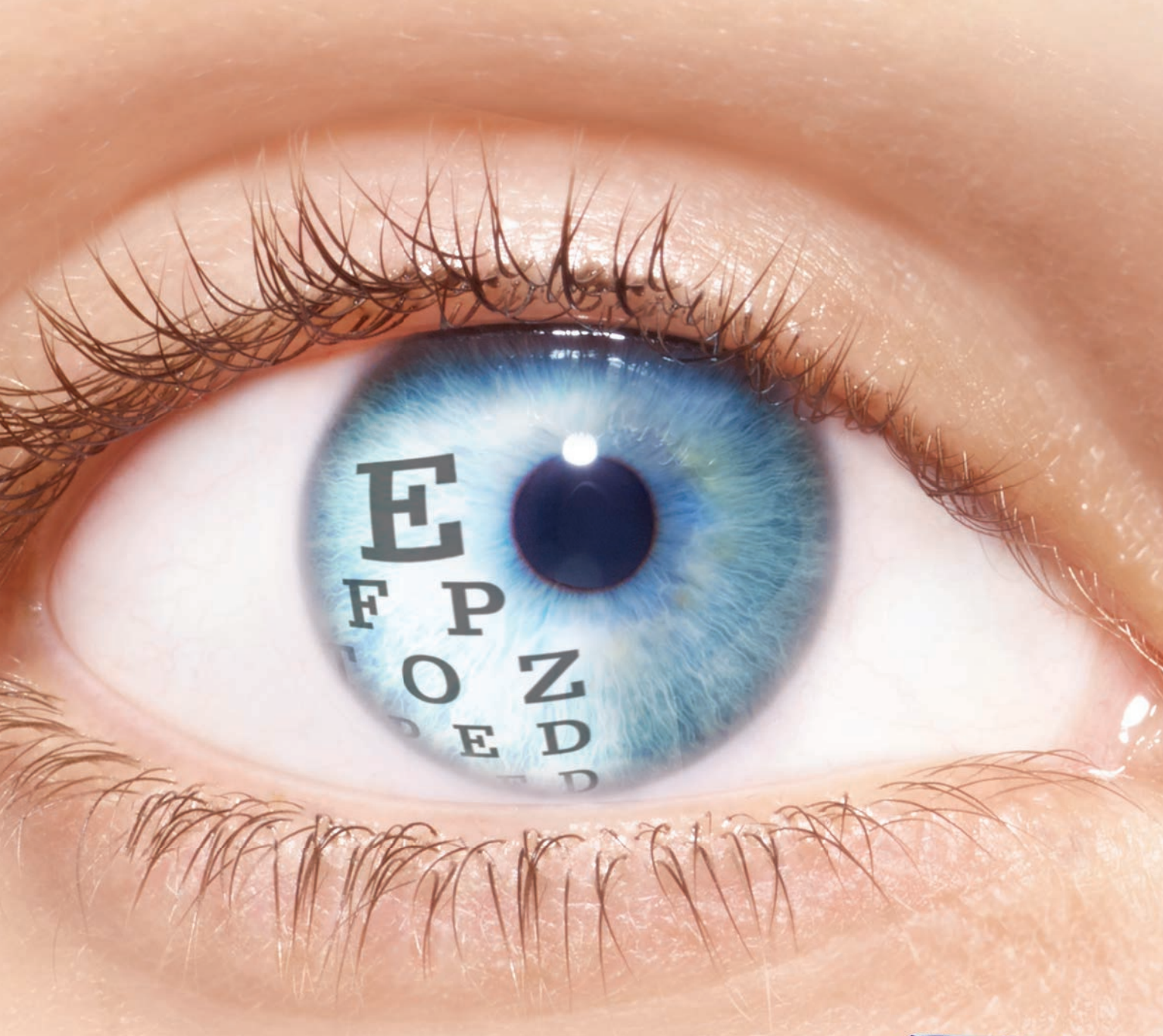
reviewofophthalmology.com



ANNUAL REFRACTIVE SURGERY ISSUE

Refractive Surgery At A Crossroads

New devices and procedures are emerging, but will they topple the tried-and-true?



YOUR PATIENTS' EYES TAKE IN A LOT.

Sometimes it's not all good. **SYSTANE® BALANCE Lubricant Eye Drops** are scientifically formulated to work on all 3 layers of the tear film, protecting the ocular surface with ingredients that **increase lipid layer thickness by 40%**.*,[1]

Recommend SYSTANE® BALANCE to your patients for the temporary relief of dry eye symptoms, and see how science leads to real relief.

*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 XXV • No. 2 • February 2018

Research Highlights from The Latest OIS Meeting

Just before this year's annual American Academy of Ophthalmology meeting, ophthalmologists and industry leaders got together at the Ophthalmology Innovation Summit to discuss the status of various nascent drugs, devices and ophthalmic companies, with an eye toward their current or future financial performance. *Review* caught up with OIS co-chair Emmett T. Cunningham Jr, MD, PhD, MPH, for his take on the highlights of the ophthalmic pipeline.

In the retina realm, several products generated buzz:

• This fall, Spark Therapeutics' gene therapy for inherited blindness, Luxturna, received a unanimous vote for approval by the FDA review panel, and followed this up with a December approval. "I think Spark's Phase III data was, in a word, tremendous," Dr. Cunningham says. "This is the first gene therapy we've seen approved in ophthalmology, and there's a clear efficacy benefit." Dr. Cunningham notes that gene-therapy trials coming up behind Luxturna include GenSight's trial for Leber's Congenital Optic Neuropathy, AGTC's trials in X-linked retinoschisis and achromatopsia; Nightstar's trial for choroideremia; and Regenxbio's trial in wet AMD.

• Novartis' brolucizumab, a small, single-chain variable antibody fragment, was shown to be noninferior to aflibercept (Eylea, Regeneron), for the treatment of wet age-related macular degeneration. "So, it looks like we'll have a fourth competitor coming to the AMD market," Dr. Cunningham says. "In the study, it was suggested that a higher proportion of patients can go to a less-frequent, 12-week dosing schedule."

• The company PanOptica is also developing a topical AMD treatment, a small-molecule tyrosine kinase inhibitor that has shown an effect. "We currently have very effective therapies in the form of intravitreal injections," Dr. Cunningham says, "so there is a high threshold for efficacy. This always makes for a high hurdle for something that's not administered in the eye, but rather is delivered topically."

• Genentech is continuing its LADDER trial for extended-release ranibizumab. "It involves a surgical procedure to implant the device needed to achieve extended release," Dr. Cunningham explains. "The intention with extended release is to decrease the frequency of injections from monthly to every three or four months, or even less frequently. It will be interesting to see how much extended-release ability LADDER shows."

• The pharmaceutical company Graybug Vision has been studying its six-month, time-release delivery of the small molecule sunitinib for wet AMD in animal models. Dr. Cunningham, who is an investor in Graybug, says that, if the approach works, it could be a broad inhibitor of the factors that promote AMD. "The current anti-VEGF agents are all targeting VEGF isoform A," Dr. Cunningham explains. "But there are other isoforms—particularly C and D—that also appear to be important. The sunitinib that the Graybug Vision implants should, theoretically, inhibit all isoforms over six months or more."

• Opthea presented evidence of add-on or combination efficacy with their anti-VEGF C/D TRAP-like molecule. "Interestingly," notes Dr. Cunningham, "they showed that they could get regression of the neovascularization in half of the patients that were treated in the current study."

• Iconic Therapeutics is working on a tissue-factor inhibitor for wet AMD, ICON-1, that has shown an ability to reduce retinal thickness and perhaps result in a more durable effect when used in combination with ranibizumab. "ICON-1 is an anti-tissue-factor fusion protein that has a unique target," Dr. Cunningham explains. "They showed that, when it was added to ranibizumab, there was more drying than with ranibizumab alone, though it was a small trial. The vision didn't change with the combination, however. I believe they plan to do a confirmatory Phase II trial."

• Allegro is working on an anti-integrin inhibitor as a treatment for diabetic retinopathy that, according to a post-hoc analysis of the Phase II data, may have enhanced efficacy in patients who are incomplete responders to anti-VEGF drugs. "There appears to be a clear drug effect." Dr. Cunningham says. "You can see some drying. And, as monotherapy, it seems to be an improvement vs. anti-VEGF. However, now they're trying to figure the way forward: Do they treat non-responders? All patients? They haven't

(Continued on p. 8)

Ophthalmic Product Development Insights

Matthew Chapin and Hal Patterson • Andover, Mass.

Nonclinical Considerations: Focus on Chemistry, Manufacturing and Controls

In this installment of Ophthalmic Product Development Insights, we'll review considerations for early-stage development of a new product as the entrepreneur charts his path to the first clinical trial. Most of the prior columns have emphasized that having the target-product profile drafted and defined early is critical to understanding key elements that contribute to designing a proper clinical development strategy. In this article, we'll specifically look at issues around CMC (Chemistry, Manufacturing and Controls), an area that's often outside the expertise and experience of the entrepreneur ophthalmologist. Proper CMC planning requires a basic understanding of the various interdependent steps of development: the design of the first clinical trial and of the toxicology studies; a preliminary idea of the commercial container closure; formulations; clinical dosing; pharmacokinetic considerations; and other components. All of these factors influence the CMC strategy.

We aren't able to exhaustively review all of the critical requirements for CMC here, but we can offer a few pearls we've picked up after taking part in many development projects. We hope these pearls are useful, and pertinent to the issues the entrepreneur/first time startup company will encounter.

Container Closure

Locally administered ophthalmic products are required to be sterile and in a container closure system that prevents contamination. This alone can cause unique issues, but also presents multiple options for proceeding in some cases.

The closure system you use in your early trials may not be the one you ultimately settle on for commercial use. It helps, however, to understand your end goal so that you can understand the overall strategy as you progress from early to later stages of development, and set expectations about requirements that may be involved at each step. This includes anticipating technology transfer, or shifting from one source or manufacturer to another, that may be required between Phases II and III. In ophthalmology, there are a few standard approaches to container closure: multidose, three-part systems (bottle, tip, cap); blow-fill seal (BFS; typically unit dose and preservative-free); and tubes, which are generally used for ointments. Other novel systems like multidose, preservative-free bottles; or dual-chamber containers that allow drug components to be separate until mixing before use, are available for consideration but are more complex solutions that often aren't used in early trials due to their time and cost requirements, which can be prohibitive for startup companies. In those cases, alternatives for use in the early trials should be considered. In some situations

in which a unit-dose blow-fill seal doesn't fit the timeframe/cost of the early program, small multidose containers can be used as single-dose units in initial studies. But we've also learned that headspace inside the bottle (the empty space inside the bottle between the top of the bottle and the drug inside) may be critical for a specific drug, and that scaling up the process to BFS later may highlight new issues when you're trying to start Phase III (e.g., problems with the heat involved in the BFS processing). Therefore, one needs to keep in mind the potential risks associated with any anticipated changes to container closure down the road. Ultimately, it's a business decision that balances time, cost and risk.

Formulations and Stability

As you plan your toxicology studies (per Good Laboratory Practices standards), it can be useful to know that the laboratory can take aliquots from bulk drug containers. (There's no specific requirement to use your intended clinical container closure system at this stage.) However, it's important to use a formulation for GLP ocular toxicology that's similar to—or, optimally, the same as—that used in your intended clinical study. In many cases, formulation and scale-up are the rate-limiting factors in ophthalmic product development, so setting your formulation early and then locking it in for the trials is important.

If changes to the formulation are necessary as you proceed through your nonclinical program, you need to consider whether you can demonstrate to the FDA that those changes don't impact safety or penetration of the drug into the ocular tissues. Adding a demulcent, for example, while a seemingly benign addition, can increase dwell time of the drug on the surface of the eye and thus, theoretically, drug penetration. Don't underestimate the implications of formulation changes as you near investigational new drug status with the FDA. It goes without saying that you want to avoid having to repeat GLP ocular toxicology.

Another aspect of formulation you don't want to underestimate is the addition of the preservative, which is usually required for multidose containers. While, again, simply adding a preservative may be considered a benign change, it's the type of change that requires a confirmation of stability as an early part of your plan, since there have been cases in which a preservative ends up compromising a drug's stability. Also, excipients have been shown to interact with preservatives. Therefore it's a good idea to perform a standard preservative effectiveness test (PET) early on as you work through formulation development, to avoid surprises that require you to make adjustments. If adjustments are required after learning that an excipient impacts preservative activity, as mentioned earlier, there's a risk that you'll need to repeat at least some bridging toxicology. These cases may not require a full toxicology study, but only a streamlined study that bridges to earlier toxicology studies. Properly sequencing these steps is paramount. Even if supplies don't use the final manufacturing process, as long as toxicology is conducted with a formulation that doesn't have a cleaner impurity profile than the intended clinical formulation, you'll have appropriate toxicology coverage.

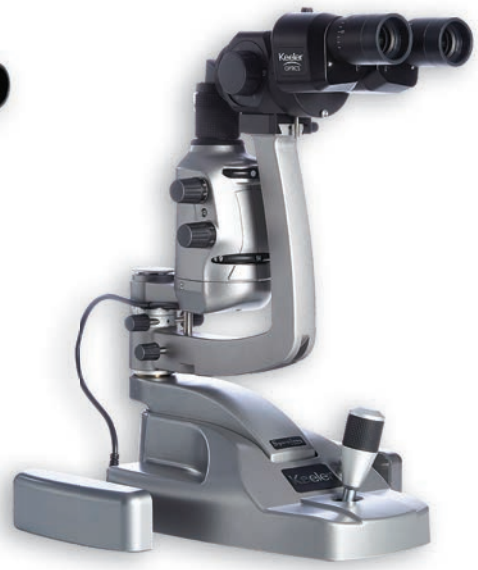
The Keeler³ Trade In Program

Buy 3 // Trade 3 // Get 1 Free

The Power of 3. Purchase any 3 Keeler Slit Lamps and trade in 3 of your old Slit Lamps and we'll send you a 4th Keeler Slit Lamp absolutely free of charge.

K Series

Q Series



Z Series

Keeler OPTICS

Keeler Instruments, Inc. • 3222 Phoenixville Pike, bldg. 50 • Malvern, PA 19355
Tel: (800) 523-5620 • Fax: (610) 353-7814 • email: keeler@keelerusa.com

Offer valid until March 31, 2018.

Contact Keeler or one of our authorized dealers for more information.

Ophthalmic Product Development Insights

Matthew Chapin and Hal Patterson • Andover, Mass.

GLP requirements state that the trial investigator needs to confirm activity and stability during the course of the study. This of course relates to the timing of when stability-indicating assays are available for the active drug in your specific formulation. This all relates to the duration of the planned clinical trial. As a side note specific to biologicals, as part of the release testing of clinical supplies prior to the study, the FDA likes to see that drug activity is also measured in an assay that is pertinent to the mechanism of action of the drug. The release of clinical supplies refers to the testing that measures the amount of the active drug, and also includes tests of pH and osmolarity, all of which have to meet predefined specifications prior to using a drug product in a trial. Therefore, setting up the appropriate assays early in the process is important. Lastly, as another side note, remember that the toxicology for a biological agent needs to be done in a species in which activity is also confirmed.

Another pearl on the sequencing of CMC centers on how to best leverage the engineering batch. This is usually a batch manufactured using the same intended process and formulation as the clinical batch, but at smaller batch size. While not a regulatory requirement per se, this batch can be used to supply the GLP toxicology study and also to show stability for the intended clinical batches. We have seen clients who, as they scale up from, for example, early lab-pharmacy-compounded drugs to full GMP manufacturing of drugs, find unexpected issues that take more time to solve. While engineering batches are standard and may seem an obvious step, make sure the timing is built in up front not only for the engineering batches themselves but for timing and work involved in developing the process.

Demonstration of stability of the intended concentrations of the drug is required for the entire length of the clinical trial. (Note that this, of course, includes the start-up time of the trial and full time that drug will be at sites, not just how long a single patient is enrolled). Your early engineering batches can serve as support for this, so that once clinical batches are manufactured and labeled they can be used in the trial.

Another point in manufacturing and testing: If you expect that your drug product will have a drop in stability during processing (e.g., down to 80 percent), you might wonder if you can just plan to manufacture at 120 percent so as it degrades it winds up at 100. This is not acceptable, because it implies that you don't have full control of your process, setting aside other concerns around what dose is being delivered to different patients. For drugs, don't simply plan that overages can solve stability issues.

There are nuances that are indication-specific, e.g., such as those for dry eye. Excipients that are already approved as monograph demulcents (see 21 C.F.R. 349), may lead to issues in the clinical/regulatory path with FDA, because those excipients in effect are already accepted to be used in dry eye as tear substitutes. This may lead to the FDA considering your drug a combination product. Therefore, if you're going after dry eye as an indication, your best bet is to make sure you don't have HPMC, CMC, PVA, etc., in monograph-level ranges early on in your formulation unless they're needed and you anticipate having a proper clinical-regulatory strategy accounting for this. This has been an issue in some projects that were thought to need a surfactant or demulcent for stability or comfort, or one of these agents was part of a product profile early on, and led to delays in reformulation or unexpectedly increased the complexity of a clinical program.

Sterilization's Impact

Ophthalmic products need to be sterile, and indeed most ophthalmic products are sterile-filtered. This highlights the importance of ensuring that the drug product can be filtered with filter validation studies early in the process. While an option, it's best not to have to resort to other methods like heat, e-beam or ethylene oxide for early work. Thicker products may have issues with standard filtering. Generally, these issues can be solved by methodically working through them, but don't underestimate the potential for filtration problems. Ointments can create cost and time delays because many manufacturers that make ointments, such as those made for dermatological applications, aren't necessarily set up to be sterile. Keep in mind the time it takes to define manufacturing site options if you're going after approval for an ophthalmic ointment.

Quality Systems

One final note: As the sponsor, the ultimate responsibility for the project and for your vendors lies with you. In order to properly demonstrate sponsor oversight, even if you're a virtual company and plan to outsource all the work, you need to establish a basic system of standard operating procedures to ensure quality. It also helps to be able to demonstrate competence in these SOPs when you attempt to find a partner to help develop the product, since it shows that you've maintained the proper level of oversight and controls. As a sponsor, for example, vendor qualifications (before any work is done) and audits should be part of your plan. Don't ignore the quality oversight required for complying with GLP (Good Laboratory Practices) and GMP (Good Manufacturing Practices) regulations.

In Conclusion

The path for CMC leading to IND and starting the first trial requires knowledge and expertise (or access to it) in the areas of formulations, GMP, sterile manufacturing, microbiology and others. It's critical to understand how the CMC components tie into toxicology, regulatory and clinical concerns, and shouldn't be viewed in isolation. A cross-disciplinary approach is needed to avoid delays or repeating activities later. This holistic view also feeds into formulating proper questions for pre-IND meetings and anticipating any specific issues your program might run into early on, so you can avoid multiple meetings with the FDA, if possible (though multiple meetings are acceptable and a separate CMC meeting with the FDA isn't uncommon).

We'll conclude with the theme that runs through all of these columns: Always keep the end goal in mind, and develop a properly defined target product profile early on. When you begin, it's critical to focus on building a multidisciplinary strategy and timeline of all activity in order to identify interdependent and/or rate-limiting steps and to effectively conduct the product-development orchestra.

Mr. Chapin is senior vice president of corporate development at the ophthalmic consulting and development firm Ora, and Mr. Patterson is vice president of quality.

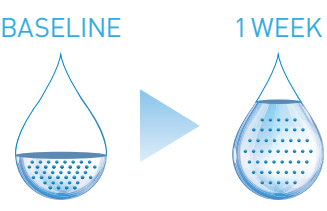
Ora provides development, clinical-regulatory and consulting services for developers, investors and pharmaceutical companies. The authors welcome your comments or questions regarding product development. Please send correspondence to mchapin@oraclinical.com or hpatterson@oraclinical.com, or visit oraclinical.com.

TheraTears® is clinically proven to **reduce the signs and symptoms** of dry eyes[1]

TheraTears® Dry Eye Therapy Lubricant Eye Drops with Osmo-Correction®

- Reduced patient symptoms (OSDI) up to 33%
- Restored tears to normal osmolarity levels within one week

Average Tear Osmolarity Level



322.8
±20.3 mOsm/L
(High Osmolarity)

305.2
±27.7 mOsm/L
(Normal Osmolarity)

thera tears
THERAPY FOR YOUR EYES

More than eye drops, dry eye therapy™

theratears.com

Study sponsored by Akorn

Reference: 1. Ng L, Nguyen A, Karpecki P, Houtman D. Evaluation of Tear Osmolarity Over Time with Sustained Use of TheraTears® Lubricant Eye Drops. Poster presented at: The American Academy of Optometry Annual Meeting; November 9-12, 2016; Anaheim, CA.

AKORN | CONSUMER HEALTH

(Continued from p. 3)

communicated their plan publicly yet."

• Another company working on a diabetic retinopathy treatment is Clearside Biomedical. In a group of patients with diabetic macular edema in the company's HULK exploratory clinical trial, Clearside's CLS-TA showed some positive results. CLS-TA is a proprietary suspension formulation of triamcinolone acetonide that's administered suprachoroidally with or without intravitreally injected aflibercept. In HULK, more than two-thirds of eyes achieved greater than 50 percent reduction in excess central retinal thickness and there was anatomic improvement in all of the treated eyes. The company will soon report results of a randomized trial in noninfectious posterior uveitis and has ongoing trials in retinal vein occlusion and diabetic macular edema.

• Drug company Aerpio is also angling to enter the diabetic retinopathy space with its twice-daily subcutaneous injection of AKB-9778, a small-molecule inhibitor of VE-PTP, which it describes as a critical regulator of Tie2 in diseased blood vessels. The idea is to restore healthy Tie2 activity. "It needs to be injected subcutaneously twice daily, but patients with diabetes are used to injections," says Dr. Cunningham, "so they might not see that as a huge issue. Also, activating Tie2 is good for vessels in general, not just in the eye, so there may be some systemic benefits from this treatment, as well.

"This is the first and only direct Tie2 activator," Dr. Cunningham adds. "Others, most notably Regeneron and Genentech, were seeking to increase Tie2 by inhibiting its inhibitor, Ang 2. This may be meaningful, and the company says it should get superior activation because of its direct Tie2 activation." Based on the results of a Phase IIa proof-of-concept study in which AKB-9778 improved patients' underlying retinopathy two or more steps on the ETDRS diabetic retinopathy scale in both eyes, the company has begun a Phase 2b study, codenamed TIME-2b.

• In the dry-AMD realm, Apellis Pharmaceuticals recently shared positive results from a Phase II trial of its complement inhibitor. Specifically, it inhibits complement-3. (Complement is believed to contribute to the pathogenesis of AMD.) "This development is fascinating because we've had multiple failures of complement inhibitors, such as eculizumab (which targeted C5) and lampalizumab (which targeted Factor D)," Dr. Cunningham muses. "But then Apellis comes with anti-C3 showing a benefit in Phase II. However lampalizumab showed a benefit in Phase II also, reinforcing the idea that Phase II doesn't always predict Phase III success. This raises the question: Why would C5 inhibitors fail but a C3 inhibitor work? Many of the diagrams we see that illustrate complement inhibition show a path that goes through C3 and then to a C5-mediated membrane attack complex. However, an equally valid depiction has three effector arms, not just one: The other two are chemotaxis—or bringing immune cells and promoting adaptive immunity so the body can learn to recognize these antigens—and coating or opsonization that will mediate phagocytosis of these bad bits in and around the sites of inflammation. C3 is important for all three effector arms, and so in this way could be the better target."

• Allergan is working on an implant designed to release brimonidine over time to battle geographic atrophy, and it showed a therapeutic benefit in a 2016 study. In the study, reported at the 2016 AAO Retina Subspecialty Day, the 132-µg and the 264-µg implants reduced the rate of geographic atrophy progression by 19 and 28 percent, respectively.

• Allergan is also studying a time-release bimatoprost implant, the Artemis, for glaucoma. The company is currently enrolling patients in its Phase III trial of the delivery system. The trial will compare two sizes of implant—10 µg and 15 µg, administered every 16 weeks—to daily timolol drops.

• Taking a different approach to glaucoma and macular telangiectasia treatment, Neurotech is pursuing encapsulated cell therapy with a therapy designated NT-501. In ECT, an implanted device releases ciliary neurotrophic factor over time, and Dr. Cunningham says the company has Phase I/II data that appear to show a drug effect. "The issue with that platform is the manufacturing complexity," he explains. "This isn't like synthesizing a small molecule and putting it in a bottle that has a two-year shelf life. It's a device with encapsulated cells." A recent communiqué from Neurotech announced positive Phase II results in macular telangiectasia, and it's expected that a Phase III trial is on its way.

• In the uveitis arena, Dr. Cunningham says that both pSivida and Clearside Biomedical are using sustained-release corticosteroids and have produced some very promising results. In pSivida's case, in a six-month study of the Durasert implant in uveitis conducted in India, 22 percent of patients in the study group vs. 54 percent of sham patients had a recurrence of the uveitis (n: 153; $p<0.001$).

Clearside has a Phase III study of a microneedle injection of 100 µL of triamcinolone acetonide. The study's enrollment is complete and data from it is expected in the first quarter of 2018.

In a somewhat surprising setback, Santen received a complete response letter from the FDA in December 2017, informing them that the submission of their uveitis treatment sirolimus was not approvable as submitted. When combined, the company's SAKURA studies of sirolimus remain the largest study of noninfectious uveitis of the posterior segment to date (n: 347 and n: 245). Officially, the company says it's reviewing the letter, and is working closely with the agency to chart the "best path forward." REVIEW

LOMBART

YOUR OPHTHALMIC PARTNER

800.LOMBART
LOMBARTINSTRUMENT.COM

LOMBART EXCLUSIVE PROMOTIONS

Product Specials · Financing Deals · Service Packages · Used Equipment

LEARN MORE AT LOMBARTINSTRUMENT.COM/PROMOTIONS

WHEN YOU THINK OPHTHALMIC INSTRUMENTS,

THINK LOMBART

Ongoing Support

Reliable Service

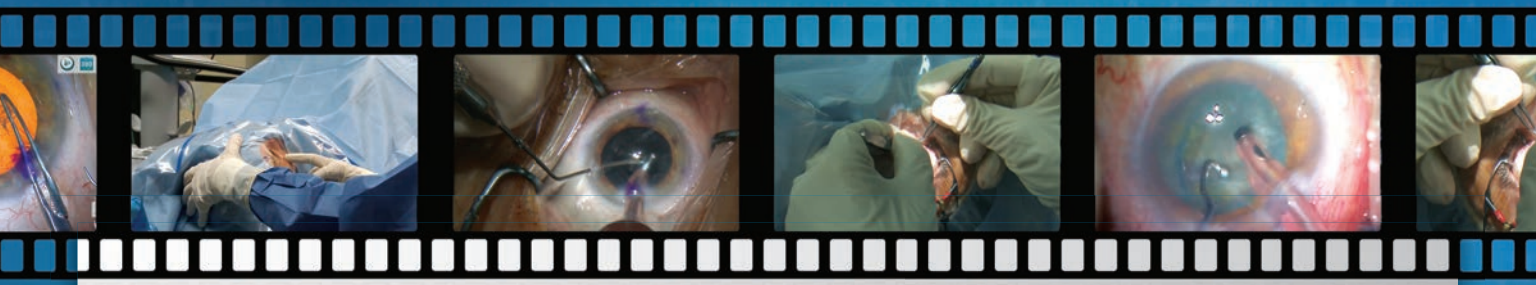
Nationwide Coverage

Lombart is committed to meeting the full range of ophthalmic needs of optometry and ophthalmology practices, universities, hospitals and the US government through customized solutions and dedicated partnerships.

Monthly

MACKOOL ONLINE CME

CME SERIES | SURGICAL VIDEOS



To view CME video
go to:
www.MackoolOnlineCME.com

Episode 26:
"Dense Nucleus: The Value of Patience"

Surgical Video by:
Richard J. Mackool, MD

Video Overview:
Patience is a critically important trait for all surgeons to develop and maintain. In this patient, Dr Mackool demonstrates its value during removal of a red/brunescent cataract in a one-eyed patient.

MackoolOnlineCME.com MONTHLY Video Series

Richard J. Mackool, MD

Welcome to the third 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:

- Assist in the development of a patient, rational approach and game plan when dealing with an extremely dense cataract.

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

Credit Designation Statement
Amedco designates this live activity for a maximum of .25 *AMA PRA Category 1 Credits*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Endorsed by:
Review of Ophthalmology®

Video and Web Production by:
JR Snowdon, Inc

Jointly Provided by:
AMEDCO & PHE

Supported by an unrestricted independent medical educational grant from:
Alcon

Additionally Supported by:
Glaukos
MST
Crestpoint Management
Carl Zeiss Meditec

REVIEW Editorial Board

Contributors

CHIEF MEDICAL EDITOR
Mark H. Blecher, MD

CONTACT LENSES
Penny Asbell, MD

CORNEA / ANTERIOR SEGMENT
Thomas John, MD

GLAUCOMA MANAGEMENT
Peter Netland, MD, PHD
Kuldev Singh, MD

MASTERS OF SURGERY
Taliva D. Martin, MD
Sara J. Haug, MD, PhD

MEDICARE Q & A
Paul M. Larson, MBA

PEDIATRIC PATIENT
Wendy Huang, MD

PLASTIC POINTERS
Ann P. Murchison, MD, MPH

REFRACTIVE SURGERY
Arturo S. Chayet, MD

RETINAL INSIDER
Carl Regillo, MD, FACS
Emmett T. Cunningham Jr., MD, PHD, MPH

TECHNOLOGY UPDATE
Steven T. Charles, MD
Michael Colvard, MD

WILLS RESIDENT CASE SERIES
Thomas Jenkins, MD.

Advisory Board

PENNY A. ASBELL, MD, NEW YORK CITY
WILLIAM I. BOND, MD, PEKIN, ILL.
ALAN N. CARLSON, MD, DURHAM, N.C.
Y. RALPH CHU, MD, EDINA, MINN.
ADAM J. COHEN, MD, DOWNERS GROVE, ILL.
UDAY DEVGAN, MD, FACS, LOS ANGELES
ERIC DONNENFELD, MD, ROCKVILLE CENTRE, N.Y.
DANIEL S. DURRIE, MD, KANSAS CITY, MO.
ROBERT EPSTEIN, MD, MCHENRY, ILL.
ROBERT D. FECHTNER, MD, NEWARK, N.J.
WILLIAM J. FISHKIND, MD, TUCSON, ARIZ.
JAMES P. GILLS, MD, TARPON SPRINGS, FLA.
HARRY GRABOW, MD, SARASOTA, FLA.
DOUGLAS K. GRAYSON, MD, NEW YORK CITY
THOMAS S. HARBIN, MD, MBA, ATLANTA
DAVID R. HARDTEN, MD, MINNEAPOLIS
KENNETH J. HOFFER, MD, SANTA MONICA, CALIF.
JACK T. HOLLADAY, MD, MSEE, HOUSTON
JOHN D. HUNKELER, MD, KANSAS CITY, MO.
THOMAS JOHN, MD, TINLEY PARK, ILL.
ROBERT M. KERSHNER, MD, MS, FACS, BOSTON
GUY M. KEZIRIAN, MD, PARADISE VALLEY, ARIZ.
TERRY KIM, MD, DURHAM, N.C.
TOMMY KORN, MD, SAN DIEGO
DAVID A. LEE, MD, HOUSTON
FRANCIS S. MAH, MD, PITTSBURGH
NICK MAMALIS, MD, SALT LAKE CITY
WILLIAM G. MARTIN, MD, OREGON, OHIO
MIKE S. MCFARLAND, MD, PINE BLUFF, ARK.
JEFFREY B. MORRIS, MD, MPH, ENCINITAS, CALIF.
MARLENE R. MOSTER, MD, PHILADELPHIA
ROBERT J. NOECKER, MD, FAIRFIELD, CONN.
ROBERT OSHER, MD, CINCINNATI
MARK PACKER, MD, WEST PALM BEACH, FLA.
STEPHEN PASCUCCI, MD, BONITA SPRINGS, FLA.
PAUL PENDER, MD, BEDFORD, N.H.
CHRISTOPHER J. RAPUANO, MD, PHILADELPHIA
AUGUST READER III, MD, SAN FRANCISCO
TONY REALINI, MD, MORGANTOWN, W.V.
KENNETH J. ROSENTHAL, MD, GREAT NECK, N.Y.
ERIC ROTHCHILD, MD, DELRAY BEACH, FLA.
SHERI ROWEN, MD, BALTIMORE
JAMES J. SALZ, MD, LOS ANGELES
INGRID U. SCOTT, MD, MPH, HERSHEY, PA.
JOEL SCHUMAN, MD, PITTSBURGH
GAURAV SHAH, MD, ST. LOUIS
DAVID R. STAGER JR., MD, DALLAS
KARL STONECIPHER, MD, GREENSBORO, N.C.
JAMES C. TSAI, MD, NEW YORK CITY
VANCE THOMPSON, MD, SIOUX FALLS, S.D.
FARRELL C. TYSON, MD, CAPE CORAL, FLA.
R. BRUCE WALLACE III, MD, ALEXANDRIA, LA.
ROBERT G. WILEY, MD, CLEVELAND
FRANK WEINSTOCK, MD, CANTON, OHIO

REVIEW® of Ophthalmology

BUSINESS OFFICES
11 CAMPUS BOULEVARD, SUITE 100
NEWTOWN SQUARE, PA 19073
SUBSCRIPTION INQUIRIES (877) 529-1746
(USA ONLY); OUTSIDE USA, CALL (847) 763-9630

BUSINESS STAFF
PUBLISHER
JAMES HENNE
(610) 492-1017 JHENNE@JOBSON.COM

REGIONAL SALES MANAGER
MICHELE BARRETT
(610) 492-1014 MBARRETT@JOBSON.COM

REGIONAL SALES MANAGER
MICHAEL HOSTER
(610) 492-1028 MHOSTER@JOBSON.COM

CLASSIFIED ADVERTISING
(888)-498-1460

VICE PRESIDENT OF OPERATIONS
CASEY FOSTER
(610) 492-1007 CFOSTER@JOBSON.COM

PRODUCTION MANAGER
SCOTT TOBIN
(610) 492-1011 STOBIN@JOBSON.COM

SUBSCRIPTIONS
$63 A YEAR, $99 (U.S.) IN CANADA,
$158 (U.S.) IN ALL OTHER COUNTRIES.
SUBSCRIPTIONS E-MAIL:
REVOPHTHALMOLOGY@CAMBEYWEST.COM

CIRCULATION
PO BOX 71, CONGERS, NY 10920-0071
(877) 529-1746
OUTSIDE USA: (845) 267-3065

SENIOR CIRCULATION MANAGER
HAMILTON MAHER
(212) 219-7870 hmaher@jhihealth.com

CEO, INFORMATION GROUP SERVICES
MARC FERRARA

SENIOR VICE PRESIDENT, OPERATIONS
JEFF LEVITZ

VICE PRESIDENT, HUMAN RESOURCES
TAMMY GARCIA

VICE PRESIDENT, CREATIVE SERVICES & PRODUCTION
MONICA TETTAMANZI

CORPORATE PRODUCTION DIRECTOR
JOHN ANTHONY CAGGIANO

VICE PRESIDENT, CIRCULATION
EMELDA BAREA

jmi
440 Ninth Avenue, 14th Floor
New York, N.Y. 10001

REVIEW OF OPHTHALMOLOGY (ISSN 1081-0226; USPS No. 0012-345) is published monthly, 12 times per year by Jobson Medical Information. 440 Ninth Avenue, 14th Floor, New York, N.Y. 10001. Periodicals postage paid at New York, NY and additional mailing offices. Postmaster: Send address changes to Review of Ophthalmology, PO Box 71, Congers, NY 10929-0071. Subscription Prices: US One Year $63.00, US Two Year $112.00, Canada One Year $99.00, Canada Two Year $181.00, Int'l One Year $158.00, Int'l Two Year $274.00. For subscription information call (877) 529-1746 (USA only); outside USA, call (845-267-3065. Or email us at revophthalmology@cambeywest.com. Canada Post: Publications Mail Agreement #40612608. Canada Returns to be sent to Bleuchip International, P.O. Box 25542, London, ON N6C 6B2.

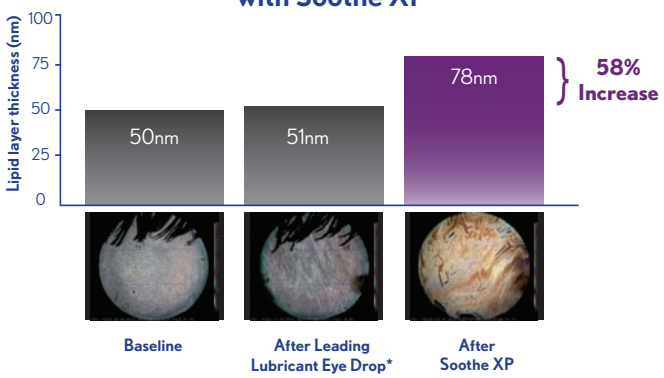
For Dry Eye/MGD Patients

The eye's protective layer is thinner than a human hair, and it's what stands between the eyes and the world.

MGD can cause the lipid layer to break down. Soothe® XP helps replenish this layer.

- Up to 86% of patients reporting dry eye symptoms have Meibomian Gland Dysfunction (MGD).[1]
- MGD can cause the lipid layer to break down, which may lead to a compromised tear film.[2]
- Soothe XP contains Restoryl® mineral oils that can benefit MGD patients by helping to restore the lipid layer, seal in moisture, and protect against tear loss.

Improved lipid layer thickness after treatment with Soothe XP



*Non-lipid containing eye drop (Systane Ultra)

Lipid layer thickness (LLT) prior to and 15 minutes following a single drop of emollient or non-emollient eye drop in dry eyes with meibomian gland dysfunction. Data are the mean (±SD) LLT based on stroboscopic video color microscope (SVCM) measurements in study eyes (qualifying eye in subjects with only one qualifying eye, or the eye with the lowest LLT at baseline in subjects with two qualifying eyes). $p<0.001$ paired t-test for the change from baseline. $p<0.001$, $n=35$, following a single drop.

[1] Lemp MA et al. Distribution of Aqueous-Deficient and Evaporative Dry Eye in a Clinic-Based Patient Cohort: A Retrospective Study. Cornea. 2012; 31:472-478.

[2] Horwath-Winter J. Prevalence of MGD in an clinical dry eye population. ActaOphthal 2011; 89 (s248)-2334.

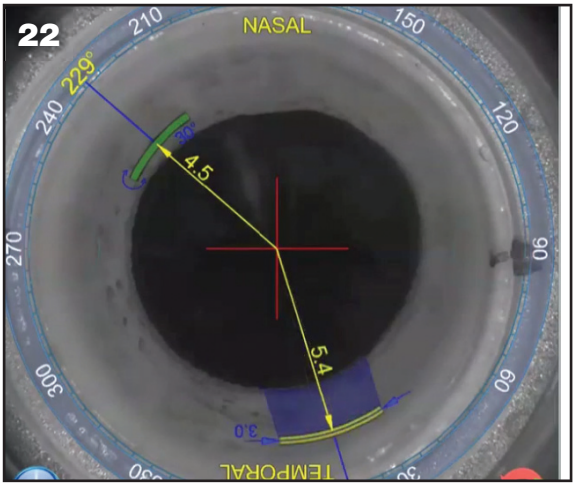
BAUSCH + LOMB
See better. Live better.

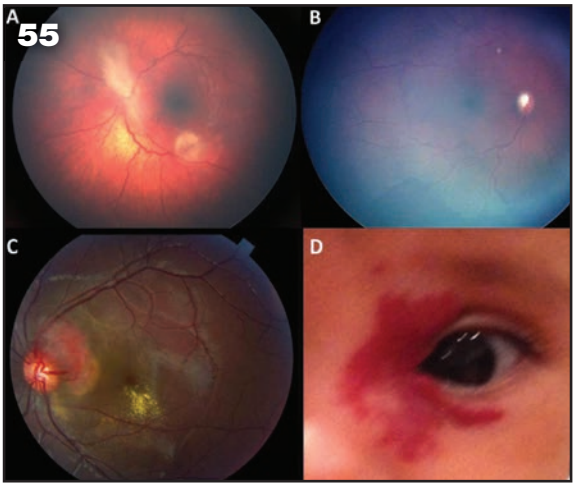
REVIEW® of Ophthalmology

February 2018 • Volume XXV No. 2 | reviewofophthalmology.com

Cover Focus

Departments





INDICATIONS AND IMPORTANT SAFETY INFORMATION FOR THE CATALYS® PRECISION LASER SYSTEM

Rx Only

INDICATIONS: The OptiMedica® CATALYS® Precision Laser System is indicated for use in patients undergoing cataract surgery for removal of the crystalline lens. Intended uses in cataract surgery include anterior capsulotomy, phacofragmentation, and the creation of single-plane and multi-plane arc cuts/incisions in the cornea, each of which may be performed either individually or consecutively during the same procedure. **CONTRAINDICATIONS:** Should not be used in patients with corneal ring and/or inlay implants, severe corneal opacities, corneal abnormalities, significant corneal edema or diminished aqueous clarity that obscures OCT imaging of the anterior lens capsule, patients younger than 22 years of age, descemetocele with impending corneal rupture, and any contraindications to cataract surgery. **IMPORTANT SAFETY INFORMATION:** Mild petechiae and subconjunctival hemorrhage can occur due to vacuum pressure of the suction ring. Potential complications and adverse events include any of those generally associated with cataract surgery. **CAUTION:** Should be used only by qualified physicians who have extensive knowledge of the use of this device and have been trained and certified by Abbott Medical Optics/OptiMedica. **ATTENTION:** Reference the labeling for a complete listing of Important Indications and Safety Information.

Johnson & Johnson VISION

REVIEW of Ophthalmology

EDITORIAL STAFF

Editor in Chief
Walter C. Bethke
(610) 492-1024
wbethke@jobson.com

Senior Editor
Christopher Kent
(814) 861-5559
ckent@jobson.com

Senior Associate Editor
Kristine Brennan
(610) 492-1008
kbrennan@jobson.com

Associate Editor
Liam Jordan
(610) 492-1025
ljordan@jobson.com

Chief Medical Editor
Mark H. Blecher, MD

Art Director
Jared Araujo
(610) 492-1032
jaraujo@jobson.com

Senior Graphic Designer
Matt Egger
(610) 492-1029
megger@jobson.com

International coordinator, Japan
Mitz Kaminuma
Reviewophthalmo@aol.com

Business Offices
11 Campus Boulevard, Suite 100
Newtown Square, PA 19073
(610) 492-1000
Fax: (610) 492-1039

Subscription inquiries:
United States — (877) 529-1746
Outside U.S. — (845) 267-3065
E-mail:
revophthalmology@cambeywest.com
Website: www.reviewofophthalmology.com

jmi BPA

REVIEW Editor's Page

Walter C. Bethke, Editor in Chief

New Procedures, Old Expectations

Almost since the very beginning of refractive surgery in the United States, surgeons have preached the importance of managing prospective patients' expectations. They say that many gung-ho patients come in expecting to throw away their spectacles and contact lenses, and to walk out seeing 20/20 or better in about 20 minutes or so. Surgeons say that if such patients don't have their sky-high expectations brought closer (if not all the way down) to earth, and they don't see like a peregrine falcon postop, you're going to have a difficult time making them happy. Looking at the larger picture, though the economic downturns in the aughts didn't do LASIK volume any favors, it's possible that the fostering of these lofty expectations by some LASIK providers—and the subsequent negative articles on LASIK complications that started to appear in the consumer press and on some patients' blogs—caused an overall souring of the public toward the procedure, and maybe helped touch off the FDA study into LASIK outcomes.

Fast forward to today, and we have new refractive procedures being approved in the United States, but with the same old temptation to build them up for patients, especially because now marketers can slap the classic "new and improved" label on them. This branding might lead patients to believe that this isn't your father's LASIK with those "gross eye flaps," but something better. Some surgeons, such as Stanford University's Edward Manche, MD, the author of this month's review of small-incision lenticule extraction on page 32, implore their colleagues to avoid this impulse. "These patients assume that because SMILE is the newest surgery, it's also the best one, an opinion that's common when new technology arrives," he says. He then raises an interesting point: If you spend your time building up SMILE as the latest and greatest, and either explicitly or by implication devalue PRK and LASIK in order to attract patients, what happens when the patient either isn't a candidate for SMILE, or worse, needs his SMILE enhanced postop with PRK? "Not only will the patient's procedure of choice have underperformed for him, but now you're telling him he's got to undergo PRK, the very same procedure you degraded during his preop visits," Dr. Manche observes.

Instead, Dr. Manche says it's better for refractive surgery in general, and the procedures individually, if new procedures such as SMILE are presented as complementary to the established ones, rather than as competitors. This message may not be what patients expect when an exciting new surgery gets approved, but it's what they deserve.

—Walt Bethke, Editor in Chief

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; RVO = Retinal Vein Occlusion.

Dosing driving efficacy outcomes across all indications.[1]
Learn more at EYLEA.us/dose

EYLEA®
(aflibercept) Injection
For Intravitreal Injection

INDICATIONS AND IMPORTANT SAFETY INFORMATION

INDICATIONS

EYLEA® (aflibercept) Injection is indicated for the treatment of patients with

- Neovascular (Wet) Age-related Macular Degeneration (AMD): The recommended dose is 2 mg administered by intravitreal injection every 4 weeks (monthly) for the first 12 weeks (3 months), followed by 2 mg once every 8 weeks (2 months). Although EYLEA may be dosed as frequently as 2 mg every 4 weeks (monthly), additional efficacy was not demonstrated in most patients when EYLEA was dosed every 4 weeks compared to every 8 weeks. Some patients may need every 4 week (monthly) dosing after the first 12 weeks (3 months).
- Macular Edema following Retinal Vein Occlusion (RVO): The recommended dose is 2 mg administered by intravitreal injection every 4 weeks (monthly).
- Diabetic Macular Edema (DME) and Diabetic Retinopathy (DR) in Patients with DME: The recommended dose is 2 mg administered by intravitreal injection every 4 weeks (monthly) for the first 5 injections, followed by 2 mg once every 8 weeks (2 months). Although EYLEA may be dosed as frequently as 2 mg every 4 weeks (monthly), additional efficacy was not demonstrated in most patients when EYLEA was dosed every 4 weeks compared to every 8 weeks. Some patients may need every 4 week (monthly) dosing after the first 20 weeks (5 months).

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

10/2017
US-LEA-13945

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.

REGENERON

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

What's New in the 2018 Medicare Update?

There are a number of changes to Medicare that practices should know about. This month, we review the most important.

Q Are there any changes to reimbursement?

A In terms of the national published Fee Schedule for physicians, after the mandated 0.5-percent MACRA increase and some of the other budget-neutrality and misvalued-code adjustments, the 2018 conversion factor went up 0.28 percent to $35.9996. Ambulatory surgical centers got a fee-schedule conversion factor increase of 1.9 percent to $45.575 if they meet quality-reporting requirements. HOPD services in eye care showed an overall +1.35-percent change.

Q In terms of payment changes, how did eye care fare for 2018?

A Of the 622 possible codes that might apply to ophthalmologists and optometrists in 2018, only 42 have a reimbursement change of more than 3 percent. Of those codes with significant changes (>3 percent), 19 had positive changes and 23 had negative changes. In 2017, ophthalmic imaging had major changes in payment. This year, for common imaging services, only fundus photography showed a significant decline. See the table above for some of these codes.

Samples of CPT Codes With Significant Changes In 2018

Visual Evoked Potential—except glauc. (95930)	-84%
Epilation (67820)	-23%
B-Scan (76512)	-23%
Allergy testing (95004)	-21%
Fundus photography (92250)	-14%
Biometry/IOL calculation (92136)	-14%
Orthoptics (92265)	+4%
Level 1 E/M (99211)	+7%
Implant corneal ring segments (65785)	+17%

Q Are there any changes to Category I CPT codes for 2018?

A Oculoplastics is the area with the most changes (related to face and head flaps and nasal sinus endoscopy coding). In this area, most important, perhaps, is that CPT code 15732 (*Muscle, myocutaneous or facsiocutaneous flap; head and neck [e.g., temporalis, masseter muscle, sternocleidomastoid, levator scapulae]*) is deleted. This was sometimes used with SOOF lifts so other codes apply now (usually 1404x and 1406x).

Other codes with changes are:

- *15730—Midface flap (i.e., zygomaticofacial flap) with preservation of vascular pedicle;*
- *15733—Muscle, myocutaneous or facsiocutaneous flap; head and neck with named vascular pedicle (e.g., buccinators, genioglossus, temporalis, masseter, sternocleidomastoid, levator scapulae); and*

This article has no commercial sponsorship.

• *95930—Visual evoked potential (VEP) checkerboard or flash testing, central nervous system except glaucoma, ~~checkerboard or flash~~, with interpretation and report* (Underlined text was added to the code and strikethrough was deleted.)

o With VEP for glaucoma (all types), code 0464T (*Visual evoked potential testing for glaucoma, with interpretation and report*) has applied since January 2017.

Q Are there any new CPT Category III codes?

A Category III codes are released twice a year. Coverage and payment for these codes are at the discretion of the individual Medicare Administrative Contractors. None are significant for eye care on January 1, 2018, but those that are in place and effective since July 1, 2017 are:

• *0469T—Retinal polarization scan, ocular screening with on-site automated results, bilateral;*

• *0472T—Device evaluation, interrogation and initial programming of intraocular retinal electrode array (e.g., retinal prosthesis), in person, with iterative adjustment of the implantable device to test functionality, select optimal permanent programmed values with analysis, including visual training, with review and report by a qualified health care professional;*

• *0473T—Device evaluation and interrogation of intraocular retinal electrode array (e.g., retinal prosthesis), in person, including reprogramming and visual training, when performed, with review and report by a qualified health care professional; and*

• *0474T—Insertion of anterior segment aqueous drainage device, with creation of intraocular reservoir, internal approach, into the supraciliary space.* (This is the code for the CyPass Micro-Stent.)

Q Are there HCPCS code changes to be aware of?

A For Medicare, the existing code for Omidria, C9447 (*phenylephrine and ketorolac, injection*) had its pass-through payment status changed. The payment indicator for this code changed from "K2" (paid separately) to "N1" (bundled). This means that on January 1, 2018, payment for C9447 is packaged in the reimbursement for the cataract procedure and is no longer separately identifiable for Part B Medicare.

An Advance Beneficiary Notice or similar financial waiver form cannot be used to shift the payment responsibility to the Medicare beneficiary.

Q Are there new things to be aware of from the Office of the Inspector General?

A The OIG no longer publishes an annual Work Plan as a separate document. It now does monthly updates on its website. Issues such as misuse of modifiers (e.g., 24, 25, and 59) continue to draw scrutiny. Oversight related to the new Quality Payment Program continues.

Q Has Medicare made changes of significance to beneficiaries?

A The 2018 Medicare Part B deductible remains the same as it was: $183. The standard monthly premium also remains unchanged at $134.

Q Are there changes to the Quality Payment Program that was new only last year?

A 2018 is the second year of QPP and there are some changes. Avoiding a Merit-based Incentive Payment reduction remains straightforward but the threshold is raised from three points in 2017 to 15 points in 2018. The maximum bonus or penalty rises to 5 percent from the current 4 percent. The Exceptional Performance threshold stays at 70 points. The exemptions for MIPS are raised to $90,000 in allowed charges or 200 Part B patients.

There were also changes to the relative weights and thresholds within the four MIPS components. In 2018, quality contributes 50 percent (down from 60 percent); advancing care information, 25 percent; clinical practice improvement activities, 15 percent; and resource use (Cost), 10 percent (up from zero). The "threshold of patient" percentage for quality in each of the six measures rises from 50 percent to 60 percent.

Q Were there changes to ICD-10?

A As with ICD-9, these go into effect on October 1 each year. There are a few subtle changes, but the biggest relate to myopic degeneration (H44.2-) and low vision/blindness coding (H54.-), each of which gained much greater specificity. REVIEW

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

icare HOME

IOP SELF-TONOMETRY

24 HOUR INSIGHT

VISIT AGS 2018 **BOOTH #39** FOR **SHOW SPECIALS**

Learn more: *info@icare-usa.com* or *www.icare-usa.com*


The Latest Technology For Toric Alignment

New ways to increase accuracy continue to appear. Here's a sampling of what's available.

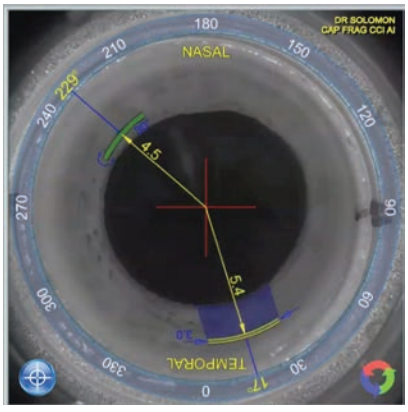
Christopher Kent, Senior Editor

As the popularity of toric intraocular lenses slowly increases, options to help align them accurately have proliferated. The time-honored method of accomplishing this was simply to use ink to mark the desired axis on the eye preoperatively. That approach has left plenty of room for better alternatives, however, since it tends to produce less-than-perfect results. Ink marks can be broad rather than precise and can fade or smudge by the time the patient is on the operating table. And as most surgeons know, a small error in rotational alignment can undercut the effectiveness of a toric IOL significantly.

Here, you'll find a sample of some of the more recent options designed to help surgeons achieve accurate toric alignment.

IntelliAxis-L System

One of the newest entries in this area is the IntelliAxis-L system, now part of the latest upgrade to the Lensar Laser System (Lensar), which was showcased at the American Academy of Ophthalmology meeting in November 2017. The company describes the laser as the only one on the market developed specifically for cataract surgery.



The IntelliAxis-L System is a new upgrade now available for the Lensar Laser System.

IntelliAxis-L uses Lensar's diagnostic capabilities, iris registration software and intraoperative imaging to precisely and "permanently" identify the location of the steep corneal axis at the capsular plane for toric IOL alignment. The system creates custom marks, which the company says can't be duplicated by any other device currently available, which remain visible postoperatively to help identify any unexpected rotation and help guide any needed realignment of the toric IOL to its optimal position.

The company notes that the Lensar System's astigmatism-management features include:

- integration of all corneal measurements, including total corneal refractive power and total corneal astigmatism, to guide placement of arcuate incisions;
- iris registration with automatic cyclorotation adjustment;
- arcuate incision planning; and
- surgeon tables for managing preexisting and surgically-induced astigmatism.

For more information, visit: lensar.com/features.php

Tocular System

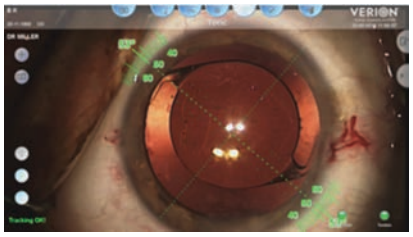
The Tocular System (Haag-Streit Surgical) is a rotatable, wide-angle ocular with a clearly visible integrated reticle in the center of the visual field. The device can be rotated manually via a sterilizable knob, and it can achieve IOL alignment within two degrees of the target axis. The eye must be marked preoperatively using a marking system of your choice. (Haag-Streit recommends the Davis

premarking system, available from John Weiss.) After the IOL is implanted, the surgeon adjusts the microscope zoom to visualize the ink marks, and then rotates the Tocular reticle to align with them. The IOL can then be aligned using the medium and small reticle markings as a guide.

For more information visit: haag-streit.com/fileadmin/Haag-Streit_Surgical/Download_documents/Brochures/Flyer_TOCULAR.pdf

Verion Image Guided System

The Verion's Reference Unit (Alcon) is a modified keratometer that takes corneal power measurements, captures a high-resolution reference image, automatically detects scleral vessels, as well as the limbus, the pupil and iris features, and then shows where the steep axis is relative to a picture of the eye. The data captured by the Reference Unit is then displayed in the Verion Digital Marker, which is compatible with the LenSx laser and most surgical microscopes.



The Verion Image Guided System is compatible with most surgical microscopes.

The Digital Marker software tracks the eye, providing a digital overlay to help with alignment. It can also provide guides for relaxing incisions, creating the capsulorhexis and positioning a multifocal lens. For more information, visit: myalcon.com/products/surgical/verion-guided-system/

RoboMarker System

According to the manufacturer (Surgilum), the RoboMarker System is the first self-leveling corneal marker with pre-inked, sterile, disposable tips and an integrated fixation light. The device has a concealed dual-pendular weight system balanced between two high-precision ball-bearings that ensures that the RoboMarker ring dial will maintain your chosen axis to within one degree.

The RoboMarker System from Surgilum.

For marking the cornea, the system provides single-use, sterile "RoboTips"— "fins" that come pre-applied with a dry marking formula. When the dry formula contacts the tear film, it produces precise marks that last up to two hours, long enough for preoperative marks to still be clear in the operating room. The system includes a fixation light to help replicate the position of the patient's eye when you measured the astigmatism preoperatively. The RoboTips are available in either visible-spectrum or infrared formulas (the latter being useful under the infrared lighting sometimes used by the Catalys and Lensar instruments, as well as intraoperative aberrometry systems).

The company claims that this marking system can save time compared to some multistep marking protocols. For more information visit: surgilum.com/products/robomarker/

EyeSuite Toric Planner

The EyeSuite Toric Planner (Haag-Streit) enables the surgeon to intuitively plan the surgery using high-resolution images of the eye. It also features an incision-optimization tool to help the surgeon minimize residual astigmatism by placing the incision in the right spot. The Planner is part of Haag-Streit's T-Cone Toric Platform, an optional addition to the LenStar biometer. The T-Cone Toric Platform complements the LenStar's comprehensive measurement spectrum with 11-ring placido topography, to help confirm the axis location and the regularity and symmetry of the astigmatism. Toric IOL calculation is accomplished with the integrated Barrett Toric Calculator.

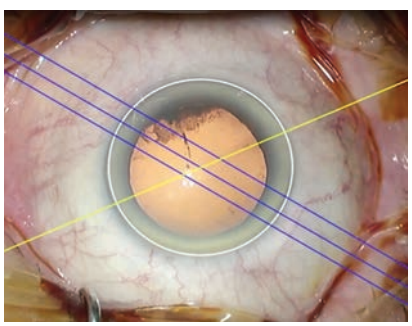
Planning the operation using high-resolution eye images allows the user to define additional guiding lines to anatomical landmarks that will be recognizable in the intraoperative view. The planning sketch can be printed and hung near the microscope.

For more information, visit: haag-streit.com/haag-streit-diagnostics/products/biometry/t-cone-toric-platform/

Cataract Suite Markerless

The Cataract Suite Markerless from Carl Zeiss Meditec is a set of interconnected instruments that enables—among other things—toric IOL and limbal relaxing incision alignment without the need to mark the eye. Data transfer between instruments is managed by Zeiss's FORUM data-management system, eliminating the need for manual transfer of information and greatly increasing surgical efficiency, according to the company.

After the IOLMaster takes its measurements and captures an image of



Zeiss' Cataract Suite Markerless works with the IOLMaster and Callisto eye system.

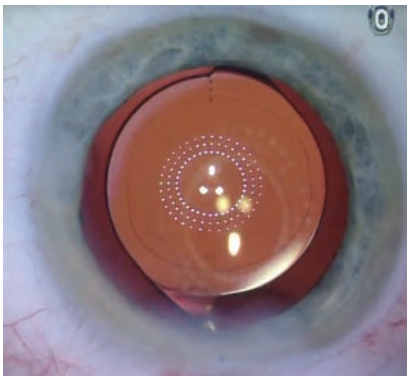
the eye, the information, including corneal astigmatism data, is transferred to the Callisto eye system. Callisto eye superimposes templates of planned surgical incisions, limbal relaxing incisions, the capsulorhexis and the toric lens target axis over the eye in the eyepiece and heads-up display of a Zeiss microscope. It matches the reference image to the patient's eye, tracking in real time using unique algorithms from Zeiss. With Callisto eye markerless alignment, Zeiss says that manual marking steps can be skipped altogether for a more precise toric IOL alignment.

This function is integrated into Zeiss's OPMI Lumera 700 microscope; for all other current Zeiss surgical microscopes, it's available as a retrofit. For more information, visit: zeiss.com/meditec/us/products/ophthalmology-optometry/cataract/zeiss-cataract-suite-markerless.html

Illuminating Surgical Keratoscope V5

The fifth-generation Illuminating Surgical Keratoscope (Mastel) features visual axis fixation/centration and lights indicating the primary meridian, adjustable from 0 to 180 degrees. The device is designed to account for cyclotorsion. The surgeon marks the eye at 3, 6 and 9 o'clock with the patient upright. Intraoperatively, while the patient fixates on a pulsating red light, the surgeon aligns the LED cardinal references with the pre-marks and sets the primary meridian to the desired position. The device can be attached to most surgical microscopes, with standard sizes for Zeiss and Leica scopes.

The manufacturer notes that this device is not intended as a sole indicator of absolute alignment, but as a complement to a systematic approach to accurate IOL alignment. With experience, the company says, the system will greatly improve the accuracy of alignment and patient outcomes. For more information, visit: mastel.com/product/mastel-isk/



When using the Illuminating Surgical Keratoscope V5, the two reflections reveal the toricity of the lens and cornea, helping the surgeon to align the lens.

Discovery System

The Discovery System (Innovative Visual Systems) measures multiple eye characteristics including white-to-white, pupil diameter, corneal topography and both corneal and whole-eye higher-order aberrations, using wavefront technology. The system provides toric IOL axis orientation (to ANSI precision standards), while iris registration corrects for head tilt and/or cyclorotation. Together, retroillumination photography and iris registration enable precise, direct assessment of IOL orientation. The Discovery System also provides postoperative astigmatism analysis and repositioning guidance, showing how to correct any error in toric IOL alignment. In addition, once the surgeon has entered the patient's corrected axis, the Discovery System will display a simulated image equivalent to a 20/30 letter on the Snellen chart, showing the expected visual acuity after IOL repositioning.

For more information, visit: ivisual-systems.com/index.html

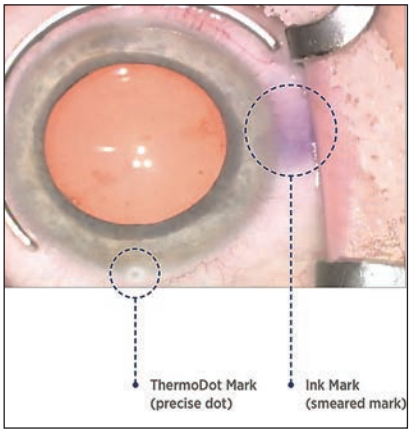
Osher Toric Alignment System

This system (from Eye Photo Systems) employs iris fingerprinting to improve the accuracy of toric implant alignment. A detailed, high-resolution photograph of the dilated pupil is captured during the initial preop examination. The keratometric meridians and the IOL goal line, transposed from the toric IOL calculator, can be overlaid on the image in the form of a protractor. That image can then be brought into the OR on a USB drive or printed as a hard-copy photograph for reference during the IOL alignment. The surgeon locates at least two unique landmarks in the iris such as crypts, nevi or brushfields. During surgery, those landmarks act as guides to help the surgeon use a Mendez guiding ring to accurately match the target meridian shown in the image.

For more information, visit: eye-photosystems.com/toric-alignment/

Wet-Field Osher ThermoDot Marker

The Osher ThermoDot Marker (Beaver-Visitec International) is a bipolar intraoperative instrument that makes a tiny pinpoint cautery mark on the cornea, eliminating the need for ink. The fine dot(s) can be used as a precise reference point for a variety of procedures, including astigmatic keratotomy and toric intraocular lens im-



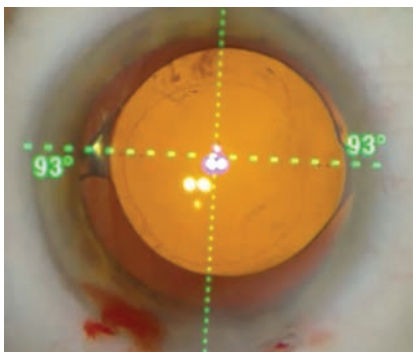
The Osher ThermoDot device creates a tiny, painless cautery mark that will not smear, but disappears after a day or two.

plantation. Because no ink is involved, the precise, easily visible mark will not smear and will last the duration of the surgery. (The mark is so small that it isn't even felt by the patient; it disappears in a day or two.) The unique curved design of the marker facilitates a perpendicular approach.

For more information visit: beavervisitec.com/upload/BVI_SellSheet_WetField_Osher_ThermoDot_LowRes.pdf

Optiwave Refractive Analysis System, with VerifEye+

The ORA intraoperative system (Alcon) measures the eye's refractive state while the patient is on the table, providing continuous assessment and recommendations for lens power—including the axis and magnitude of astigmatism. Because this approach measures the total refractive state of the eye, including posterior corneal astigmatism, it helps to improve astigmatic outcomes, the company states.

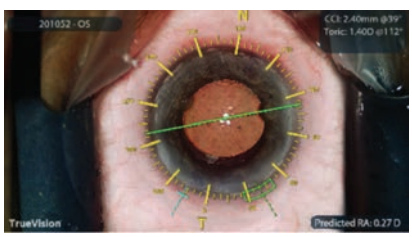


The ORA intraoperative system shows real-time streaming data, taking posterior corneal astigmatism into account.

The system provides overlays showing the optimum positioning for limbal relaxing incisions, and then provides continuous validation of LRI placement and the anticipated impact on visual outcomes. The real-time streaming data allows surgeons to rotate a toric lens within one degree of the desired axis. In addition, the system's AnalyzOR feature collects and analyzes postop data to aid in variable optimization. According to Alcon, the ORA System can reduce the number of patients falling outside of the intended astigmatic target by almost 54 percent compared to conventional preoperative calculations. For more information, visit: myalcon.com/products/surgical/ora-system/

TrueGuide

TrueGuide (TrueVision 3D Surgical) is a software application that generates templates in the surgeon's surgical field of view, in real time, to aid in IOL alignment and incision creation, employing customized surgeon profiles. It uses autoregistration with a preoperative image and 3-D eye-tracking that helps to eliminate parallax errors during the alignment.



The TrueGuide system generates templates in the surgical field of view in real time.

TrueGuide provides real-time vector analysis for incision optimization and toric IOL and LRI positioning, taking all variables into account; it updates its calculation of predicted residual astigmatism as the surgeon proceeds. Touchscreen capability at the microscope enables surgeons to change toric IOL alignment, incision parameters and targeted astigmatic outcomes at any time. After surgery, it employs regression analysis of postop diagnostics to improve the surgeon's nomogram. The company says the system is compatible with any surgical microscope; it allows cloud-based input of patient data from any location and also acts as an archiving system.

Visit truevisionsys.com/trueguide.html for more information. REVIEW

Can Corneal Inlays Work for Your Practice?

Kristine Brennan, Senior Associate Editor

Surgeons discuss the pros and cons of this new approach to refractive correction.

Corneal inlays are intended to be simple, lifelong interventions to end or reduce spectacle dependence—and its accompanying inconvenience—for presbyopes, who, according to one 2008 study, are projected to number approximately 1.37 billion globally by 2020.[1] Speaking to surgeons who are in the know, however, you learn that their colleagues have been slow to adopt this new technology, as demonstrated by the recent shuttering of ReVision Optics, maker of the now-discontinued Raindrop inlay. Potential roadblocks to success with inlays include variations in individual wound healing postoperatively and tear-film difficulties, as well as potential unwanted side effects from postop topical steroids.[2]

Here, surgeons who offer corneal inlays—both the Kamra and the defunct Raindrop—weigh in on who's getting them, the mechanics of implanting them, their pros and cons, and where they think the future of inlays is headed.

Slow Adoption

John A. Hovanesian, MD, clinical instructor at the Jules Stein Eye Institute, University of California, Los Angeles, and in practice at Harvard Eye Associates in Laguna Hills, believes that incorporating corneal inlays into refractive practice is well worth the effort, but notes that they haven't penetrated the market deeply. "I think we surgeons as a population have been pretty hesitant to take up inlays. There is a learning curve for us, and a phase of patient education that we need to go through," he says. He says ReVision Optics' closing and discontinuation of the Raindrop was a result of several factors. "The technology itself was a good performer," he says. "It was good enough for me to implant two inlays in close, personal friends, both of whom were quite happy. Personally, I believe the slow adoption of the Raindrop inlay was attributable to the 'competition' of great results with LASIK and premium IOLs. While neither procedure is ideally suited to the emmetropic presbyope who was a candidate for Raindrop, both have received wide public acceptance and adoption by surgeons. In addition, achieving a quiet eye with the Raindrop inlay required more follow-up and diligence after surgery than other refractive procedures."

Currently, ophthalmology has been slow to dive into inlays. It's possible that, as Dr. Hovanesian notes, surgeons aren't interested in cresting

This article has no commercial sponsorship.

a new learning curve. In terms of safety and efficacy, in the absence of a lot of large-scale, postmarket data, U.S. ophthalmologists have the FDA trials to go on for the Kamra (AcuFocus; Irvine, California) and the discontinued Raindrop. The FDA's summary report on the Kamra shows that of the 508 operated eyes studied, 44 (8.7 percent) had had the inlay removed at 36 months, with unacceptable hyperopic shift (25/44) cited as the most frequent cause. (For the subgroup of 166 eyes implanted per the instructions currently in force, seven had the Kamra removed.)[3] For the Raindrop, 27 of 373 operated eyes (7.2 percent) studied in the FDA trial had that inlay removed at 36 months. Haze and patient dissatisfaction with visual outcome after three months postop were tied as the top reasons for explantation at 10 cases out of 27 apiece.[4]

"We know they can work, because there are practices that are really succeeding with them," Dr. Hovanesian says. "We refractive surgeons need to try and make this a successful addition to our surgical armamentarium."

Who's Getting Them?

Surgeons say that, in the right patients, the inlays can work well.

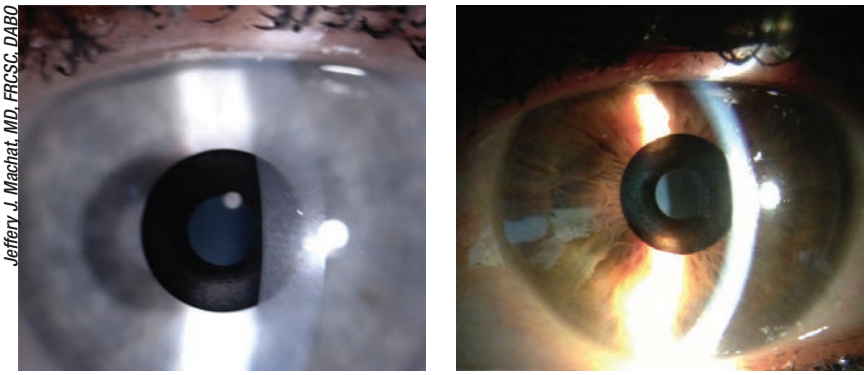
Dr. Hovanesian says that inlays are aimed at emmetropic presbyopes, who are a tricky group to satisfy. "These patients have low refractive error but desire freedom from eyeglasses for reading. Such patients tend to be in their late 40s to 50s," he says. "They don't have significant cataract yet and they're highly motivated to do something. They have heard of LASIK; most of them have heard of monovision, but many have a bias against it. A traditional approach is unlikely to apply very well to them, making inlays a good fit."

Jeffery J. Machat, MD, FRCSC, DABO, medical director of Nvision Eye Centers in Toronto and San Francisco, became part of the inlay market in August 2012, when he decided to get a Kamra implanted in his own eye. "There's sort of a moment that hits you where all of a sudden, you feel your age," he says. "For me, it was the size of the font on my iPhone—and my teenage daughter who tormented me about it for an entire day. I said to myself, 'Okay, that's it. I need to do something.' "

A refractive surgeon with 27 years of experience at the time, Dr. Machat sought a treatment with a high safety profile. "A corneal inlay made a lot of sense to me," he recalls. At the ASCRS meeting that year, he listened to John A. Vukich, MD, present early FDA data on the Kamra. Dr. Vukich closed with a case presentation, in which he revealed that he was in fact the subject. Dr. Machat recalls that he was convinced to proceed after questioning Dr. Vukich post presentation. "I went ahead and had it done myself with Dr. Minoru Tomita in Japan, and I was really thrilled. I had a very fast visual recovery. The very next day I was already J1, and three days later I was operating," he says.

Shortly after the procedure, Dr. Machat integrated the Kamra into his Toronto practice. "We got approval [from Health Canada] in September 2012. At that time, they were still doing thick corneal flaps, not pockets, for insertion of the inlay. But we rapidly learned that a pocket deeper in the cornea was a better approach surgically and we got far better results, so there was definitely a learning curve," he says.

The current version of the Kamra inlay is a dark polyvinylidene fluoride ring etched with perforations, 6 µm thick and 3.8 mm in diameter. Its central aperture is 1.6 mm, and it is placed over the first Purkinje image when implanted into a stromal pocket 200 to 250 µm deep. Long-term data suggest that the Kamra



Jeffery J. Machat, MD, FRCSC, DABO

Because it is made of dark polyvinylidene fluoride, the Kamra small-aperture inlay may be visible in eyes with light-colored irises.

results in notably improved monocular and binocular uncorrected near and intermediate vision, with a small loss of monocular and binocular uncorrected distance visual acuity. In a study with five-year follow-up, mean UNVA at 60 months was improved from J7/J8 preoperatively to J3 ±2 lines. Of 32 patients, two required recentration of the inlay at six months; one Kamra was explanted due to unsatisfactory hyperopic shift; one patient had epithelial ingrowth in the early postop period.[5] Notably, the study patients got their inlays from 2006 to 2007, and so were implanted with an earlier version of the Kamra that was 10 µm thick, etched with fewer holes and that allowed more unfocused light onto the retina.

John A. Vukich, MD, associate clinical professor of ophthalmology at the University of Wisconsin Madison School of Medicine and in private practice at Davis Duehr Dean Eye Care in Madison—and the impetus for Dr. Machat's decision to get his own inlay—says that most of his inlay patients present as prospective LASIK patients. "The most common inlay patients that we treat are individuals who are interested in LASIK to begin with, and then this creates a value-added option," he explains. "Patients who are looking for LASIK in the presbyopic range are generally either higher myopes (-4, -5, -6 D) or they are hyperopic. They understand that they have to wear reading glasses over their contact lenses if they're hyperopic; or if they're myopic above -4 D, they can't take their glasses off and read comfortably. These individuals all understand the inconvenience of presbyopia, and they also understand that being able to have that extended depth of focus and freedom from reading glasses—or a least a significantly diminished need for them—is a real benefit," says Dr. Vukich, who offers the Kamra inlay to his patients.

Making It Work

Dr. Hovanesian notes that a patient's preop refraction is important when placing an inlay. "I tend to prefer the Kamra for patients who are slightly myopic," he says. "As we know, the ideal patient for the Kamra is about -0.75 D. For the Raindrop, the ideal patient was more like a +0.75 D.

"Another thing to consider is that there is a little cosmetic concern with the Kamra, particularly for people with lighter-colored eyes, because it can be visible to the patient," continues Dr. Hovanesian. "I've not actually had anyone who's received it and been unhappy with it, regardless of eye color, but I think it's a conversation worth having with patients." Of the 44 explanted Kamras in the FDA pivotal study cohort, two were removed for cosmesis.[3]

When he combines inlays with LASIK, Dr. Hovanesian notes it's important to adjust the refractive target. "In those who are more myopic it's best to undercorrect the nondominant eye with the intention of later putting in a Kamra," he explains.

Dr. Hovanesian looks forward to the FDA approval of the Flexivue Microlens (Presbia Coöperatief U.A.; Irvine, California), a refractive inlay 3 mm in diameter made of clear UV-blocking copolymer. The central zone has zero refractive power and a 0.15-mm hole. Its peripheral zone comes with add powers ranging from +1.25 to +3.5 D in 0.25-D increments. The Microlens varies in thickness from 15 to 20 µm, depending on add power. "It's still undergoing FDA trials. But so far, the data look good and it should offer promise as another valuable entrant into this market," he says. The multicenter Phase III trial will follow approximately 412 patients between 45 and 60 years old implanted with the Microlens. The study is expected to wrap up in early 2019 (ClinicalTrials.gov Identifier: NCT02110472).

In a study of 47 emmetropic presbyopes with the Microlens inserted in a femtosecond laser-created corneal pocket 280 µm deep, no complications occurred over the 12-month follow-up period, and 75 percent of the patients achieved uncorrected near visual acuity of 20/32 or better in the operated eye. The operated eyes' mean uncorrected distance acuity dropped from 20/20 preop to 20/50 ($p<0.001$), while mean binocular UDVA did not change significantly ($p=0.516$).[6]

"I've done the Microlens in Canada," says Dr. Machat. He observes that patients could start with one Flexivue lens power and then replace it with a higher one as presbyopia progresses,

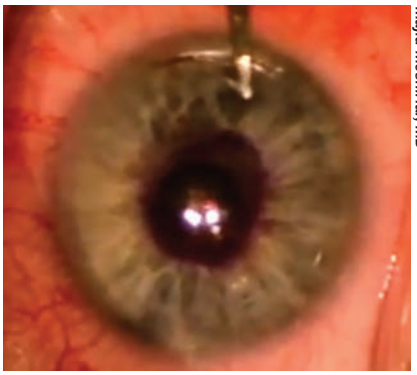
but also that patients getting inlays generally won't do this. "We have found in our very limited experience that patients do not want to put in an inlay and then come back in two or three years for another one. From a patient's-reality perspective, most people will just put in a +2.25 D Microlens and that's it. Patients were losing more distance than we expected, but getting good reading," he says.

Lifelong Implant

"I'm excited about corneal inlays because I think of them as a lifelong procedure for patients. With the Kamra, we're altering the cornea to allow depth of focus, and that change in shape lasts the rest of the patient's life, even after a cataract surgery," says Dr. Hovanesian. "We have in fact done cataract surgery on patients who have previously undergone Kamra as part of the FDA study prior to approval, and those patients have done very well."

Dr. Machat concurs that corneal inlays can last a lifetime without complicating future ophthalmic interventions. "The Kamra inlay and the Raindrop inlay continue to work until someone develops a cataract," he says. "I'm going to leave my corneal inlay in once I develop lenticular opacities, and just put in a monofocal IOL and target -1 D for reading. I won't need to put a multifocal in my left eye; I won't need to remove it. I won't need to do anything," he says.

Dr. Machat will do LASIK and inlays on the same day or break up the procedure, depending on the clinical indications. "LASIK takes about six minutes; a Kamra inlay, once you get experienced, takes about six minutes," he says. "But if someone has a high prescription or a complex prescription, or a lot of preoperative dry-eye concerns, then I'll break up the procedure because I want to make sure that I have achieved my target refraction. Let's say they're +3 D and I'm targeting -1 D, which would be about the maximum I would do on a cornea that's flat and not dry. Or let's say they're -8 D. I want to wait and make sure that they don't regress. In those cases, I'll do LASIK, wait a month, refract them to make sure I've hit my target refraction, and then I'll go ahead and insert the inlay. But if there's no clinical reason not to, then I do it all the same day.



Majid Moshirfar, MD

A surgeon opens the pocket in preparation for sliding in the Kamra presbyopic intracorneal inlay.

"I'll do LASIK for about 80 percent of my corneal inlays," Dr. Machat continues. "So this has increased my LASIK practice. We often have patients who are early presbyopes and we just leave them a little bit undercorrected; that'll put off their need for readers for about five years, and then they'll come back as soon as they need a corneal inlay. All of a sudden, that inlay takes the -0.75 D and gives them 3 D of accommodative range, so they're thrilled. We've done them in pseudophakes; we've done them in post-LASIK patients and post-PRK patients, as well as in virgin corneas. It's definitely worked well for us."

"In terms of this being a treatment for life, our experience has been that you can certainly do a cataract surgery with these inlays in place, and it really doesn't get in the way," concurs Dr. Vukich, who also says that the majority of his Kamra patients need to be brought to plano or -0.5 to -0.75 D of sphere correction in their nondominant eye to prepare for the inlay.

The Kamra obstructs the view of a small portion of the retina. The FDA summary report on the Kamra warns that medical laser treatments for certain eye conditions may warrant extra caution or even removal of the inlay.[3] "Retinal surgeons initially felt like there might be some obstructed view, but that hasn't turned out to be the case," says Dr. Vukich. "You can see around them quite easily."

Dr. Hovanesian doesn't think they pose much of a visibility problem in the event of future retinal evaluation and treatment, either. "Some retinal specialists are concerned about this with the Kamra, but if you have a pupil that dilates reasonably well then it's really not an issue to see around it," he says. "It's like looking around a tiny corneal scar: You still see around it if the cornea is clear outside the area of the inlay."

Challenges with Inlays

Some surgeons think the slow adoption rate of corneal inlays among surgeons may just be explained by their relative novelty on the refractive scene.

"The challenge with inlays is a lack of familiarity on the part of the general public," says Dr. Hovanesian. "When we started doing LASIK years ago, it was perceived as a cutting-edge, possibly risky new procedure. People had questions about safety; they had questions about long-term stability of results. Today, 20 years later, everyone has friends who've been through LASIK and who've had positive things to say about it. Inlays are like LASIK was 20 years ago. We have to help patients understand what they are, how they work, and

what their benefits are."

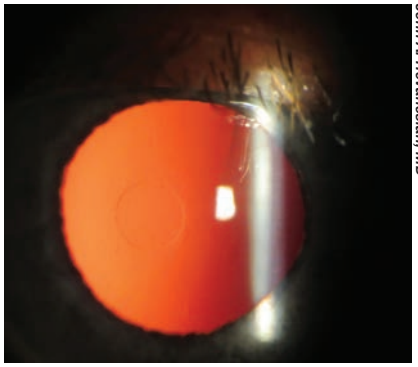
"It's not unlike the early days of LASIK surgery," agrees Dr. Vukich. "It took a couple of years before patients really understood and knew someone who'd had it done," he says. "It's true that we're not seeing huge numbers at this point, but it is quietly and steadily gaining momentum."

Dr. Machat introduces a corneal inlay as an improvement on LASIK alone. "We present it to patients as an upgrade, he says. "If you get LASIK, you're going to get distance vision but you're going to need reading glasses. Patients ask if there are any other options. We like the corneal inlay because patients retain binocular distance vision. If someone has -1 D monovision, that monovision will only last so long, whereas with an inlay it will last for decades. It's resistant to the progression of presbyopia.

"The word of mouth has been quite dramatic," Dr. Machat continues. "If you think of myopes, one in four of their friends are myopic: When you think of presbyopes, 100 percent of their friends are presbyopic. Having presbyopic solutions that go beyond multifocal IOLs is a vital part of any refractive practice."

Dr. Hovanesian says that his staff and co-managing optometrists help get the word out about corneal inlays. "We have folks in the practice who do that very well, along with some docs outside. Just like there was with LASIK, there's a bit of education mode that the co-managing doctors have to engage in," he says.

"Train your staff," urges Dr. Machat. "Get them on board. Really make sure that they understand, because this is a new but highly effective treatment. Also, have an age-appropriate patient consultant. We hired patient consultants who were in their 50s, because someone who's in their 50s doesn't want to talk to a 24-year-old. They want to talk to someone who can actually relate to them and understand presbyopia. I gave a patient consultant on my staff LASIK because she was a moderately high myope, and I inserted a Kamra inlay. She was then able to really talk to our patients about it."



John A. Hovanesian, MD

The Raindrop was a nonrefractive inlay made of clear hydrogel. It approximated the cornea's refractive index.

In addition to educating patients about the benefits of corneal inlays, setting their expectations is also key. "You have to tell patients ahead of time that vision does improve, but it may take a couple of weeks, and sometimes, it may take even a little longer before they get the full effect," stresses Dr. Vukich. "I simply tell patients, 'It's going to take a little while, so if you're not getting the full effect, we anticipate that. It takes awhile for things to settle down and for the ocular surface to optimize and for the healing to take place,'" he says. "Patients need to know what to expect."

Fine-tune Your Follow-up

"There is clearly a period of postoperative care that is necessary with inlays," Dr. Vukich continues. "These patients are treated with steroids, typically for up to a month or longer after the procedure on a tapering schedule. Typically, we see them at one day, one week, and one month, but of course we'd adjust that as necessary."

Dr. Hovanesian says that you may need to train your staff to do a little more handholding for postoperative inlay patients than for post-LASIK patients. "There's a little bit of healing time. There's a little bit more follow-up care," he notes. He adds that some inlay patients may need a reminder of their preop vision to appreciate how far they've come postoperatively. "Some patients get an inlay, and six months later they kind of forget what their preop vision was like. One thing that we actually learned to do from the FDA study—and I recommend this to all surgeons—is to take a little handheld 8.5 x 11-inch reading card, and have the patient read the smallest print they can on it. Have them sign it, and put it in their chart. Later, if they're wondering if their inlay is doing anything for them, you can pull that card out and show them. They can always read much better after the procedure than before and sometimes they're amazed at what a difference it's made. They simply forgot how bad their previous reading vision was. Sometimes you just have to remind patients of what you've done for them."

Having experienced the Kamra as both a patient and a surgeon affords Dr. Machat insight when answering patients' questions about potential near-vision difficulty under mesopic conditions. "All presbyopes have trouble when it's dark," he says, "but it's not like the inlay makes your vision much darker, so that you suddenly have to use a light when you didn't previously. But there is also retinal adaptation occurring. It's very interesting." Dr. Machat says he experienced this adaptation firsthand as his vision in low-light conditions steadily improved during the postoperative months. Dr. Machat's clinical director, Sondra Black, OD, reported the same thing after her Kamra procedure, he says. "She found that her vision under low light improved over

an entire year. When you talk to scientists like Jay Pepose, he says that this is exactly what occurs. I got to live it. I was very surprised by it and it didn't make sense to me, but it's true," he says.

For all the potential benefits corneal inlays can confer, the procedure also confers the risks that come with putting a foreign body into the eye. "There is no such thing as a surgery that has a zero complication rate. Anytime we do something, there's the possibility of an unexpected or untoward outcome," Dr. Vukich notes of his experience with the Kamra. "One of the things we have seen is epithelial implantation: At the time the implant was placed, a nest of epithelial cells was brought in with the implant. We believe it occurs in less than a fraction of 1 percent of patients, and it's easily fixed. We can simply rinse out the epithelial cells. We've also had one patient in which the implant was slightly irregular because of a micro-fold. That was early on in my experience, so there is a bit of a learning curve in terms of how to place the implant quickly, atraumatically and in the location that you're looking for," he says, "but inlay surgery is well within the skill set of any anterior segment surgeon."

One potential plus of corneal inlays is that they are strictly additive and removable. "There's no such thing as a reversible operation, but the inlay is clearly removable. So to the extent that we can restore the native architecture—with the exception of the incision we've made—by removing the implant, I think people find that reassuring," says Dr. Vukich, who reports that he has explanted one Kamra. Although patients who have their refraction set for anisometropia in anticipation of an inlay are left in that state if the inlay later comes out, Dr. Vukich says that this has not been problematic over the course of his experience with the Kamra. "If and when an implant needs to be removed, the opportunity for enhancement to bring patients to emmetropia exists and we'll tell them we can do that, but we really have not had anyone ask for it," he says, adding that patients enjoy the near component created by LASIK in the nondominant eye despite a slight loss of distance visual acuity.

> *"There's no such thing as a reversible operation, but the [Kamra] is clearly removable."*
> — John Vukich, MD

Check Your Technology

Dr. Machat notes that you need the right tools to offer corneal inlays. "You have to keep a really high-quality femtosecond laser with a really tight raster pattern," he says. "So that was one of the advantages of using the Raindrop: You just needed to make a flap that was one-third of the central corneal thickness, so you didn't need pocket software," he says.

Although he acknowledges that obtaining the requisite technology for corneal inlays might be prohibitively costly for surgeons not currently offering LASIK, Dr. Vukich says that investment is minimal for those already offering it. "For a surgeon who is already doing LASIK surgery, there is almost no startup cost to this," he says.

Dr. Machat says he purchased the AcuTarget HD, the forerunner of the HD Analyzer (Visiometrics; Costa Mesa, California) when he started offering the Kamra. The costly imager is pretty much a must-buy for Kamra surgeons, a fact that may have discouraged some from getting involved with Kamra. Dr. Machat also suspects that the system's name at that time led to some surgeons declining to adopt inlays because of a mistaken belief that the AcuTarget was only good for inlay centration. "What they're not realizing is that I use it for Kamra only 5 percent of the time; 95 percent of the time, I use it for refractive lens exchange, dry eye and other procedures," he says.

Dr. Vukich also says that the HD Analyzer is a great help with inlays, but that it its use isn't limited to that area of practice. "I think that in the setting of using inlays it's quite valuable to have, but quite frankly, we use it far more widely than just for implanting inlays," he says. REVIEW

Dr. Hovanesian was a consultant for ReVision Optics and consults for AcuFocus. Dr. Machat is on the medical advisory board for AcuFocus and is a consultant for Viseometrics. Dr. Vukich is a consultant for AcuFocus, and was an investigator and part of the FDA regulatory team.

1. Holden BA, Fricke JR, Ho SM, et al. Global vision impairment due to uncorrected presbyopia. Arch Ophthalmol 2008;126:1731-39.
2. Moarefi MA, Bafna S, Wiley W. A review of presbyopia treatment with corneal inlays. Ophthalmol Ther 2017;6:55-65.
3. Food and Drug Administration. FDA summary of safety and effectiveness data (SSED). PMA P120023. https://www.accessdata.fda.gov/cdrh_docs/pdf12/P120023B.pdf. Retrieved 1/17/2018.
4. Food and Drug Administration. FDA summary of safety and effectiveness data (SSED). PMA P150034. https://www.accessdata.fda.gov/cdrh_docs/pdf15/P150034B.pdf. Retrieved 1/17/2018.
5. Dexl AK, Jell G, Strohmaier C, et al. Long-term outcomes after monocular corneal inlay implantation for the surgical compensation of presbyopia. J Cataract Refract Surg 2015;41:3:566–75.
6. Limnopoulu AN, Bouzoukis DI, Kymionis GD, et al. Visual outcomes and safety of a refractive corneal inlay for presbyopia using a femtosecond laser. J Refract Surg 2013;29:1:12-18.

What's Behind That SMILE

Edward Manche, MD, Stanford, Calif.

A look at patient selection, technique and how SMILE compares to LASIK.

There aren't many procedures that can install themselves alongside perennial stalwarts PRK and LASIK as reliable, effective methods to treat refractive errors, but small-incision lenticular extraction has shown the potential to do so. Approved by the FDA in 2016, SMILE has been shown to be safe and effective, both in FDA trials and in international studies. If you're curious about the nuts and bolts of the procedure, are about to perform your first cases or are already performing SMILE but are open to some new tricks, this article is for you. In it, I'll share my tips and techniques for managing SMILE patients preop, intraop and postop, and give you some idea where it stands when compared to LASIK.

A SMILE Refresher

Since SMILE is relatively new on the refractive scene in the United States, it might be helpful to describe the procedure.

What makes SMILE unique is that it's an all-femtosecond laser refractive procedure. The only laser currently able and approved to perform SMILE is the VisuMax femtosecond laser (Carl Zeiss Meditec). The surgeon uses the laser to cut a lenticule-shaped disc of tissue within the cornea and then create a side cut through which this lenticule is removed. The removal of the lenticule is what causes the change in refraction.

In the United States, SMILE is approved for the treatment of -1 D to -8 D of myopia, with no more than -0.50 D of astigmatism and a manifest refraction spherical equivalent of -8.25 D, which has been stable for a year.

Preop Screening and Exam

When evaluating SMILE candidates, the selection criteria are similar to those used for LASIK.

I exclude patients with suspicious corneal topography or thinner-than-average corneas. I know that some SMILE surgeons feel SMILE has better biomechanical stability than LASIK, and there have been some studies to that effect, but I still strive to maintain a minimum preop corneal thickness of 500 µm. Some surgeons think SMILE will expand the number of patients you can treat by including those with corneas that would be risky for LASIK, but I disagree. I think the indications will be virtually identical to LASIK's. Since you sever fewer corneal nerves, however, I believe that patients experience less dry eye with SMILE than LASIK, and papers have borne this out.[1,2]

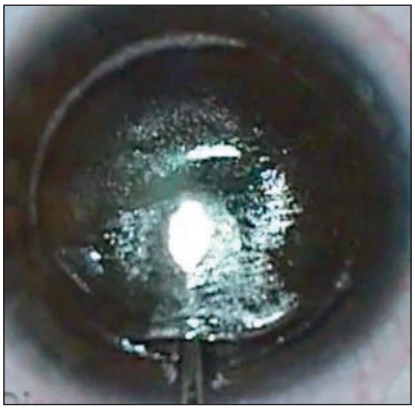
This article has no commercial sponsorship.

When selecting candidates, we're somewhat limited in the United States in that we can only treat between -1 and -8 D. The machine will, however, allow you to treat up to -10 D, though you'll get a yellow warning light indicating that the treatment is above the approved range and that there's not enough information on treatments above that range. Internationally, however, SMILE has been shown to work very well in myopia above -8 D. The other aspect of the treatment ranges you'll notice is that you can't program any astigmatism correction into the treatment, at least in the United States. This makes patient selection a bit more challenging because, typically, many patients will have some degree of myopia and astigmatism. For instance, one eye might have 0.25 or 0.5 D of astigmatism, while the other has 0.75 D. This limits the pool of patients who can undergo SMILE surgery at this time.

In addition to the cornea and refractive aspects, we also look for other signs of ocular health. In other words, there should be no corneal staining, no epithelial basement membrane dystrophy and no external eye disease like blepharitis. If there's meibomian gland dysfunction, we'll also treat that preop.

The preop discussion with the patient needs to be handled a certain way. Some patients, having heard about SMILE online or from the news, will come in and say, "I only want SMILE surgery." These patients assume that because SMILE is the newest surgery, it's also the best one, an opinion that's common when new technology arrives. Unfortunately, in many cases, these gung-ho patients aren't good candidates for the new technology for some reason, such as having too much astigmatism. Also, the only reliable way we currently have to enhance a less-than-satisfactory SMILE outcome is PRK, which patients need to be made aware of.

In light of these issues, I present SMILE in an evenhanded way, and I make sure that I also talk about LASIK and PRK. SMILE is a complementary procedure to LASIK and PRK, not a competitive one. You shouldn't bash one procedure, such as PRK, to build up SMILE, because this can come back to haunt you should you need to perform a PRK enhancement on the SMILE patient. This goes the other way as well: Most of the patients who come in for refractive surgery want LASIK because of the lack of pain and the rapidity of visual recovery but may not know about SMILE. I inform them that they're also candidates for SMILE, which has a lot of the same characteristics they're looking for.



It helps to perform the anterior dissection first because the posterior side is tethered down and keeps it stable during dissection.

It might also be worth informing the patient that even though he'll see well immediately after SMILE, the vision won't be as sharp as with LASIK, at least for approximately the first week postop. It takes a little bit longer for vision to recover with SMILE. Most patients' vision, however, is equivalent to what you'd get with LASIK after about that first week to the first month.

Procedure Pearls

Getting good at SMILE requires a knowledge of both the technology involved, and the art of manipulating the fragile corneal lenticule.

- ***Managing preop astigmatism.*** Since SMILE is only approved for patients with no or almost nonexistent astigmatism, surgeons often ask about performing other procedures beforehand to address cases with astigmatism that's beyond the approval range. Some surgeons might just perform an AK, combining it with SMILE. But if you do this, I feel you're shortchanging the patient and the procedure. Astigmatic SMILE should be approved in the next six months or so in the United States. During that time, you have to ask yourself if you'd rather do an AK and combine it with SMILE or just wait until you can simply program the VisuMax to do a compound astigmatism treatment. The latter option is better, in my opinion. If someone with significant astigmatism wants SMILE, I would just tell him to wait another few months, or to have LASIK or PRK now. I don't think the results of combined AK and SMILE are going to be as accurate as an all-laser SMILE procedure will be.
- ***VisuMax idiosyncrasies.*** It helps to become familiar with the VisuMax laser, because it's different from the IntraLase. The latter is a great machine that works well, but its suction is different than the VisuMax's. The IntraLase suction is very strong and can cause the patient's vision to brown- or black out during the procedure, which means suction breaks are very rare with the IntraLase.

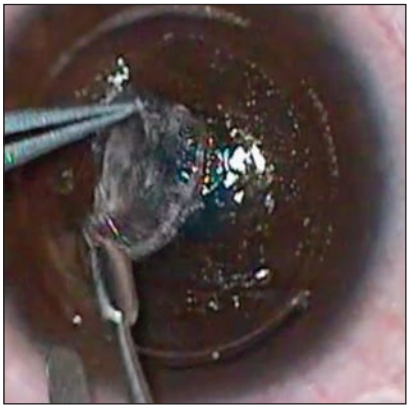
With the VisuMax, on the other hand, the suction from the curved applanation cone that goes against the cornea is much lighter than with the IntraLase. Because of this, you really need to get used to the system. In fact, the company requires something in the neighborhood of 30 to 50 LASIK flaps be performed with the VisuMax before it'll even allow you to perform SMILE with the device, just to help make you comfortable with its suction process. In my experience, this is very astute advice, since I've performed upward of 2,000 VisuMax LASIK flap treatments,

and I've only had a couple of suction breaks, all of which occurred in my first 50 cases. Since then, I've had none. Because it has such light suction, then, you have to be aware of patient movement or eye-squeezing, either of which can break VisuMax suction quite easily.

• ***Controlling patient movement.*** You'll find that, when you make flaps or perform SMILE, as soon as you place the speculum or attempt to put in any drops, you can tell if the patient is an eye-squeezer. If he is, tell him to relax and not to clench his jaw or shoulders, which may translate into eye-squeezing. Put your finger on the lid on top of the speculum and note if the patient's squeezing. If he is, just say, "I can feel you squeezing. Please don't," and use your finger in this spot to monitor how much squeezing is occurring, telling him to stop when it happens. This maneuver also helps stabilize the head.

It's also important to make sure the patient is relatively comfortable and doesn't move his head or feet. Even moving the feet can cause a movement of the head. I talk to the patients throughout the procedure, informing them what is about to happen and then reassuring them as it does. "As the applanation lens comes down on your eye, there'll be a circle of white light with a green light in the center," I say. Once it applanates, the green light will become sharply focused. "Look at the green light," I say, engaging suction. Once suction is engaged, I tell him not to worry about chasing the light around, but just keep looking straight. I inform the patient that it will take just under 40 seconds, but the first 18 are the most critical because that's when the power cut is made. If you break suction during that part of the cut, you have to abort the procedure and switch to PRK or LASIK. If you break suction after the power cut, you can just restart the treatment with the anterior or the side cut without a problem.

• ***After the cut.*** On the VisuMax, there's an operating microscope separate from the microscope that you use for the lenticule dissection and removal. Once the cut is completed, you bring the patient beneath that second scope and then use a SMILE dissector instrument to open the side cut, which is 5 mm in length.



After removing the lenticule, place it on the cornea and look for any missing pieces.

With the side cut open, you use a SMILE dissector to identify the anterior and posterior aspects of the dissection. To facilitate this, I'll move the dissector to one side, for instance the temporal side on the right eye, and identify the anterior-most plane. On the nasal side, I'll go through the side cut and identify the posterior portion enough so that I can put this spoon-shaped SMILE tissue separator in afterward. Many companies offer SMILE instruments. I started out with SMILE instruments made by Malosa Medical (malosa.com). Malosa makes a pack of single-use instruments exclusively for the steps of the procedure. Today, I use sterilizable SMILE instruments of my own design made by ASICO (www.asico.com).

You always want to separate the anterior lenticule first. If you don't, the procedure can become quite challenging because there will be nothing to tether the lenticule down. You dissect out the anterior lenticule first, followed by the posterior lenticule. Leave a small bridge of tissue either nasally or temporally to help keep the lenticule tethered in place during the dissection. If you save that tissue bridge for last, you can sweep it aside to easily complete the dissection.

Generally, once you've dissected the anterior portion, to access the posterior portion, look for some tension when you pull up a little on the posterior lenticule. The instrument will feel snug under the posterior lenticule, and there will be no space like that between the anterior lenticule and overlying cap. You may have trouble locating the posterior lenticule when you first begin performing SMILE surgery. If you have trouble locating the posterior portion, you sometimes have to move your instrument to find an area where you can achieve access to the posterior lamellar resection.

After you've dissected out the lenticule, it's critical to then pull it out and lay it on top of the cornea. Inspect it to make sure that it's perfectly circular, and that you haven't inadvertently left any pieces in the interface. Laying it out like this will reveal any tears or retained lenticule material. If the tear is small, you can go back into the interface and tease out the remaining tissue. (A feature of the VisuMax that's helpful for this step is a light similar to that of a slit lamp.)

As you perform your initial cases, you'll find that visualization of the lenticule can be challenging. Usually, the anterior plane of the lenticule will separate pretty easily, while the posterior one can be somewhat challenging to find. Because of this, I'd strongly recommend that those who are just starting out with SMILE spend time with an experienced SMILE surgeon. Alternatively, have one of the company's representatives assist you with your first cases.

• ***Dealing with low corrections.*** In contrast to LASIK, with SMILE lower corrections are actually some of the trickiest ones. Though this may sound counterintuitive, it makes sense when you think about the mechanics of

the procedure: The lenticules in a low correction of, say, -2 or -3 D, are much thinner than those in higher corrections, and are therefore more prone to tears. For example, a -1 D lenticule could be about 25 µm thick, compared to those in -8 or -10 D treatments, which are around 140 µm. Therefore, when you start out with SMILE, it's probably best to start with corrections in the -4 to -6 D range. This will yield the most satisfying result for the patient and will be easier for you.

Possible Complications

Many of the complications of SMILE stem from the manipulation of the lenticule. However, if you're careful, you can avoid them in most cases.

• ***Lenticule issues.*** If you're not careful, you can perforate the overlying corneal cap as you're doing the dissection, causing a tear. If you're struggling to remove the lenticule, you can accidentally tear the edge of the incision so that it almost becomes more flap-like. Some surgeons have recounted cases in which they couldn't identify the anterior/posterior lenticule and couldn't dissect it out. In one such case, the surgeon couldn't remove the lenticule completely—so he left the piece in the cornea. The patient was dissatisfied with the refractive results and eventually went to another surgeon, who ended up extracting the remaining piece of lenticule a year later without any problem. The patient had a complete recovery and was ultimately satisfied with his SMILE surgery. There have also been cases where this occurred, and the surgeon was able to complete the dissection several months later without incident.

When compared with LASIK, I feel the flap vs. lenticule issues are comparable, but different: You can have lenticule complications with SMILE just as you can have flap complications with LASIK. You can also get a complication such as epithelial ingrowth with SMILE, which is, for the most part, treatable.

• ***Docking/suction issues.*** One area where SMILE lags somewhat behind LASIK is in the margin for error you have while creating the lenticule vs. creating a flap. Since this isn't an excimer laser, there's no auto-centration or auto-registration. Therefore, it's critical that you're docked over the corneal vertex, which usually corresponds to the pupil center. This is because if you get a decentered docking, then you're going to get a decentered lenticule, which can cause a number of optical issues such as induced aberrations, degraded quality of vision, induced coma and astigmatism, and is very difficult to correct. With LASIK, on the other hand, if your LASIK flap creation is off superiorly or inferiorly by 1 or 2 mm, for instance, and it's a 9-mm flap, you've got some margin for error. This isn't the case with a lenticule. Centration and not breaking suction are critical parts of the surgery.

• ***Handling enhancements.*** As mentioned earlier, the current go-to procedure for a SMILE enhancement isn't SMILE, but PRK.

If we need to perform an enhancement, we wait a minimum of three months, depending on the amount of initial myopia. For low myopes, such as -3 or -4 D, three months is usually sufficient. For a higher correction, however, we might wait a little longer, maybe six months. Though we haven't had to do one of these yet, a number of surgeons have shown that PRK works well.

Follow-up and Results

For SMILE, I use the same follow-up schedule as LASIK: topical steroids and a fourth-generation fluoroquinolone, both q.i.d., for a week. I usually see patients on day one, week one, one month, three months and one year.

In terms of results, I'm currently performing my own prospective, contralateral eye study in which one eye gets LASIK and the other undergoes SMILE. I plan to enroll 70 patients. Until that study's complete, however, there are a few published studies, and the FDA approval data, to draw upon.

In the FDA data, though there were no eyes preoperatively with an uncorrected vision of 20/40 or better: At the six-month visit, 99.7 percent (327/328) and 87.5 percent (287/328) of treated eyes saw 20/40 or better and 20/20 or better, respectively. In terms of predictability, 93 and 98.5 percent achieved an MRSE within ±0.50 D and ±1 D of the attempted correction, respectively. The average preop myopia was -4.75 D (range: -1 to -10 D).

On the complication side, 35 patients out of 336 (10.4 percent) reported moderate or severe glare, and 20 (6 percent) had moderate or severe halos. By month 12, however, there were only four reports of the former (1.1 percent) and one of the latter (0.2 percent). At one year, 2.5 percent (8/311) of patients had lost a line of best-corrected vision vs. preop; no patients lost two or more lines. The rest either improved or stayed the same.

As my experience, and the FDA trials, have shown, SMILE is a safe, effective procedure. However, rather than being LASIK's replacement, I believe it shines the brightest—and patients and doctors are better served—when it's positioned as a complementary refractive procedure. REVIEW

Dr. Manche is the director of cornea and refractive surgery at the Stanford University Eye Laser Center, and a professor of ophthalmology at the university. He is a consultant for Allergan, Avedro, Shire, J & J Vision, Carl Zeiss Meditec, Ocular Therapeutix and Avellino Labs.

1. Denoyer A, Landman E, Trinh L, Faure JF, Auclin F, Baudouin C. Dry eye disease after refractive surgery: comparative outcomes of small incision lenticule extraction versus LASIK. Ophthalmology 2015;122:4:669-76.
2. Xu Y, Yang Y. Dry eye after small incision lenticule extraction and LASIK for myopia. J Refract Surg 2014;30:3:186-90.

Is There Still a Place For Manual LRIs?

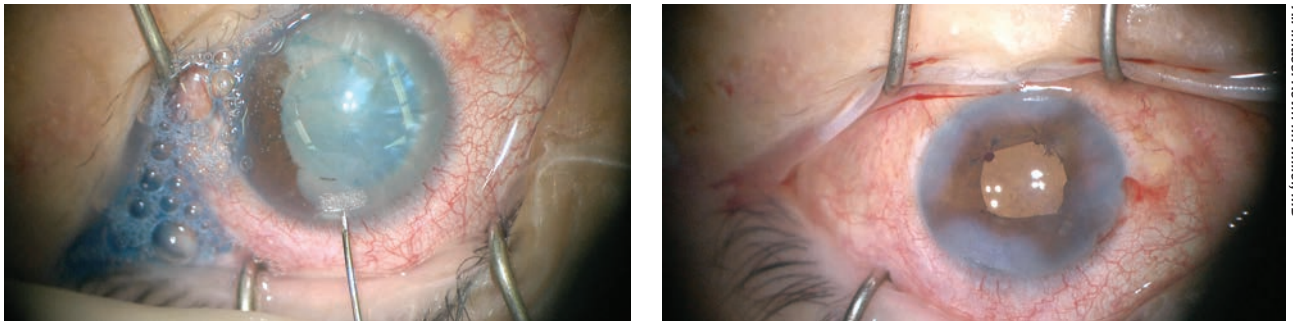
Michelle Stephenson, Contributing Editor

Not only is there a place for them, but some surgeons say they're performing them more than ever.

Although toric IOLs and excimer laser photoablation are superior to limbal relaxing incisions for treating moderate to severe astigmatism, there is still a place for manual relaxing incisions for treating smaller amounts of astigmatism, and every surgeon should know how to perform them.

According to Eric D. Donnenfeld, MD, Ophthalmic Consultants of Long Island, manual LRIs are as vibrant and important to optics and ophthalmology as they have ever been. "The reason for this is that, as patient expectations have increased, the management of residual astigmatism associated with cataract surgery has become of paramount importance," he says. "The previous generation of LRIs were performed to debulk the patient's astigmatism. The plan today is to eliminate astigmatism, so that we no longer do manual LRIs for high degrees of astigmatism. We have better technology now than we had in the past. Toric IOLs and excimer laser photoablation are our plan of action for most patients with moderate to severe astigmatism. When I'm performing cataract surgery on a patient who has 1.5 D or more of astigmatism, I feel very comfortable offering him or her a toric IOL, whether it be a monofocal lens, extended-depth-of-focus, or a multifocal or accommodating IOL."

However, when the cylinder drops down to 1 D or less, Dr. Donnenfeld feels that the advantages of a femtosecond laser are significant. "I like to combine the advantages of femtosecond laser technology with a femtosecond LRI so that the patient can have the perfect capsulotomy and the



All images: Kevin M. Miller, MD

Figure 1. (A) This patient suffered trauma, resulting in a white intumescent cataract, iris damage and posterior synechiae. A femtosecond laser phaco incision was placed in the steep corneal meridian to deal with astigmatism of less than 1 D. (B) The appearance of the eye after the surgery.

lens disassembled. However, postoperatively, I routinely continue to perform manual LRIs for patients who have residual astigmatism. The amount that's tolerated has gone down dramatically as patient expectations have increased. We used to tolerate 1 D of residual astigmatism, but the current conventional wisdom is 0.5 D. However, I've seen many patients who will not even tolerate 0.5 D based on their visual expectations and the knowledge that, with a manual LRI, I can reduce the cylinder very commonly to 0.25 D or less," he adds.

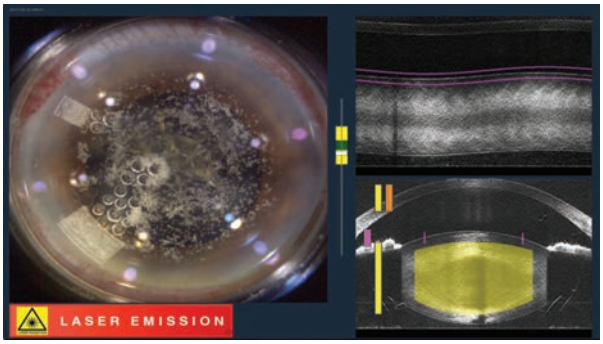


Figure 2. An Alcon LenSx femtosecond laser in the process of making corneal incisions. The phaco incision was placed on the steep corneal axis in a superotemporal meridian to correct less than 1 D of corneal astigmatism.

Small Amounts of Astigmatism

According to Kevin M. Miller, MD, from UCLA, "For high amounts of astigmatism, nobody argues the benefits of a toric lens over relaxing incisions," he says. "But when you get down to smaller amounts, you can still make a compelling case for why you might want to do a relaxing incision instead of implanting a low-power toric lens. A benefit of toric lenses is that the power is going to be uniform from lens to lens, which is not always the case with LRIs. If you make the exact same incision in 100 different corneas, you're going to get a spread of effect with 100 slightly different outcomes. So, the predictability of relaxing incisions is just not as good as with the torics. However, toric IOLs are not perfect, either."

If the toric lens sits in the presumed effective lens position, then the toric power calculation is accurate. But if it sits a little anterior or posterior to the ELP, then its calculated power is not its effective power. So, there is variability of toric lens power based on vertex distance, but there is also variability of effect based on axis alignment. "If the lens is sitting exactly on the correct corneal axis, you get the full effect of the lens. However, if it's 3 degrees, 5 degrees, or 10 degrees off of that, you start losing power, and you rotate the axis of residual astigmatism to some new location, which might be harder for patients than what they were used to before the surgery. So, toric lenses aren't perfect. There are issues on both sides. When we're dealing with small amounts of astigmatism, generally, we only need to make it a little bit better, and you can almost always do that with a relaxing incision," he explains.

"As time has gone on, and as toric lenses have nibbled a larger portion of the astigmatism market away from incisions, I think we've seen a resurgence of incisions to touch up postoperative refractive errors," he adds. "So, if a patient has mixed astigmatism, such that the spherical power of the eye is dead-on and the spherical power of the lens implant is good, but there is residual mixed astigmatism, either right after surgery, a couple of weeks later, a year later, or five years later, the surgeon can touch up those mixed astigmatisms with relaxing incisions and get a nice result."

Dr. Donnenfeld says he's performing increasing numbers of LRIs for smaller and smaller amounts of astigmatism. "The majority of LRIs that I perform today are for 0.5 D to 1 D of residual cylinder, with 0.5 to 0.75 D being my sweet spot," he says. "I like doing my manual LRIs at the slit lamp because it's an easier procedure for the patient. One incision is all that's required, and I use a pre-set diamond knife at 600 µm depth with a curved interface that hits the cornea. This creates a deeper, more regular incision. So, for patients whose expectations have not been met and who have residual astigmatism, rather than bringing them back for an excimer laser ablation or a femtosecond LRI, these small amounts of cylinder are easily treated with manual LRIs. The visual rehabilitation is almost immediate, and for patients who are receiving a premium IOL, specifically multifocal and extended-depth-of-focus, the quality of vision and the added reading vision that's obtained by reducing this 0.5 D or so of astigmatism can be very dramatic. It can turn a dissatisfied patient into a very grateful postoperative patient."

Techniques

According to Dr. Miller, many surgeons believe that LRIs must be performed in pairs, one on each side of the cornea. That simply isn't true, he says. "You can perform a relaxing incision on just one side of the cornea," he notes. "Eighty percent of my astigmatism management at the time of cataract surgery is simply moving my phaco incision onto the steep axis. If a patient has 1 D or less of corneal cylinder, I will just place the phaco incision on the steep axis, and I can get that down to 0.5 D or so without a matching incision on the other side, and without a toric lens. So, 75 to 80 percent of my astigmatism management is still just a single relaxing incision instead of a pair of incisions. So, in a sense, it's still the driving force of astigmatism management, at least for my practice, and I

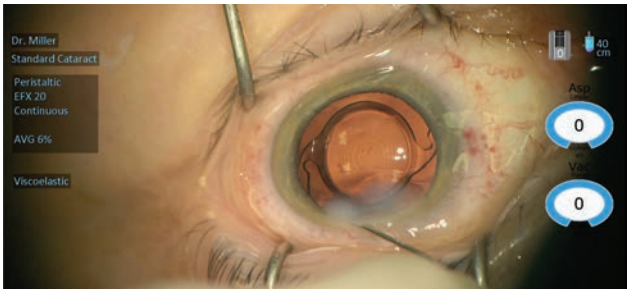


Figure 3. This eye underwent standard femtosecond laser-assisted cataract surgery with implantation of a multifocal IOL. The phaco incision was placed superonasally in the steep corneal meridian.

suspect that's probably true for a lot of practices. This is especially true with the rise in popularity of femtosecond laser-assisted cataract surgery."

However, Dr. Miller notes that many surgeons don't feel comfortable moving their chair and microscope to operate on the steep axis. For example, some surgeons always like to sit on the temporal side of the cornea. "Then, they'll use a toric lens and rotate it to whatever axis is necessary to nullify whatever the patient comes in with, plus whatever they're inducing by making their temporal corneal incision. But, that's going to cost the patient more money, and it's going to mean more time calculating before the surgery," he adds.

"I like relaxing incisions because they're something that can correct small amounts of astigmatism. Relaxing incisions don't rotate; when you make them on the right axis, they don't rotate off that axis. Toric lenses sometimes will rotate off. So, for a lot of reasons, LRIs work, and they will remain one of my most important tools," Dr. Miller concludes.

A Lost Art

According to Elizabeth Yeu, MD, who is in practice at Virginia Eye Consultants, "all cataract surgeons who are refractively minded should be offering astigmatic keratotomies without forgetting how useful manual LRIs actually are. It's a skill and an art that, if we haven't embraced it yet, we should be embracing. And there are several reasons for this. The most obvious one is that, for those patients who have astigmatism in the 1 D or lower range, it is a very nice way to predictably reduce the astigmatism enough to really give them great quality uncorrected vision, because toric IOLs start at 1 D or more of corneal astigmatism correction," she says. "There are many patients who could have better uncorrected vision, and manual LRIs are a very nice, low-capital, cost-efficient way to reduce lower levels of astigmatism."

Dr. Yeu explains that the contribution of posterior corneal curvature affects the overall refractive corneal astigmatism. Specifically, she doesn't offer these patients a toric IOL until she sees at least 1.4 D of anterior with-the-rule astigmatism, but preferentially offers a toric IOL to patients with any more than 0.70 D of anterior against-the-rule astigmatism.

"Lastly, in those cases where something happens intraoperatively that demonstrates that the patient should not be getting a toric IOL, but would instead be best served with an LRI, it's important for surgeons to understand and be comfortable with manual LRIs," she explains. "Such scenarios include a complex cataract procedure where the toric IOL could not be implanted, or if intraoperative aberrometry calls for a standard, non-toric monofocal IOL. This can really help to improve the outcome for the surgeon. So, there are many reasons why we should not forego the art form that is the manual LRI," she explains.

Jeremy Z. Kieval, MD, from Lexington Eye Associates in Massachusetts, agrees. "I think being able to perform a manual LRI is a really important skill to have, no matter what other treatment options exist out there," he says. "It's a skill that all surgeons should have, especially for managing a patient's residual astigmatism. For me, the place that I use manual LRIs the most is in the office. I have been transitioning from a procedure that I exclusively did in the operating room at the time of cataract surgery to a minor procedure that I can do in the office at the slit lamp to adjust the patient's residual astigmatism that they may have after implantation of a toric lens or after a femtosecond limbal relaxing incision."

Dr. Kieval believes that femtosecond lasers are probably the best choice for performing LRIs in most cases. "However, what if your laser goes down? It's a nice skill to have to be able to go on with your day in the event that your laser isn't working. Surgeons have been saying for the past 15 years that new surgeons aren't learning how to do extracap surgery. Everybody knows how to do phaco, but extracapsular cataract extraction is a skill that comes in handy every once in a while. The same is true for being able to perform manual LRIs," he says.

The Future

Dr. Donnenfeld believes that there will still be a role for manual LRIs for the foreseeable future. "The light-adjustable lens, which just got approved by the FDA, may reduce the need for manual LRIs in a subset of patients. For those patients who want to have a better result, and specifically for patients who don't want to or can't afford to pay a premium for cataract surgery, I routinely bundle manual LRIs into my procedure at no cost to the patient if I feel it's in their best interest and if they aren't in the position to pay out-of-pocket for a costly astigmatic procedure," he says. REVIEW

ONSITE REGISTRATION AVAILABLE

SAVE THE DATE

2018 Ophthalmology Update

FEBRUARY 17-18, 2018 • CARLSBAD, CALIFORNIA

An interdisciplinary faculty of ophthalmic subspecialists will review the continuing progress in Cataract and Refractive Surgery, Glaucoma, Retina, Neuro-Ophthalmology, Pediatric Ophthalmology, Ocular Surface Disease, Cornea and Oculoplastics.

LOCATION

Cape Rey Carlsbad, A Hilton Hotel
1 Ponto Road, Carlsbad, CA
P: (760) 602-0800
Limited rooms reserved at $209/night. Please visit registration site for reservation information.

PROGRAM CHAIRS

Don O. Kikkawa, MD, FACS
Robert N. Weinreb, MD

DISTINGUISHED INVITED SPEAKERS

Nisha Acharya, MD
C. Gustavo De Moraes, MD, MPH
Audrey C. Ko, MD
Daniel M. Schwartz, MD
Jonathan C. Song, MD, MBA
Benjamin Y. Xu, MD, PhD

PROGRAM TIMES

Saturday, February 17
8:00am — 5:00pm
Reception to follow

Sunday, February 18
8:00am — 12:15pm

KEYNOTE SPEAKER

Larry Smarr, PhD

UCSD SPEAKERS

Natalie A. Afshari, MD, FACS
Andrew S. Camp, MD
Daniel L. Chao, MD, PhD
William R. Freeman, MD
Michael H. Goldbaum, MD
Weldon W. Haw, MD
Chris W. Heichel, MD
Bobby S. Korn, MD, PhD, FACS
Eric D. Nudleman, MD, PhD
Shira L. Robbins, MD, FAAO, FAAP
Peter J. Savino, MD
Derek S. Welsbie, MD, PhD
Kang Zhang, MD, PhD

FOR MORE INFORMATION

www.reviewofophthalmology.com/Update2018
Email: Reviewmeetings@jobson.com
Phone: 855-851-9964

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

Credit Designation Statement
Amedco designates this live activity for a maximum of 11.25 *AMA PRA Category 1 Credits*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity

Shiley Eye Institute
UC San Diego

Jointly provided by
AMEDCO PHE

Review of Ophthalmology®


Supplements & Glaucoma: Advising Your Patients

Given the popularity of questionable "alternative" treatments, your patients are counting on you to set them straight.

Lisa S. Gamell, MD, Tampa, Fla.

Today, Americans often take vitamins, herbs and other supplements—and they're usually aware of many more that they may not actually be taking. So it's no surprise that our patients sometimes ask our opinion on the value of these supplements, in particular how they may or may not impact glaucoma. Furthermore, with marijuana becoming legal in more and more states, questions about its reputed ability to lower intraocular pressure are likely to come up as well.

Our patients look to us for evidence-based information about these substances. Here, I'd like to review a little bit of what the studies to date have shown, to offer some guidance regarding what you might want to say to your patients when these questions arise.

The Value of Vitamins

It's not unreasonable to believe that supplements such as vitamins could impact the progression of glaucoma. Doctors dealing with age-related macular degeneration have already demonstrated the potential of this approach. As we all know, the Age-Related Eye Disease Study found that a combination of antioxidants and zinc was able to reduce the progression of disease in macular degeneration patients with intermediate and large drusen by 25 percent,[1] so it is possible to find something in the world of complementary and alternative medicine that can help address eye disease. In glaucoma, we just haven't yet found the perfect mixture. The reason for that may be, in part, that glaucoma is actually a cluster of related diseases. Treating it may ultimately involve addressing both pressure issues and neuroprotective issues.

Vitamin supplements that have been posited to have an effect on glaucoma include B1, B3, B12, C, A and E. The chart on the facing page shows some of the studies, pro and con, concerning five of the most commonly taken vitamins. Notably, the results of different studies are often contradictory.

A few observations:

• ***Vitamin B1 (thiamine).*** Edward Asregadoo, MD, theorized that B1-deficient patients might be more prone to glaucoma. He noted that low levels of vitamin B1 are associated with increased cortisol, which in turn increases IOP. A study he published did find lower serum thiamine in glaucoma patients.[2] However, vitamin B1 didn't significantly lower IOP, and unfortunately, the study wasn't well-designed. Other evidence suggests that B1 levels may not impact glaucoma; alcoholics, for example, tend to be deficient in vitamin B1, but there's no correlation between alcoholism and glaucoma.

• ***Vitamin C.*** The evidence for vitamin C's impact on glaucoma is mixed. One study found that intravenous vitamin C lowered IOP 20 percent over two hours; it does appear to have a significant osmotic effect, similar to mannitol.[3] However, IOP climbs back up over 10 to 12 hours, and it's not really practical to give someone IV vitamin injections. Other studies, looking at vitamin C supplements, didn't show much of a change in pressure.[4,5] And while vitamin C has a benign reputation, it can cause kidney stones and gastrointestinal upset, and it should be avoided in those with a glucose-6-phosphate dehydrogenase (G6PD) deficiency, B-thalassemia or hemochromatosis.

This article has no commercial sponsorship.

Vitamin Supplements and Glaucoma

Vitamin	Proposed Action	Results: Pro	Results: Con	Side Effects
B1 (thiamine)	Low B1 increases cortisol level, which increases IOP (Asregadoo, 1979)[2]	Lower serum thiamine found in glaucoma patients (n=38)[2]	B1 not shown to lower IOP in study[2]	None
C (ascorbic acid)	Creates osmotic gradient and lowers IOP. May be neuroprotective	IV vitamin C 20% lowered IOP 20% over two hours (Virno)[3]	Oral vitamin C, 2 gm/day: no effect (Linner)[4] Oral vitamin C, 4.5 gm/day: no change (Fishbein)[5]	Kidney stones; GI upset; Avoid in G6PD, B-thalassemia, hemochromatosis
A (retinol)	Antioxidant properties protect retinal ganglion cells	Protects photoreceptors in AMD (AREDS)[1]	No association between serum levels or supplementation and POAG prevalence (Wang)[6]	Hair loss; fatigue; increased intracranial pressure; cirrhosis. Beta carotene increased lung cancer in smokers
E (alpha tocopherol)	Antioxidant properties protect retinal ganglion cells	May lower serum lipid peroxidation products in glaucoma patients (Birich)[7]	No association between serum levels or supplementation and POAG prevalence (Wang)[6]	Increased bleeding perioperatively, or if patient is on anticoagulants
B12 (cobalamin)	Neuroprotective: Deficiencies cause optic neuropathy	Improved GVF function with oral B12 (Azuma)[8] Less GVF deterioration with oral B12 (Sasaki)[9]	No baseline B12 levels noted in either study. Azuma study[8] only had nine months follow-up	None

• ***Vitamin A (retinol).*** As an antioxidant, vitamin A might be expected to protect retinal ganglion cells, and the AREDS study did find evidence that it protects photoreceptors in macular degeneration patients. However, a study by Sophia Wang, MD, found no association between vitamin A supplementation or serum levels and primary open-angle glaucoma prevalence.[6] Meanwhile, retinol can have side effects including hair loss, fatigue, increased intracranial pressure and cirrhosis.

• ***Vitamin E (alpha tocopheral).*** Vitamin E does have antioxidant properties, and one study found that it may lower peroxidation products in glaucoma patients.[7] However, the previously mentioned study by Dr. Wang[6] found no association between vitamin E and glaucoma prevalence, and vitamin E can potentially cause increased bleeding perioperatively, as well as in patients already taking an anticoagulant.

• ***Vitamin B12 (cobalamin).*** B12 is neuroprotective, and we know that deficiencies in B12 are associated with optic neuropathy. Two studies found visual field improvement with vitamin B12 supplementation,[8,9] but no baseline B12 levels were done in these studies, and they had very short follow-up.

Other supplements have produced interesting results in animals and in *in vitro* studies. Vitamin B3 (nicotinamide), for example, may be neuroprotective. One animal study reported in *Science*[10] found that vitamin B3 could help to mitigate mitochondrial dysfunction, which has been linked to retinal ganglion cell damage and death. In this study, mice were fed a supplement equivalent to 2.5 grams a day in humans; it prevented the structural and functional loss of ganglion cells and nerve axons, and the effect persisted, even with elevated pressure. Furthermore, intravitreal injections of a gene that produces nicotinamide protected 70 percent of mice from glaucomatous damage for 12 months. In addition, combining the two approaches provided more protection than either one alone. So in vitamin B3 we have the potential for an agent that not only has a neuroprotective effect but can also continue having that protective effect in the presence of elevated pressure. The idea that nicotinamide may have beneficial effects has been proposed for further investigation in humans.[11] So far, however, this has only been shown in animal studies.

One of the main problems with vitamin studies is that studies tend to involve very small numbers of patients, and a lot of the reports have been anecdotal. The reality is that since the U.S. Food and Drug Administration doesn't need to approve any of these agents, there's no incentive for large studies to be conducted, the way there might be with drugs that need FDA approval. As a result, very few large, controlled studies have been done.

There's also another significant problem: Many of these studies are done *in vitro*, where, for example, the agent may protect ganglion cells.

Herbs and Glaucoma

Herb	Proposed Action	Results: Pro	Results: Con	Side Effects
Gingko (Gingko biloba extract EGb 761)	Potent antioxidant effects inhibit platelet activating factor and glutamate-induced neurotoxicity	40 mg p.o. t.i.d. increased ocular blood flow with color doppler imaging (Chung, Harris)[13] improved HVF in NTG (Quaranta)[14]	Found no change in blood flow with Heidelberg Retinal Flowmeter (Ritch)[15] No effect on visual field or contrast sensivity (Guo)[16]	Increased risk for hemorrhage in patients with amyloid, hypertension or on anticoagulants
Bilberry (vaccinium myrtillus)	Anthocyanidins have antioxidant effects that protect against ischemic reperfusion and neurotoxicity	Ameliorated NMDA damage in mouse model (Matsunaga)[17]	No studies in humans showing effects on IOP or visual function; Reports of improved night vision among WWII pilots were anecdotal	May interact with ASA and warfarin. GI upset; icterus; cachexia; anemia
Forskolin (coleus forskohlii)	Adenylate cyclase-mediated reduction of aqueous flow	Topical 1% forskolin reduced IOP and aqueous flow in rabbits, monkeys, humans (Caprioli)[18]	Hyperemia; Tachyphylaxis limited long-term efficacy	Oral preparations: Arrythmogenic; Promotes androgen activity on prostate cancer cells

But when a person ingests a supplement, it has to go through all of the metabolic processes in the body, so the potency could be significantly diminished by the time it gets to the nerve cells. That makes it difficult to know what the proper dose should be for humans.

Other Supplements & Nutrients

The problem of potency following ingestion is an issue with two non-vitamin supplements that have shown promise with glaucoma: co-enzyme Q and resveratrol. These have been shown to reduce mitochondrial susceptibility *in vitro*, and I believe they show promise for neuroprotection.

One study found that topical micelles of co-enzyme Q10 with vitamin E d- -tocopheryl polyethylene glycol 1000 succinate, twice a day, significantly reduced the number of apoptotic retinal ganglion cells three weeks after induction of ocular hypertension. Furthermore, the effect was independent of IOP.[12] Another study found that resveratrol retarded apoptosis of RGS's *in vitro* and decreased the level of caspace-3 (a marker of apoptotic events), while stimulating increased quantities of mitochondria.[13] Unfortunately, when a person ingests co-enzyme Q or resveratrol in supplement form, the efficacy may be dramatically altered by the metabolizing process. Clinical trials in humans could do a lot to pin down the quantities and concentrations required to produce similar effects in our patients.

A few herbal supplements are also believed to have positive effects on the eyes and glaucoma. The chart above shows some of the data relating to three popular herbal supplements that sources on the Internet claim will help treat glaucoma.

A few observations about these three herbal supplements:

• ***Gingko biloba.*** This is a well-known antioxidant used widely in Europe to treat breathing problems and Reynaud's phenomenon, which is a vascular disorder. Gingko is known to inhibit glutamate cytotoxicity, which leads to ganglion cell death, and it's been shown to increase blood flow.[14,15] However, these were very small studies, and there were a couple of contrasting studies that found no effect on visual field or contrast sensitivity, as well as one that found no change in blood flow.[16,17] One of the challenges when studying gingko's effect on blood flow is that we still don't have agreement on the best way to measure ocular blood flow, making it difficult to draw any conclusions about how helpful gingko actually may be.

One other important consideration when suggesting that a patient try gingko: Gingko increases the risk of bleeding. For that reason, you have to make sure your patient is not on warfarin, aspirin or any other blood thinners, because your patient could be prone to getting pretty severe hemorrhages.

• ***Bilberry (vaccinium myrtillus).*** The bilberry plant is a cousin of the blueberry. In World War II, fighter pilots took bilberry to increase their night vision, but to date, no study has been done to confirm that this effect is real. As an anthocyanidin, bilberry has a very potent antioxidant effect that can protect against ischemic reperfusion and neurotoxicity, and it's been shown to decrease retinal ganglion cell damage in a mouse model.[18] However, no studies in humans have shown any effect on IOP or visual function. Bilberry can also interact with aspirin and warfarin and potentiate bleeding; and it has been

associated with gastrointestinal upset, icterus, cachexia and anemia.

• ***Forskolin (coleus forskohlii).*** This herb has been shown to lower IOP in rabbits, monkeys and humans by reducing aqueous flow. This was first demonstrated back in the mid-1980s.[19,20] However, further studies were abandoned because forskolin caused significant hyperemia and tachyphylaxis. Furthermore, after a month or two the pressure would shoot back up, so there wasn't a lot of long-term promise. Oral preparations are available, but when you take forskolin orally it doesn't have any effect on IOP. Downsides include that forskolin is arrythmogenic, and it can promote androgen activity on prostate cells in patients with prostate cancer.

Some nutrient-rich foods show promise for impacting glaucoma progression. The Osteoporotic Fractures Research Group found that patients who ate three or more servings of fruit such as peaches or oranges, or fruit juices, per day were 79 percent less likely to have POAG. In addition, those who ate more than one serving of collard greens or kale, which are nitrate-rich, leafy green vegetables, per week decreased their odds of having POAG by 57 percent.[21,22] The Nurses Health Study and Health Professionals Follow-up Study found that a greater intake of nitrate-rich foods and leafy green vegetables decreased the risk of POAG by 20 to 30 percent.[23] These are large, well-designed population studies. Granted, they were large cohort studies that relied on statistical analysis, and the data was based upon patient self-reporting, so they could contain an element of bias. It's also possible that individuals eating large quantities of these foods may have a healthier lifestyle overall, and that might be contributing to their reduced POAG. Nevertheless, the statistics are pretty impressive.

Although early studies suggested that marijuana may reduce IOP for a few hours, a host of side effects and practical concerns make its use as a glaucoma treatment controversial at best.

One of the take-home messages here is that although we often hope to get relief from supplements in pill form, there may be an advantage to ingesting beneficial nutrients in their natural dietary form. Other pro-nutrients in these vegetables and fruits may also be contributing protective effects.

Medical Marijuana

The herb patients most often ask about, not surprisingly, is marijuana. Medical marijuana is currently legal in 30 states, including the District of Columbia, and recreational marijuana is legal in a handful of states, most recently California (as of January 1, 2018). The interesting thing about marijuana is that it's a Schedule I controlled substance, while opioids, amphetamines and cocaine are Schedule II. That means that, unlike marijuana, they're available for research.

The original studies on marijuana were done back in the 1970s.[24] Those studies, using a small sample of participants, showed a significant reduction in IOP (25 to 30 percent) in 65 percent of patients. However, participants' eyes got red, tear production decreased, pupils got smaller, and the decrease in pressure only lasted three to four hours. It's also difficult to evaluate these studies relative to today's marijuana use because marijuana potency is difficult to verify. In the early studies, individuals were smoking 2% marijuana cigarettes; today the concentration of THC in a marijuana cigarette may be much higher.

A few years later, Keith Green, PhD, did similar studies using oral ingestion (e.g., eating marijuana brownies).[25] The results were mixed; in some patients this lowered IOP, but in others it didn't. In any case, oral ingestion requires larger quantities of the drug to produce the same effect, which makes sense because the drug is being taken in through the gastrointestinal tract where it must be metabolized by the liver, etc. That's going to decrease the potency and availability of any active compounds.

Of course, marijuana can have numerous side effects. These include ocular side effects such as conjunctival hyperemia, decreased lacrimation, diplopia, impaired accommodation, photophobia, nystagmus and blepharospasm. Systemic side effects in the short term may include increased pulse, orthostatic hypotension, and of course, euphoria.[26] Over the long term, side effects may include emphysema-like lung changes, decreased immune function, decreased cognitive function and potential alterations in the growth of a fetus. (It would be helpful to conduct long-term studies, but as long as marijuana remains a Schedule I agent, that's unlikely to happen.)

Encouraging patients to smoke marijuana to address glaucoma is controversial at best. Smoking inherently carries some risk for emphysema and lung cancer, along with the other aforementioned side effects. The orthostatic hypotension issue may also be significant, because of the likelihood that the drug is decreasing blood flow to the optic nerve, which

could be damaging. The CNS side effects are problematic, especially for older patients. Moreover, current topical medications usually have a better efficacy profile for lowering IOP. For all of these reasons, both the American Academy of Ophthalmology and the American Glaucoma Society currently do not recommend the use of marijuana to treat glaucoma.

A promising approach in the future may be the use of cannabinoids, the active compounds found in marijuana, which are receiving research attention. Cannabinoids such as delta9-THC and cannabidiol have been shown to decrease IOP; they act on cannabinoid receptors in the trabecular meshwork and increase aqueous outflow, and they also have neuroprotective qualities. One study of WIN55212-2 found that it decreased IOP 20 to 30 percent, achieving maximum effect within 60 minutes, although the effect did not last long.[27]

Some more recent research involving THC prodrugs such as THC-Val-HS has been more promising. Coupling the drug with cyclodextrins and surfactants helps to increase solubility, so there's more availability and better penetration through the cornea. In a rabbit model this produced a better IOP lowering than timolol, although it had a shorter duration of action, similar to pilocarpine.[28]

The main point is, while smoking marijuana isn't something that we as ophthalmologists currently stand behind, cannabinoid agents may have the potential for ocular penetration without the potential for side effects such as orthostatic hypotension and euphoria. In the meantime, the potential for benefits from the occasional adjunctive use of marijuana in addition to prescribed glaucoma treatment regimens, and the effects of marijuana in glaucoma patients who regularly use it for nonmedical reasons, have not been investigated.

Managing Patient Questions

Patients ask me about smoking marijuana all the time; they want me to prescribe it for them. If you haven't already encountered this, you probably will.

Here are a few strategies that may help you manage this situation when it arises:

• ***Be aware of the marijuana laws in your state.*** Use of marijuana, even for medical reasons, is subject to law. To keep yourself and your patients out of trouble, do your homework about the legal ramifications in your state.

• ***Be ready with an answer before your patients ask questions.*** I explain to my patients that so far it's not clearly defined how marijuana should be used to treat glaucoma. Even though it's approved for glaucoma treatment here in Florida, there are no guidelines. In addition, the American Academy of Ophthalmology and American Glaucoma Society do not advocate its use for treating glaucoma. For these reasons—among others—the majority of doctors I know won't prescribe it. (I don't, either.)

• ***Educate and inform interested patients regarding the efficacy, side effects and drug interactions associated with marijuana use.*** Most interested patients have little, if any, idea about this aspect of mariuana use. It's worth pointing out that while marijuana may lower IOP in the short term, in the long term it may do them more harm than good.

• ***Consider prescribing an oral cannabinoid like Marinol (dronabinol) instead.*** Marinol has been used for decades in cancer patients to treat nausea and other gastrointestinal side effects of chemotherapy. The few times I've prescribed it for patients, it's had a modest effect on IOP, lowering it 10 to 15 percent. Notably, it appears that it's not completely free of the euphoric effects. Some patients complain that they still experience effects such as lightheadedness or confusion—while other patients are not bothered at all. (Hopefully the research into topical cannabinoids will bear fruit, thus taking any systemic side effects off the table.)

Playing It Safe

Given the popularity of supplements and marijuana today, it's essential that we be prepared to help our patients navigate the rational use of these substances. We have to be ready to educate patients on their efficacy and side effects. A few points worth making:

• ***Patients should be careful with any of these supplements because even if they may potentially help, no one knows the proper dosage.*** The reality is, these treatment possibilities haven't been seriously studied, so we're making choices based on minimal information.

• ***Be careful about the purity of the substance in question.*** Many herbs are sold mixed with other herbs, and some individuals can have pretty dramatic side effects from those additional herbs.

• ***Do your homework before proceeding.*** Your patients should talk to their internist if they're planning on using supplements, to make sure they don't interact with any prescription drugs they may be taking. Some supplements will interact with blood thinners, or may exacerbate other problems like prostate cancer or gastrointestinal issues. While some supplements may be helpful, they are not totally benign.

• ***Encourage a healthy diet with antioxidant and nitrate-rich foods including citrus fruits, peaches, salad, kale and collard greens.*** These foods not only limit the possibility of side effects, they

have some of the most impressive supporting evidence in the literature. Citing some of the statistics found in the research may surprise and impress your patients. REVIEW

Dr. Gamell is an associate professor of ophthalmology at the University of South Florida Health Morsani College of Medicine, and Glaucoma Fellowship Director at the USF Eye Institute in Tampa.

1. Age Related Eye Disease Study Group. A randomized, placebo-controlled, clinical trial of high-dose supplementation with vitamins C and E, beta carotene, and zinc for age-related macular degeneration and vision loss: AREDS report no. 8. Arch Ophthalmol 2001;119:10:1417-1436.
2. Asregadoo ER. Blood levels of thiamine and ascorbic acid in chronic open-angle glaucoma. Ann Ophthalmol 1979;11:1095–1100.
3. Virno M, Bucci MG, et al. Intravenous glycerol-vitamin C (sodium salt) as osmotic agents to reduce intraocular pressure. Am J Ophthalmol 1966;62:824–833.
4. Linner E. The pressure lowering effect of ascorbic acid in ocular hypertension. Acta Ophthalmol (Copenh) 1969;47:685–689.
5. Fishbein SL, Goodstein S. The pressure lowering effect of ascorbic acid. Ann Ophthalmol 1972;4:487–491.
6. Wang SY, et al. Glaucoma Vitamins A, C, and E supplement intake and serum levels in a population-based sample of the United States. Eye 2013; 27:4:487-494.
7. Birich TV, Birich TA, Marchenko LN: [Vitamin E in multiple-modality treatment of primary glaucoma patients]. Vestn Oftalmol 1984;102:10–3.
8. Azumi I, Kosaki H, Nakatani H. Effects of metcobolamin (Methycobal) on the visual field of chronic glaucoma—a multicenter open study. Folia Ophthalmol Jpn 1983;34:873–878.
9. Sasaki T, Murata M, Amemiya T. Effect of long-term treatment of glaucoma with vitamin B-12. Glaucoma 1992;14:167–170.
10. Williams PA, et al. Vitamin B3 modulates mitochondrial vulnerability and prevents glaucoma in aged mice. Science 2017;355:756-760.
11. Williams PA, Harder JM, John SW. Glaucoma as a metabolic optic neuropathy: Making the case for nicotinamide treatment in glaucoma. J Glaucoma 2017;26;12;1161-68.
12. Davis BM, et al. Topical Coenzyme Q10 demonstrates mitochondrial-mediated neuroprotection in a rodent model of ocular hypertension. Mitochondrion 2017; 36: 114-123.
13. LiuXQ, Chen MM, et al. Resveratrol Mitigates Rat Retinal Ischemic Injury: The roles of matrix metalloproteinase-9, inducible nitric oxide, and heme oxygenase-1. Jour Oc Pharm Ther 2013;29:1:33-40.
14. Chung HS, Harris A, et al. Ginkgo biloba extract increases ocular blood flow velocity. J Ocul Pharmacol Ther 1999;15:3:233-40.
15. Quaranta LR, et al. Ginkgo biloba extract improves visual field damage in some patients affected by normal-tension glaucoma. Invest Ophth Vis Sci 2014;55:2417.
16. Gurses-Ozden R, Harris A, et al. Ginkgo biloba extract does not alter peripapillary retinal hemodynamics using Heidelberg Retina Flowmetry in open-angle glaucoma. Invest Ophthalmol Vis Sci 2002:42(Suppl)
17. Guo X, et al. Author Response: Effect of Ginkgo biloba on visual field and contrast sensitivity with NTG in Chinese patients: A randomized, crossover clinical trial. Invest Ophth Vis Sci 2014;55:110-116.
18. Matsunaga N, et al. Bilberry and its main constituents have neuroprotective effects against retinal neuronal damage in vitro and in vivo. Mol Nut Food Res 2009;53:7:869-77.
19. Caprioli J and Sears M. Forskolin lowers intraocular pressure in rabbits, monkeys, and man. Lancet 1983;1:958-960.
20. Caprioli J, et al. Forskolin lowers Intraocular pressure by reducing aqueous inflow. Inves Ophthalmol Vis Sci 1984;25:268-277.
21. Coleman AL, Stone KL, Kodjebacheva G, et al. Glaucoma risk and the consumption of fruits and vegetables among older women in the study of osteoporotic fractures. Am J Ophthalmol 2008;145:6:1081–1089.
22. Giaconi JA, et al. The association of consumption of fruits/vegetables with decreased risk of glaucoma among older African–American women in the study of osteoporotic fractures. Amer J Ophthal 2012;154:4:635-644.
23. Kang, JH, et al. Association of dietary nitrate intake with primary open-angle glaucoma, a prospective analysis from the Nurses' Health Study and Health Professionals Follow-up Study. JAMA Ophthalmology 2016;13:3:294-303.
24. Hepler RS, Frank IR. Marihuana smoking and intraocular pressure. JAMA 1971;217:1392.
25. Green K. Marjuana smoking vs cannabinoids for glaucoma therapy. Arch Ophthalmol 1998;116:1433-1437.
26. Merritt JC, et al. Effect of marijuana on intraocular and blood pressure in glaucoma. Ophthalmology 1980;87:3:222-8.
27. Porcella A, Maxia C, Gessa GL, Pani L. The synthetic cannabinoid WIN55212-2 decreases the intraocular pressure in human glaucoma resistant to conventional therapies. Eur J Neurosci 2001;13:2:409-12.
28. Adelli GR, et. al. Development of a delta9-tetrahydrocannabinol amino acid-dicarboxylate prodrug with improved ocular bioavailability. Inves Ophth Vis Sci 2017;58:4:2167-2179.

Left your *Review of Ophthalmology* magazine at the office? No problem!

Read *Review* on the go from any mobile device!

Simply go to www.reviewofophthalmology.com and click on the digimag link to get your current issue.

Some New Tricks With Gore-Tex

Two ways to use the resilient suture material for fixating intraocular lenses in challenging surgical cases.

Walter Bethke, Editor in Chief

The Gore-Tex suture material is strong, but doesn't respond to external forces the way other sutures, such as vicryl or nylon, might. Because of these differences, and the comforting familiarity of other suture material, some surgeons are hesitant to employ Gore-Tex for maneuvers like fixating an IOL in the setting of inadequate capsular support. In this article, a surgeon experienced in working with Gore-Tex for specific surgical maneuvers shares his tips and tricks.

Intrascleral Haptic Fixation

Mesa, Arizona, ophthalmologist Yuri McKee, MD, says that Gore-Tex has a lot of potential to assist surgeons with difficult cases such as those requiring some sort of intrascleral fixation of the haptics.

"One of the problems that we run into when performing intrascleral haptic fixation," Dr. McKee explains, "is that, with a glued IOL, sometimes there's not enough haptic in patients with large eyes to really secure it to the sclera. The next thought is, 'Well, just use longer haptics,' but that would mean developing a new IOL at the cost of millions of dollars for just a limited distribution. Industry isn't interested in doing that." As a solution, Dr. McKee makes, in effect, a longer haptic with a Gore-Tex suturing technique. He credits New York surgeon Ken Rosenthal for being one of the first, if not the first, surgeon to use Gore-Tex in ocular surgery.

"I use a lasso technique to make a 'longer' haptic," Dr. McKee explains. "The technique is useful because it doesn't really matter what the white-to-white diameter is, because the lasso technique gives you centimeters worth of haptic, rather than just millimeters. To perform the technique, you first go to a spot near the tail of the Gore-Tex suture and poke a hole through the Gore-Tex with a 30-ga. needle. You can then take the needle itself, trailing the Gore-Tex, and pass it part of the way through the hole you've made, but leave the suture on the metal of the needle. Then, take low-temperature loop cautery and hold it near the suture hole where the needle passes through it—but don't touch it. The heat melts the suture material around the needle, creating a buttonhole in the very end of the suture, which reinforces it. This is similar to the way a shirtmaker takes extra thread and sews it around the buttonhole of a shirt; the

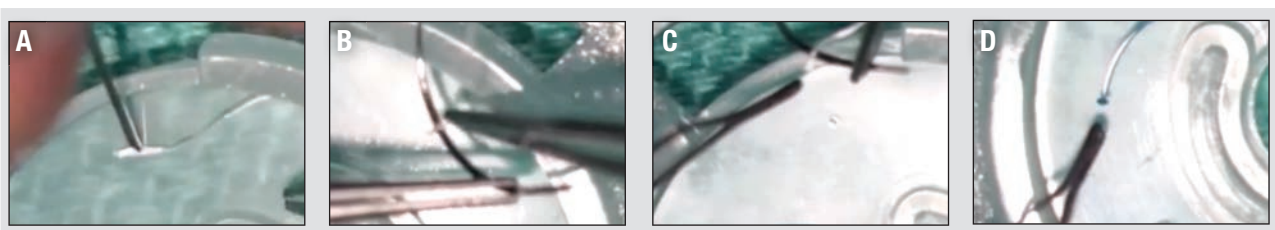


Figure 1. (A) To create a Gore-Tex lasso, first punch a hole near the tail of the suture, then (B) pass the needle through the hole and (C) expose the hole to cautery to reinforce it. (D) Creating a bulb at the end of a haptic with cautery.

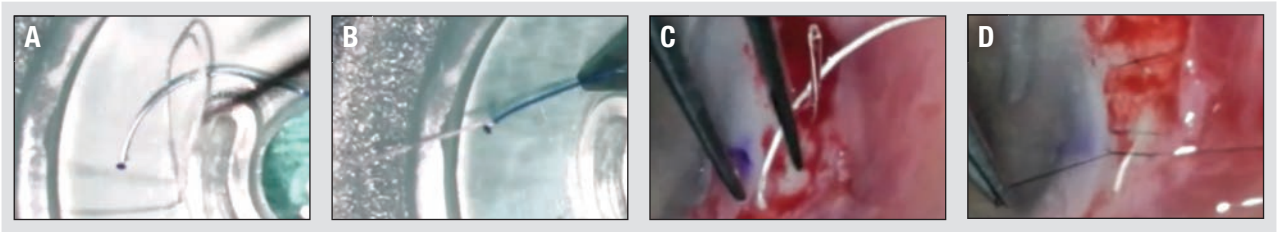


Figure 2. (A) Looping the lasso from Fig. 1 around the haptic then pulling it tight (B). The bulb at the end of the haptic helps keep it in place. A surgical shot of an externalized haptic with Gore-Tex being run through a strut (C) and the haptic is then sutured down (D).

extra reinforcement around the hole prevents the hole from propagating in different directions. This step is critical, because if you were to just take the suture and poke it through its own tail and then pull on it, it tears out instantly with hardly any force being applied. But, when you make that little hole in the tail of the suture and then heat seal it, you have a very strong lasso."

To sclerally fixate an IOL, Dr. McKee first implants the IOL, then creates scleral tunnels directly opposite each other. Through one tunnel, he pulls one of the IOL haptics and snares it with the Gore-Tex suture. He then sutures down the haptic. Through the other scleral tunnel, he uses a different technique.

"With the lasso created, you have a lot of options," Dr. McKee continues. "You can lasso an eyelet, around a haptic or through an IOL strut. I take the three-piece IOL and apply the heat loop cautery near the end of the haptic, which creates a small bulb on the end. I then take the Gore-Tex lasso and tighten it around the haptic and pull until it until it eventually stops at the little bulb I created with the cautery. This results in a surface in which there's basically no bulk in the knot, the lasso or the connection you made between the haptic and the suture."

With this in mind, Dr. McKee pulls the other haptic through the other scleral tunnel, exposes the tip to the cautery, and ties the lasso around it. "I then pass the Gore-Tex in an intrascleral pass in the same direction and plane that the haptic would have traveled in, and then double the Gore-Tex backward along that same path parallel to it," he says. "That basically makes a haptic that would be two or three times longer than it would have been normally. Then, where it exits the sclera, I just heat-seal the tip or cut the suture, and it just flattens out to a mushroom there, making for a stable closure and extension of the haptic."

Forget the Knot

Dr. McKee says that, when dealing with IOLs with a strut or loop such as the B+L enVista or Akreos, some surgeons pass the Gore-Tex through the strut/loop and then push it through the sclera, tie it on top of the sclera and then rotate it back into the eye. This isn't ideal in his opinion. "For me, rotating the knot back into the eye is a problem," he says, "because you have a full-thickness pass through the sclera, which can be a source for an infection; and you have to rotate a big knot through a small hole, which can be the source for a leak. It's also hard to do and the suture might break."

As an alternative, Dr. McKee makes a modification to the Gore-Tex suture that allows surgeons to get a tight closure without a knot. "I make four or five holes in a line along the tail of the Gore-Tex, separated by 0.5 mm," he explains. "I then bring the cautery near the holes—but not touching—to strengthen them. That's one end of the suture. I pass this through the sclera, around the loop or strut of the IOL, and then bring it back out of the sclera. Then, rather than tie it, I pass the needle through some sclera, then through one of the holes in the suture, then back through the sclera, et cetera, zigzagging it back and forth like a sewing machine, incorporating some sclera and suture with each bite. The tension created by looping your suture through four or five holes and then running it back through the sclera is actually stronger than a knot. The harder you pull it, the tighter it gets." REVIEW

Dr. McKee has no financial interest in any of the products mentioned.

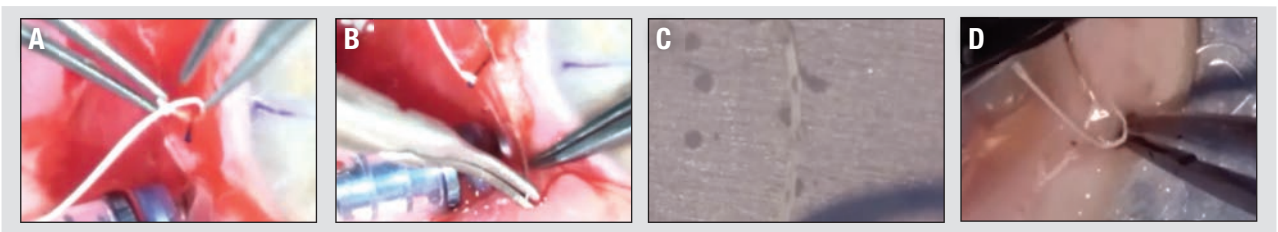


Figure 3. (A, cont'd from Fig. 2) The other externalized haptic is captured with the Gore-Tex lasso and then sutured in place (B). in a second technique, multiple holes are made in the suture (C). The needle is passed through the holes and sclera, making a tight closure.

EVERY MONDAY

E-NEWS YOU CAN USE

Have you been receiving and reading custom e-blasts from *Review of Ophthalmology*?

If not, you're missing out on valuable information!

You're a busy practitioner and not surprisingly, your e-mail inbox is often full. Fortunately, when you scan through the sender list, determining which messages to delete and which to save or read, you can feel confident knowing that e-blasts from *Review of Ophthalmology*, a Jobson Medical Information LLC publication, contain the most current and comprehensive information available in the field to keep you on the cutting edge.

Review of Ophthalmology's online stable of products includes editorial newsletters and promotional information about new products, treatments and surgical techniques, as well as alerts on continuing education courses for ophthalmologists.

Our FREE weekly e-newsletter, *Review of Ophthalmology Online*, brings you the latest in ophthalmic research, as well as industry news. In an effort to keep eyecare professionals informed, this resource is waiting in your inbox every Monday morning.

***Retina Online*, our free monthly e-newsletter, is for retina specialists and general ophthalmologists interested in enhancing their knowledge on the topics of retina and related disease diagnosis and treatment, as well as the latest in surgical procedures.**

Your time is valuable — and so is your practice. These e-products are the most effective way for you to receive updates on breaking news and research — all just a click away.

DON'T MISS OUT!

Unfamiliar with our products? Visit www.reviewofophthalmology.com and check out our newsletter archives.
Go to www.jobson.com/globalEmail/default.aspx to sign up for the e-newsletters that interest you.


Posterior Scleritis: A Diagnostic Challenge

A detailed look at the signs and symptoms to watch for, and how to follow up diagnosis with the appropriate therapy.

Lana M. Rifkin, MD
Boston

Posterior scleritis is a rare but potentially vision-threatening condition that's often underdiagnosed due to its perplexing and varied clinical presentation. It's a painful inflammation of the sclera posterior to the ora serrata which can be seen in all age groups and all ethnicities, although it more commonly occurs in middle-aged women.[1] Posterior scleritis represents approximately 10 percent of all cases of scleritis, half of which can be associated with systemic disease—most commonly rheumatoid arthritis—but sometimes with more rare but life-threatening conditions such as systemic lupus erythematous and granulomatous polyangiitis. A thorough review of systems is crucial in the evaluation of these patients, with a particular focus on systemic signs of rheumatoid arthritis such as joint pain, sinus issues or epistaxis that may be associated with GPA, breathing trouble that may lead one towards a diagnosis of sarcoidosis, and skin disorders that may lead towards a diagnosis of psoriasis or lupus.

Table 1. Diagnostic Tests

Test	Associated Disease
PPD or quantiFERON Gold	Tuberculosis
RPR FTA-Abs	Syphilis
Rheumatoid Factor Anti-CCP	Rheumatoid arthritis
ANA	Sytemic lupus erythematous
ACE Lysozyme Chest X-ray	Sarcoidosis
ANCA	Granulomatous polyangiitis; Polyarteritis nodose
HLA-B27	Ankylosing spondylitis; Psoriasis

Clinical Presentation

The hallmark presenting symptom of posterior scleritis is moderate to severe pain. Patients will often describe a deep, dull, boring pain that, classically, wakes them from sleep. There may be associated pain with extraocular motility, proptosis or other orbital signs. The degree of effect on vision can be variable, from minimally affected to significant vision loss. Intraocular pressure may be elevated in up to half of patients with scleritis, which may be due to rotation of the ciliary body and iris root into the angle causing angle closure without pupillary block, blockage of the outflow track due to inflammation, elevated episcleral venous pressure, peripheral anterior synechiae or neovascularization.

Deep redness and tenderness to palpation due to anterior scleritis also may or may not be present in cases of posterior scleritis. On physical examination, it's important to lift the eyelids and ask the patient to look in all directions of gaze, as subtle anterior

scleritis may not be immediately evident. Patients with strictly posterior scleritis may not have ocular redness but will describe discomfort with motility and may show restriction of eye movement.

Slit lamp biomicroscopy may demonstrate corneal edema, shallowing of the anterior chamber with anterior bowing of the iris and mild to moderate anterior chamber cell.

Fundus examination may show swelling of the optic nerve, exudative retinal detachment or choroidal effusions.

Workup

All patients presenting with scleritis should be worked up for associated systemic disease. First and foremost, it's imperative to rule out infection with tuberculin skin testing or serum interferon gamma release assays such as quantiFERON Gold, as well as RPR and FTA-Abs testing for syphilis. Rheumatoid factor and anti-citrullinated protein antibodies, ANA, ACE (if the patient is not on an ACE inhibitor), lysozyme, ANCA, HLA-B27, as well as a CBC and CMP and chest X-ray should be obtained.

Imaging in Posterior Scleritis

Various imaging methods can yield important information in suspected cases of posterior scleritis.

• ***B-scan ultrasonography.*** This can be crucial to the diagnosis of posterior scleritis, with the pathognomonic T-sign due to fluid collecting in the posterior episcleral space and extending around the optic nerve.

• ***Optical coherence tomography.*** OCT, particularly with enhanced depth imaging, can be quite helpful in the diagnosis of posterior scleritis, demonstrating increased thickness of the choroid. Often, subretinal fluid can be noted, even presenting in multiple foci.

• ***Fluorescein and indocyanine green angiography.*** While posterior scleritis doesn't have characteristic signs on FA, this modality can also be helpful in distinguishing posterior scleritis from other, similarly presenting issues, such as central serous retinopathy. Other characteristics often associated with posterior scleritis, such as optic nerve edema or serous retinal detachment, can also be demonstrated on FA. ICG can demonstrate fluorescent pinpoints in active inflammation.[2]

• ***Orbital CT scan.*** CT can help identify posterior inflammation, demonstrating increased choroidal thickness. In general, ultrasonography is considered superior to CT in imaging for posterior scleritis, but the latter can be helpful in ruling out idiopathic orbital inflammation and myositis.

Treatment

The treatment of posterior scleritis can be quite challenging. Topical NSAIDs and topical corticosteroids aren't typically helpful, so systemic therapy is often initiated. Oral nonsteroidals can be effective with various appropriate regimens, such as ibuprofen 600 to 800 mg q.i.d., piroxicam 20 mg daily and naprosyn 375 mg b.i.d., to name a few. In cases unresponsive to oral NSAIDs, high-dose systemic corticosteroids are often used, with typical doses of 1 mg/kg/day or approx-

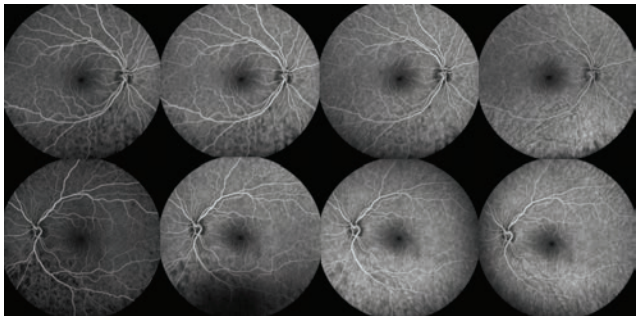


Figure 1. Fluorescein angiography demonstrating hypofluorescent spots outside the arcades, bilaterally.

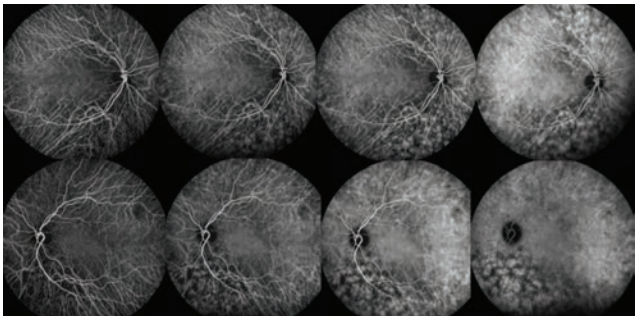


Figure 2. Indocyanine green angiography showing hypercyanescent spots outside the arcades, bilaterally.

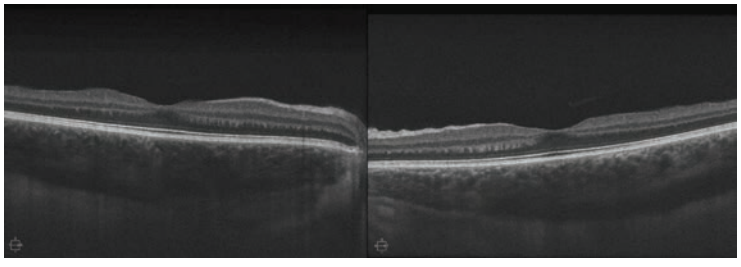


Figure 3. OCT with extended-depth imaging of right and left eye showing increased choroidal thickness bilaterally, as well as mild retinal folds.

imately 60 mg of prednisone daily. These are tapered slowly over several weeks, with careful consideration of potential side effects such as weight gain, mood instability, blood-sugar abnormalities, etc.

If the patient continues to demonstrate active disease or is unable to tolerate corticosteroids, prompt corticosteroid-sparing immunosuppression is often warranted. Anti-metabolites such as methotrexate and mycophenolate mofetil are employed, often to their maximal doses of 25 mg/week of methotrexate or 1,500 mg b.i.d. of mycophenolate. These medications may take up to six months for full effect and some patients may require a faster-acting solution. In these cases, biologics such as TNF inhibitors (e.g., adalimumab, infliximab) may be necessary. Rituximab has demonstrated good efficacy in the treatment of scleritis, particularly in cases associated with systemic disease. Scleritis associated with GPA may require the use of cyclophosphamide. These patients are typically co-managed with rheumatologists, with guidance from the ophthalmologist regarding treatment dosing and response.

Prompt recognition and appropriate, often aggressive, treatment is key to recovery and preservation of vision.

Case Example 1

A 27-year-old Caucasian woman presented with bilaterally decreased vision and pain. Her visual acuity was 20/200 bilaterally, with a signficant myopic shift. Intraocular pressure was measured to be 55 mmHg in both eyes and slit lamp examination revealed shallow angles bilaterally with 360 degrees of iridocorneal touch. Fundus examination was notable for bilateral choroidal effusions. Fluorescein angiography *(Figure 1)* demonstrated hypofluorescent spots outside the arcades with no evidence of leakage. Indocyanine green *(Figure 2)* showed hypercyanescent spots in the same areas. Both eyes showed diffusely thickened choroid on OCT *(Figure 3)*.

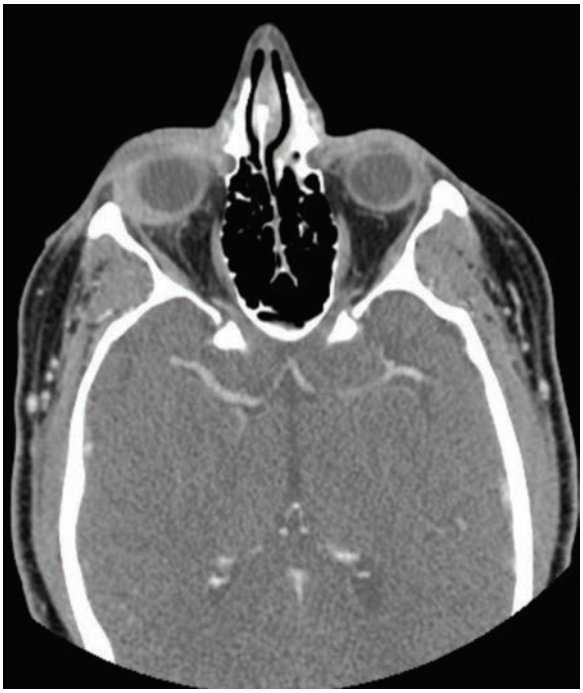


Figure 4. CT scan (axial view) showing increased choroidal thickness of the right eye, with a normal left eye.

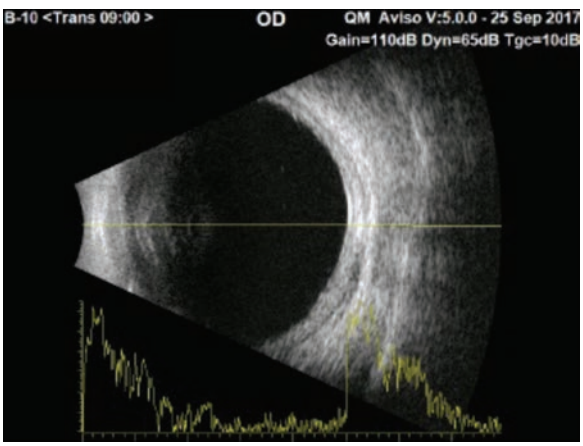


Figure 5. B-scan ultrasound demonstrating thickened choroid with fluid in sub-Tenon's space.

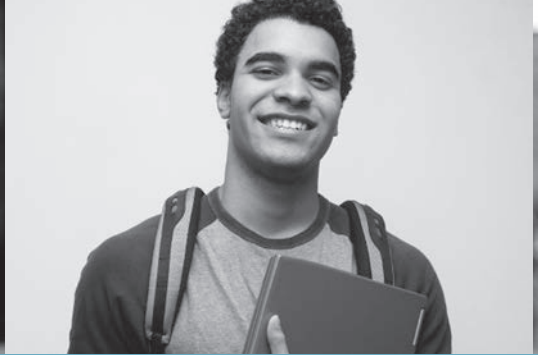
The patient was started on IOP-lowering drops and cycloplegics, as well as 60 mg of oral prednisone. One week later, IOP returned to normal, vision improved, and OCT showed clear improvement, in choroidal thickness. The patient's systemic corticosteroids are currently being tapered.

Case Example 2

A 43-year-old Caucasian man presented to an outside ophthalmologist with a complaint of a red right eye. He was initially diagnosed with episcleritis and started on topical steroids. He then developed pain waking him from sleep, along with proptosis and restriction in eye movement. An orbital process was suspected and CT was ordered, demonstrating increased choroidal thickening of the right eye *(Figure 4)*. He was referred to the uveitis service, where B-scan was performed *(Figure 5)* and he was diagnosed with anterior and posterior scleritis and started on oral prednisone. He was tapered over several weeks but flared, and thus required steroid-sparing systemic immunosuppression with methotrexate. The patient's inflammation has resolved and he's quiet and pain free. REVIEW

Dr. Rifkin is a uveitis specialist who practices at Ophthalmic Consultants of Boston. She's also director of the Uveitis Service at New England Eye Center, and is an assistant professor of ophthalmology at Tufts School of Medicine. She can be reached at lana.rifkin@gmail.com.

1. Lavric A, Gonzalez-Lopez JJ, Majumber PD, et al. Posterior Scleritis: Analysis of Epidemiology, Clinical Factors, and Risk of Recurrence in a Cohort of 114 Patients. Ocul Immunol Inflamm 2016;24:1: 6-15.
2. Auer, Herborn, Indocyanine green angiographic features in posterior scleritis. Am J Ophthlmol. 1998;126:3:471-6

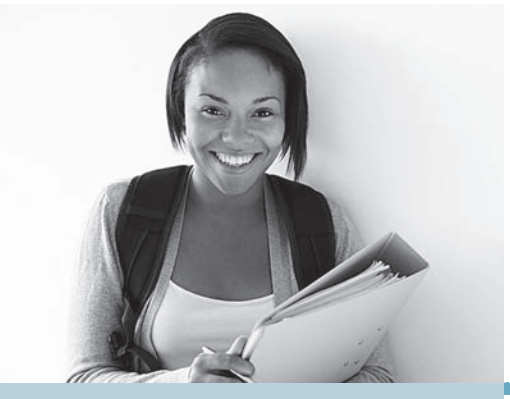




The Rick Bay Foundation

for Excellence in Eyecare Education

www.rickbayfoundation.org

Support the Education of Future Healthcare & Eyecare Professionals



About Rick

Rick Bay served as the publisher of The *Review* Group for more than 20 years.

To those who worked for him, he was a leader whose essence was based in a fierce and boundless loyalty.

To those in the industry and the professions he served, he will be remembered for his unique array of skills and for his dedication to exceeding the expectations of his customers, making many of them fast friends.

Scholarships are awarded to advance the education of students in both ***Optometry*** and ***Ophthalmology***, and are chosen by their school based on qualities that embody Rick's commitment to the profession, including integrity, compassion, partnership and dedication to the greater good.

Interested in being a partner with us?

Visit www.rickbayfoundation.org

(Contributions are tax-deductible in accordance with section 170 of the Internal Revenue Code.)

THE RICK BAY FOUNDATION®
for Excellence in Eyecare Education

(The Rick Bay Foundation for Excellence in Eyecare Education is a nonprofit, tax-exempt organization under section 501(c)(3) of the Internal Revenue Code.)

Surgical Outcomes Of GATT in POAG

In a retrospective chart review, researchers from Wills Eye Hospital's glaucoma research center, Sidney Kimmel Medical College and the Department of Biostatistics at Thomas Jefferson University evaluated the efficacy and safety of gonioscopy-assisted transluminal trabeculotomy in patients with open-angle glaucoma.

In this study, researchers conducted a chart review of adult patients who underwent GATT due to inadequately controlled intraocular pressure or poor tolerance to medication. Main outcome measures were success rate, IOP and number of glaucoma medications. Success was defined as IOP reduction >20 percent from baseline or IOP between 5 and 21 mm Hg, and no need for further glaucoma surgery. When success criteria were not met for any postoperative visit longer than three months after surgery, failure was determined.

In total, 66 patients, average age 62.9 ±14.9 years (50.8-percent female) were included in the analysis. Average follow-up was 11.9 months (range: three to 30 months) and overall success rate was 63 percent. Mean IOP was 26.1 ±9.9 mmHg preoperatively and 14.6 ±4.7 mmHg at 12 months (a 44-percent IOP decrease; $p<0.001$). Mean number of medications decreased from 3.1 ±1.1 preoperatively to 1.2 ±0.9 at 12 months ($p<0.001$). The rate of hyphema at one week and one month postoperatively was 38 percent and 6 percent, respectively. Overall GATT success rates among white and black patients were 69 percent and 42 percent, respectively, which was statistically significant ($p<0.05$).

The future of GATT as a minimally-invasive glaucoma surgery in adults seems promising, these researchers claim. This position is supported by GATT's low rate of long-term complications and the conjunctiva-sparing nature of the surgery.

J Glaucoma 2017 Dec;16:1137-1143
Rahmatnejad K, Pruzan NL, Amanullah S, et al.

Savings From Research

Researchers compared patient and Medicare savings from the use of optical coherence tomography in guiding therapy for neovascular age-related macular degeneration, with funding from the National Institutes of Health and the National Science Foundation in developing OCT, as part of an observational cohort study. (Several of the study's authors have a financial interest in OCT devices and/or companies.)

The main outcome measures were spending by Medicare, as tracked by Current Procedural Terminology codes for intravitreal injections (67028), retinal OCT imaging (92134) and anti-vascular endothelial growth factor treatment–specific J-codes (J0178, J2778, J9035, J3490 and J3590). Researchers identified claims using the Medicare provider utilization and payment data from the Centers for Medicare and Medicaid Services among fee-for-service Medicare beneficiaries from 2012 to 2015; 2008 claims were acquired from the 100-percent FFS Part B Medicare claims file. Researchers determined OCT research costs by searching for grants awarded by the NIH and NSF from inception to 2015. They discounted all costs and savings by 3 percent annually and adjusted for inflation to 2015 dollars.

The researchers determined that between 2008 and 2015, the U.S. government accrued an estimated savings of $9 billion, while nvAMD patients saw an estimated savings of $2.2 billion, from the use of OCT to guide personalized anti-VEGF treatment. The $9 billion represents a 21-fold return on government investment into developing the technology through NIH and NSF grants, they added.

The researchers added that, although an overall cost-benefit ratio of government-sponsored research is difficult to estimate because the benefit may be diffuse and delayed, their findings reveal that the investment in OCT over two decades was recouped many times over within a few years through better personalized therapy.

Am J Ophthalmol 2017;185:115
Windsor MA, Sun SJJ, Frick KD, et al.

This article has no commercial sponsorship.

Pearls In Pediatric Ocular Oncology

A brief review of diagnosis and treatment for these life-threatening disorders.

Raafay Sophie, MD, and Aparna Ramasubramanian, MD
Louisville, Ky.

Though pediatric eye tumors are rare, it's vital to diagnose them in a timely fashion in order to save the eye and, in many cases, the patient's life. This article reviews key highlights for the common spectrum of ocular tumors in the pediatric population.

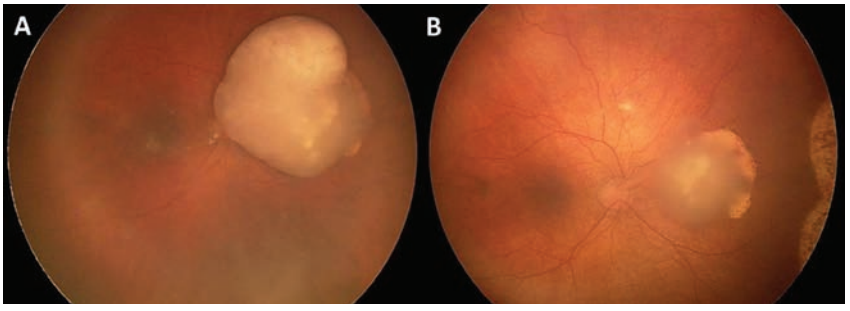


Figure 1. (A) Nasal retinoblastoma with overlying vitreous seeds treated with three cycles of intraarterial melphalan, showing good tumor response and calcified vitreous seeds (B).

Retinoblastoma

Retinoblastoma is the most common primary intraocular tumor in children, with an incidence of 11.8 per million in the United States.[1] It's caused by mutations in the tumor suppressor RB1 gene (located on Chromosome 13q14); both alleles must be affected for tumorigenesis. These mutations can occur sporadically, if so, typically presenting with unilateral disease at around 24 months. However, in 40 percent of patients, retinoblastoma involves an autosomal-dominant inherited heterozygous germline mutation followed by a subsequent mutation on the second allele. This heritable form (approximately 10 percent have a positive family history) classically presents earlier, at around 12 months with bilateral (or multiple unilateral) disease, and patients are more prone to developing a pineoblastoma and have a higher risk of developing secondary tumors. Following is a description of diagnosis, treatment and screening considerations.

• ***Clinical diagnosis.*** The most common presenting sign of retinoblastoma is leukocoria followed by strabismus. On exam the tumor appears as a translucent or white mass, and may be endophytic (into the vitreous cavity), exophytic (towards the subretinal space), or diffusely infiltrating. Ultrasound will show calcification in 90 percent of cases, while CT-scan should be avoided in suspected cases. The differential diagnosis for retinoblastoma includes persistent fetal vasculature, toxocariasis and Coats' disease *(Table 1) (Figure 2A&B).*

• ***Treatment.*** Patients with unilateral disease may undergo focally destructive therapy (cryopexy, laser photocoagulation, hyperthermia and plaque irradiation) in conjunction with systemic chemoreduction. Recently, intra-arterial chemotherapy is being employed for treatment *(Figure 1)*, while enucleation is reserved for large tumors or recalcitrant cases. Bilateral cases will require systemic chemotherapy.[2]

• ***Family screening and genetic counseling.*** In patients with bilateral retinoblastoma there is a 50-percent chance of the offspring being affected. If these patients have an identified germline mutation, DNA testing can

This article has no commercial sponsorship.

Table 1: Differentiating Features Between Retinoblastoma and Coats' Disease*

	Retinoblastoma	Coats' Disease
Features		
Family History	10 percent of patients	Sporadic
Mean Age of Onset	1.5 years	5 years
Gender	Male=female	Mostly affects males
Laterality	Unilateral or bilateral	Unilateral
Genetics	Mutation in RB1 on chromosome 13q14	± Somatic mutation on NDP gene on chromosome Xp11.[4]
Ocular Exam		
Vitreous	White fluffy seeds	Normal
Intraocular Mass	White/translucent mass	No mass, may present as subretinal gliotic nodule
Retinal Vessels	Dilated feeding artery and tortuous draining vein	Irregular dilation of retinal vessels, telengiectasia
Retinal Exudation	Absent	Present
Retinal Detachment	Exudative with fluffy white subretinal seeds	Exudative with yellow-white cholesterol crystals
Imaging		
Ultrasound	Solid retinal mass with intratumoral calcifications (high-intensity echoes); Retinal detachment	Retinal detachment; Linear calcification at level of RPE in rare cases
Computed Tomography	Hyperattenuated intraocular mass with calcification	Retinal detachment with hyperattenuating subretinal exudates; no calcification
Magnetic Resonance Imaging	T1- isotense or slightly hyperintense to vitreous; T2-hypointense to vitreous	T1- and T2-hyperintense to vitreous due to exudates
Fluorescein Angiography	Early arterial filling within tumor with leakage on venous phase. Late phase demonstrates intense, well-circumscribed hyperfluorescence of tumor	Early arterial and venous phase demonstrate areas of nonperfusion and arterial and venular telangiectasia with light bulbs. Late phase shows leakage of dye

*adapted from Ramasubramanian A, Shields CL. Retinoblastoma. First ed: Jaypee Brothers Medical Publisher (P) Ltd.; 2012

be performed in pregnancy or in neonates to establish the risk to the offspring. If testing of the patient fails to identify a germline mutation, the child must undergo surveillance eye exams.

In patients with unilateral retinoblastoma, a germline mutation may occur in 10 to 15 percent of patients, the risk to an offspring is similarly 50 percent. In the remaining patients, if tumor cells test positive for a somatic mutation, there is less than a 5-percent risk for the affected offspring.

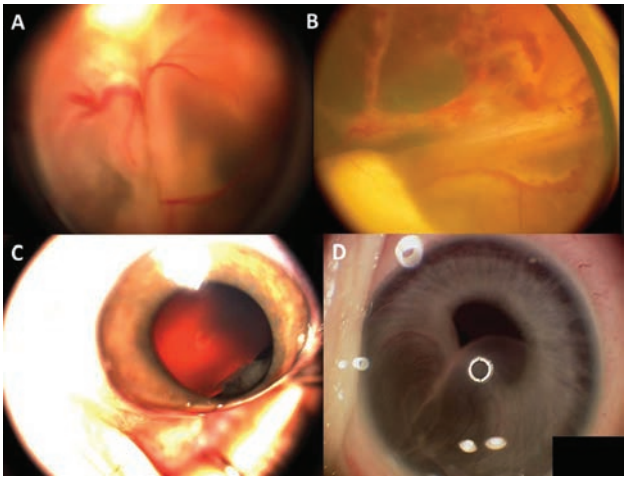


Figure 2. (A) Retinoblastoma with total retinal detachment showing the dilated tortuous vessels that dip in to feed the tumor. (B) Coats' disease with total retinal detachment showing the telangiectatic vessels in the periphery. (C) Fleshy tumor arising from the ciliary body in a child suggestive of medulloepithelioma. (D) Iris stromal cyst in a child.

In either case, DNA testing can be pursued in pregnancy or in neonates to establish risk. If patients with unilateral retinoblastoma have no germline mutation and no tumor is available for testing, the risk to the offspring is less than 5 percent, no testing is possible and the child must undergo surveillance eye exams.

The recommended screening for familial retinoblastoma is for an initial exam within two weeks of birth, monthly exams up to age 3 months, bi-monthly exams till age 1, tri-monthly exams till age 2, an exam every four months till age 3 and then semi-annual exams until age 4.[3] Using this protocol, nearly 100 percent of familial tumors are detected by 12 months.

If a germline mutation is identified in a child and the parents tested negative, it's possible that one parent could have germline mosaicism, in which case testing of siblings is recommended. If mosaicism for germline mutation is identified in the child, the mutation was a post-zygotic event and no testing of siblings is warranted.[2]

Medulloepithelioma (Diktyoma)

This is a rare embryonic tumor of the non-pigmented ciliary epithelium. It's the second most common pediatric primary intraocular tumor. The difficult direct visualization of these tumors may lead to late diagnosis, misdiagnosis and improper initial management. Even after symptoms develop, the possibility of a tumor is often overlooked, as patients are treated for secondary complications of the tumor such as cataract or glaucoma. Later, as the tumor slowly grows, it may be seen in the pupil, distort the iris, or

invade adjacent tissues. The tumor appears as an irregularly shaped, smooth, fleshy pink lesion arising from the ciliary body *(Figure 2C)*, oftenwith large cystic spaces that contain vitreous-like material. These cysts may break and float off into the aqueous or vitreous humor. Ultrasound biomicroscopy and AS-OCT are useful for visualization of the medium-to-highly reflective ciliary body mass with intratumoral cystic spaces.[4] A characteristic retrolental neoplastic cyclitic membrane may be found in half of the cases.[5] Histologically it's classified as non-teratoid or

Table 2. Phakomatoses and Their Diagnostic Features

Disorder	Diagnostic Criteria	Ocular Features
Neurofibromatosis-I (Von Recklinghausen disease) Autosomal dominant, (Chromosome 17) Prevalence: 1:4,000	• six or more cafe-au-lait spots *(Figure 3A)*; • two or more neurofibromas of any type, or one or more plexiform neurofibroma; • freckling in the axilla or groin; • optic glioma; • two or more Lisch nodules; • a distinctive bony lesion: dysplasia of the sphenoid bone or dysplasia or thinning of long bone cortex; and/or • a first-degree relative with NF I	• Eyelid: Neurofibroma *(Figure 3B)*, cafe au lait • Conjunctiva: Plexiform neurofibroma • Cornea: Prominent corneal nerves • Iris: Iris ectropion *(Figure 3D)*, nevus, Lisch nodules • Glaucoma: Ipsilateral to the plexiform neurofibroma • Retina/Choroid: Retinal glial hamartoma, choroidal thickening • Orbit: Optic nerve glioma *(Figure 3C)*, Pulsating exophthalmos (absence of sphenoid wing), neurofibroma, schwannoma
Neurofibromatosis-II Autosomal dominant (Chromosome 22) Prevalence: 1:40,000	• detection of bilateral acoustic neuroma by imaging procedures; • first-degree relative with NF II and the occurrence of neurofibroma, meningiomas, glioma, or schwannoma; • first-degree relative with NF II and the occurrence of juvenile posterior subcapsular cataract	• Lens: Cortical cataract, posterior subcapsular cataract • Retina: Combined hamartoma, Epiretinal membrane • Orbit: Optic nerve sheath meningioma, optic nerve glioma
Tuberous Sclerosis (Bourneville Syndrome) Autosomal dominant, 60 percent are sporadic mutations TSC1 (Chromosome 9): familial TSC2 (Chromosome 16): sporadic, more aggressive Prevalence: 1:6,000	Mental retardation, seizures and facial angiofibroma CNS features: • subependymal astrocytic hamartomas; and • cortical astrocytic hamartomas. Systemic features: • renal angiomyolipoma; • cardiac rhabdomyoma; • pleural cysts; and/or • occasional similar hamartomas of liver, thyroid, pancreas, testes, etc.	• calcified or non-calcified hamartoma *(Figure 4A)*, seen in 40 to 50 percent of TS patients; • early-onset cataracts; • hamartomas of the iris pigment epithelium and ciliary body epithelium; • eyelid angiofibromas; • strabismus; • colobomas; and/or • iris depigmentation
Sturge-Weber Syndrome (Encephalofacial Angiomatosis) Not genetically transmitted Prevalence: 1:50,000	CNS Features: • leptomeningeal angiomatosis; • cerebral calcification (rail road track sign); • mental retardation; and/or • convulsions	• facial hemangioma; • diffuse choroidal hemangioma *(Figure 4B)*; • glaucoma
Von Hippel Lindau Syndrome (Retinal Angiomatosis) Autosomal dominant (Chromosome 3) Prevalence: 1:50,000	CNS features: • cerebellar hemangioblastoma; and/or • syringomyelia. Systemic features: • pheochromocytoma; • renal cysts; • hypernephroma; • pancreatic cysts; and/or • epididymal cysts	• screening usually starts at age 5; • retinal capillary hemangioma *(Figure 4C)*; • usually multiple tumors, peripheral more common; • treatment consists of laser, cryotherapy or PDT

(Continued on next page)

Table 2. Phakomatoses and Their Diagnostic Features *(continued from p. 57)*

Disorder	Diagnostic Criteria	Ocular Features
Ataxia Telengiectasia (Louis-Bar Syndrome) Autosomal recessive (Chromosome 11) Prevalence: 1:30,000	CNS features: • cerebellar ataxia Systemic features: • skin telangiectasias; • immune deficiency, thymic hypoplasis; and/or • a tendency to develop malignancies such as lymphoma and leukemia	• bilateral bulbar conjunctival telangiectasias that develop between 3 and 5 years of age; and/or • ocular motor apraxia
Wyburn-Mason Syndrome (Retinal Racemose Angioma) Not genetically transmitted Prevalence: fewer than 100 reported cases Unilateral	CNS/Systemic/Ocular features: • ipsilateral vascular malformation of brain, orbit and mandible	• arterio-venous malformation of the retina; fluorescein angiogram shows no leakage
Incontinentia Pigmenti (Bloch-Sulzberger Syndrome) X-linked dominant ("NEMO" gene) Prevalence: 1:390,000	CNS features: • seizures; • developmental delay; and/or • mental retardation. Systemic features: • skin abnormalities ("Splashed-paint" appearance); • alopecia; and/or • dental abnormalities	• proliferative retinal vasculopathy similar to retinopathy of prematurity

teratoid (it often has hyaline cartilage), and as benign or malignant. Unlike medulloepithelioma of the central nervous system, metastasis is rare. Treatment options include cryotherapy, local resection, plaque radiotherapy and external beam radiotherapy but, often, enucleation is required.

Iris Stromal Cysts

In children, these are often primary cysts; acquired cysts mostly occur in adults.[6] In contrast to iris pigment epithelium cysts, these tend to enlarge aggressively, especially in children. Iris stromal cysts appear as a translucent mass occupying the anterior iris, expanding to fill much of the anterior chamber and covering the pupil, leading to angle occlusion and glaucoma *(Figure 2D)*. Occasionally, the cyst can rupture, causing anterior uveitis, secondary glaucoma and an increased risk for epithelial downgrowth. These cysts are often difficult to manage and a variety of treatment strategies have been used, including aspiration, cryotherapy, laser and surgical removal.[7,8] Recently, physicians have had considerable success treating these cases with sclerosing therapy using absolute alcohol.[9]

Phakomatoses

Tumors often occur in combination with neurocutaneous disorders or phakomatoses. Some salient features of common phakomatoses are outlined in Table 2.

In cases of optic nerve glioma (as can occur with neurofibromatosis, seen in Table 2), there are some screening guidelines to note: Although there is some non-uniformity regarding screening frequency and duration in the literature, in most centers screening is performed every six months until age 6 and then annually up to ages 16 to 18.[10] This includes visual acuity testing, pupillary reflex testing and fundoscopy, while a brain MRI is usually reserved for when there is clinical suspicion. Optical coherence tomography and newer imaging modalities are currently being investigated for detection purposes. Once a glioma is detected, it's monitored with regular ophthalmic exams and MRI, with the frequency depending on the institution's protocol.

Capillary Hemangioma

These hamartomatous growths composed of proliferating capillary endothelial cells are the most common benign tumors of infancy. They occur in 1 to 3 percent of term newborns, are more common in premature infants and occur in varying frequency across races (10 to 12 percent in white, non-Hispanic infants; 1.4 percent in black infants and 0.8 percent in Asian infants). The salient features are the following:

• ***Clinical presentation.*** Most hemangiomas are clinically insignificant at birth. They present as erythematous macules or telangiectasia

(Figure 4D). The natural history is of rapid proliferation in the first several months of life, typically followed by regression after a year. Rarely, they may ulcerate or bleed. A large, facial, plaque-like capillary hemangioma involving one or more dermatomes may be associated with an X-linked dominant systemic condition called PHACES Syndrome (posterior fossa brain malformation, facial hemangiomas (segmental, >5 cm), arterial anomalies, cardiac anomalies and aortic coarctation, eye abnormalities, sternal cleft and supraumbilical raphe syndrome).

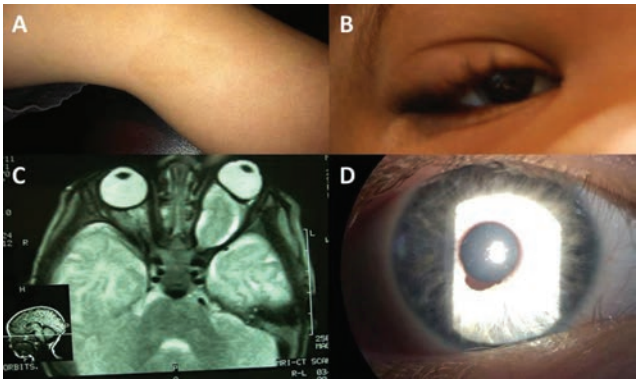


Figure 3. Features of neurofibromatosis-1 include café-au-lait spots (A), upper eyelid plexiform neurofibroma (B), optic nerve glioma (C) and congenital iris ectropion (D).

• ***Treatment.*** Indications for intervention include occlusion of the visual axis, induction of astigmatism, corneal exposure due to severe proptosis and optic nerve compression by a rapidly growing tumor. A deep hematoma causing proptosis merits imaging to assess the tumor size. Non-ocular indications include hypertrophy of epidermal and subcutaneous tissue leading to maceration, erosion of epidermis; or even cardiac, hematologic and pulmonary complications, as in the case of a sizeable hematoma. Therapies include beta-blockers (topical or systemic), steroids (intralesional or systemic), surgery, laser and radiation.

We prefer using systemic propranolol as follows: After performing a complete ocular exam and ruling out the possibility of PHACES, the patient is sent to a pediatrician where heart rate, blood pressure, blood sugars and an ECG are performed. If the ECG is abnormal, then cardiology consultation, echocardiogram and inpatient treatment may be required. If the pediatrician clears the patient, we start outpatient treatment with propranolol at a dose of 1.2 mg/kg/day (b.i.d.) for the first week. This is escalated to 2.1 mg/kg/day (b.i.d.) in the second week and treatment response is assessed. If the treatment is successful, this dose is continued, or the dose may be escalated to 3.4 mg/kg/day (b.i.d.) and continued. At the start of each dose increment, heart rate and blood pressure should be monitored for two hours.

Side effects of this treatment include bradycardia, hypotension, hypoglycemia and gastrointestinal disturbances. Propranalol should be administered along with feeding and should be withheld if a child is not eating or is vomiting. Therapy is continued until the complete regression of hemangioma occurs or until 9 months of age. The child is then weaned off of this over two to three weeks (similar to initiation) and the hemangioma observed for any signs of recurrence. If there is any recurrence, propranalol is restarted.

Pulsed dye laser may be used to treat residual telangiectasias, and residual texture irregularities can be improved by resurfacing with carbon dioxide or erbium lasers. Topical timolol may be used for superficial hemangiomas. Steroids are rarely used due to the side effects and the efficacy of propranolol. Interferon alpha-2a and/or vincristine may be used in severe cases, and surgery may be required either as a primary or reconstructive procedure. REVIEW

Dr. Sophie is a resident physician and Dr. Ramasubramanian is an assistant professor at the University of Louisville's Department of Ophthalmology. They have no financial interest in any products mentioned here.

This work was supported in part by an unrestricted institutional grant from Research to Prevent Blindness, New York, N.Y.

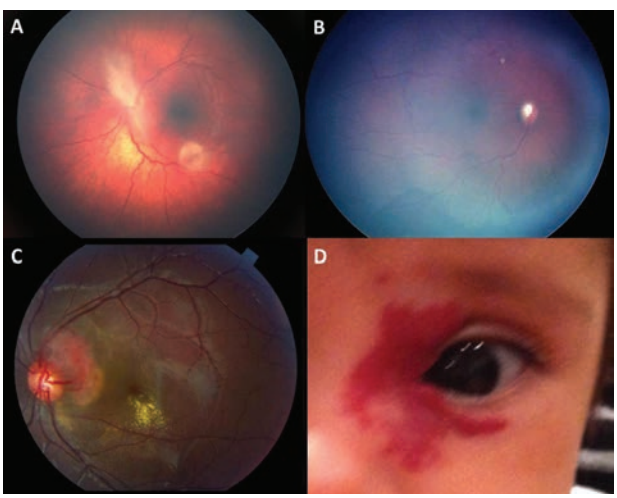


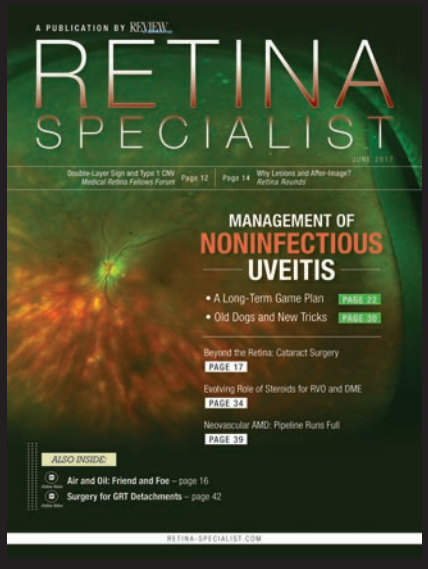
Figure 4. Astrocytic hamartoma in a patient with tuberous sclerosis (A). Diffuse choroidal hemangioma in a patient with Sturge-Weber syndrome, note the dark pigment, optic nerve cupping and peripheral vessel shunting (B). Retinal capillary hemangioma in Von Hippel-Lindau disease (C) and capillary hemangioma (D).

1. Broaddus E, Topham A, Singh AD. Incidence of retinoblastoma in the USA: 1975-2004. Br J Ophthalmol 2009;93:21-3.
2. Ramasubramanian A, Shields CL. Retinoblastoma. First ed. Jaypee Brothers Medical Publisher Ltd.; 2012.
3. Moll AC, Imhof SM, Meeteren AY, Boers M. At what age could screening for familial retinoblastoma be stopped? A register-based study 1945-98. Br J Ophthalmol 2000;84:1170-2.
4. Gunduz K, Hosal BM, Zilelioglu G, Gunalp I. The use of ultrasound biomicroscopy in the evaluation of anterior segment tumors and simulating conditions. Ophthalmologica 2007;221:305-12.
5. Kaliki S, Shields CL, Eagle RC, Jr., et al. Ciliary body medulloepithelioma: Analysis of 41 cases. Ophthalmology 2013;120:2552-9.
6. Shields CL, Kancherla S, Patel J, et al. Clinical survey of 3680 iris tumors based on patient age at presentation. Ophthalmology 2012;119:407-14.
7. Shields JA, Shields CL, Lois N, Mercado G. Iris cysts in children: Classification, incidence, and management. The 1998 Torrence A Makley Jr Lecture. Br J Ophthalmol 1999;83:334-8.
8. Lois N, Shields CL, Shields JA, Mercado G, De Potter P. Primary iris stromal cysts. A report of 17 cases. Ophthalmology 1998;105:1317-22.
9. Shields CL, Arepalli S, Lally EB, Lally SE, Shields JA. Iris stromal cyst management with absolute alcohol-induced sclerosis in 16 patients. JAMA Ophthalmol 2014;132:703-8.
10. Caen S, Cassiman C, Legius E, et al. Comparative study of the ophthalmological examinations in neurofibromatosis type 1. Eur J Paediatr Neurol 2015;19:415-22.

A PUBLICATION BY REVIEW of Ophthalmology

RETINA SPECIALIST

Retina Specialist focuses on the latest advances in the diagnosis, medical management and surgical treatment of diseases of the retina, along with practical, real-world advice from leading clinicians and other experts on managing the successful retina practice.



The new addition to the *Review* family serves the entire Retina Specialist marketplace.

Look for your issues in 2018:

» **MARCH**

» **JUNE**

» **SEPTEMBER**

» **NOVEMBER**

For inquiries contact

RETINASPECIALIST@JOBSON.COM

Advertising opportunities

JIM HENNE • PUBLISHER • 610-492-1017 • JHENNE@JOBSON.COM

MICHELE BARRETT • 215-519-1414 • MBARRETT@JOBSON.COM

MICHAEL HOSTER • 610-492-1028 • MHOSTER@JOBSON.COM

www.retina-specialist.com

Bausch + Lomb's Crystalsert Approved

In early January, Bausch + Lomb received FDA approval for its Crystalsert 2.6 injector, designed for use with the entire diopter range of Crystalens and Trulign toric intraocular lenses. According to Bausch + Lomb, the Crystalsert allows for smooth and easy lens delivery through an incision as small as 2.6 mm.

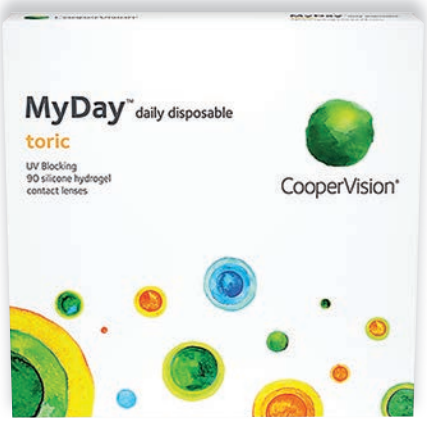
The Crystalsert features an oval-shaped tip, which B+L says allows for easy wound entry and helps prevent tissue snagging. The tip of the device also features a straight delivery channel to help reach the capsular bag without stretching the wound. In addition, the Crystalsert features a haptic guide and modified plunger tip to support the leading and trailing haptics during surgery.

The Crystalsert delivery system is a sterile, disposable plastic device, with a small pathway in which the lens can be placed into the eye in one continuous motion, B+L says. It is designed for single use only.

For more information on Bausch + Lomb's Crystalsert, visit Bausch.com/our-company/recent-news.

CooperVision's MyDay Toric

CooperVision recently announced the introduction of its MyDay toric daily disposable contact lenses in the United States, combining the design features of the Biofinity toric with the "smart silicone" chemistry of MyDay.



This new premium silicone hydrogel one-day lens brings together the advantages of silicone hydrogel, uncompromised comfort and handling, and lens stability and visual acuity, CooperVision claims.

MyDay toric lenses are currently available in sphere powers from plano to -6 D (in 0.25-D steps), and -6 to -10 D (in 0.50-D steps), with cylinder options of -0.75 D, -1.25 D and -1.75 D in axes of 10, 20, 70, 80, 90, 100, 110, 160, 170 and 180 degrees, and -2.25 D in axes of 10, 20, 90, 160, 170 and 180 degrees. CooperVision says plus powers will be added soon. MyDay toric lenses have a base curve of 8.6 mm and a diameter of 14.5 mm.

For more information on CooperVision's MyDay toric, visit prescribemyday.com/toric.

Bausch + Lomb's Lumify

In late December, Bausch + Lomb received FDA approval for Lumify (brimonidine tartrate ophthalmic solution 0.025%). This is the first over-the-counter eye drop developed with low-dose brimonidine tartrate for the treatment of ocular redness. Brimonidine, first approved by the FDA in 1996 for intraocular pressure reduction in glaucoma patients, is available at higher doses in prescription eye-care products.

Low-dose brimonidine, the active ingredient in Lumify, selectively constricts veins in the eye, increasing the availability of oxygen to surrounding tissue, reducing the potential risk of side effects associated with nonselective redness-relieving eye drops to treat ocular redness, Bausch + Lomb claims. Lumify is expected to be available in the second quarter of 2018.

For more information on Lumify, visit Bausch.com/our-company/recent-news.

This article has no commercial sponsorship.

Practice For Sale

Career Opportunities

OPHTHALMOLOGISTS
Danbury, CT

Ophthalmologists to share office with long standing Ophthalmologist in Danbury, CT. High quality equipment. $2,250 per month or adjoining office without equipment- $1,750 per month.

203-545-3539 or email mehrimd@aol.com

Career Opportunities

A yellow pupillary reflex brings a 2-year-old boy in for consultation and treatment at Wills Eye Hospital.

Douglas Matsunaga, MD, Kunal Malik, BA, and Carol L. Shields, MD

Presentation

A 2-year-old boy presented to the ophthalmologist two weeks after his mother noticed his left pupil appeared "cloudy" compared to prior photographs. The patient's mother didn't notice any other local changes such as trauma, infection or pain, and the child was otherwise healthy.

Medical History

The patient was a fraternal twin born at 36 weeks by caesarean section. The neonatal period was complicated by a neonatal intensive care unit admission for 23 days secondary to lung prematurity, and the infant was monitored in an oxygen tent. Past eye and medical history were otherwise unremarkable. Family history was positive for liver cancer in his paternal grandfather, cervical cancer in his maternal grandmother, and colon cancer in his maternal great grandmother.

Examination

On ocular examination at age 2, uncorrected visual acuity was 20/40 OD by Allen testing, and it was fix and follow OS. Pupils were round and reactive bilaterally without relative afferent pupillary defect. Xanthocoria (yellow pupillary reflex) was noted in the left eye. In-office fundus examination revealed normal findings OD, and a yellow-white macular mass OS. The child was referred for an ocular oncology consultation.

Examination under anesthesia revealed prominent macular exudation in the left eye and a superiorly located retinal cyst 10 mm in diameter *(Figure 1A and 1B)*. Subretinal and intraretinal macular exudation was confluent and intermixed with subretinal fluid, and extended to the ora serrata temporally and inferiorly. There was subtle temporal retinal telangiectasia.

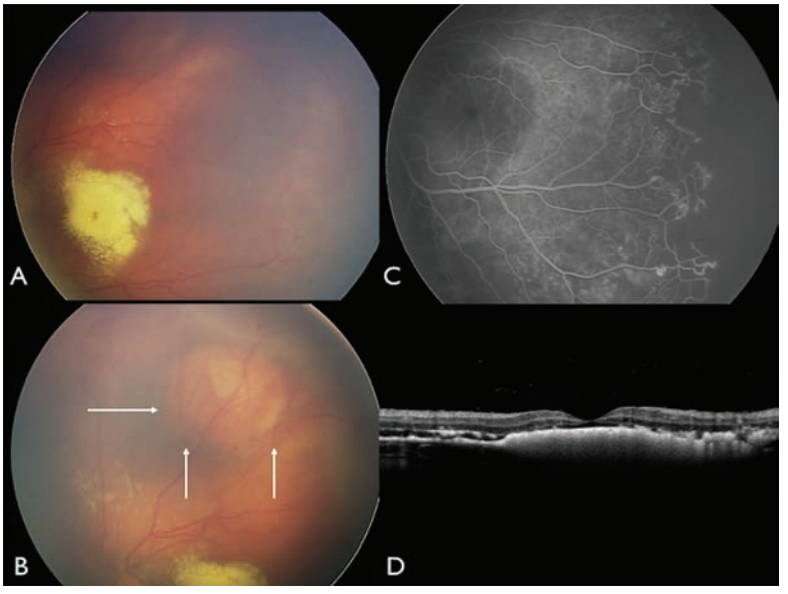


Figure 1. (A) Fundus photography of the left eye on initial examination under anesthesia shows dense macular exudation and extensive subtle telangiectasia temporally. (B) A large macular cyst is seen superiorly (arrows). (C) Fluorescein angiography highlights the telangiectasia and areas of non-perfusion. (D) OCT shows dense debris under the fovea and mild cystoid macular edema.

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

Workup, Diagnosis and Treatment

Ancillary imaging with fluorescein angiography, ocular ultrasonography and optical coherence tomography were obtained. On FA, the left eye showed temporal and inferior telangiectasia and peripheral non-perfusion without traction *(Figure 1C)*. Ocular ultrasonography disclosed shallow retinal detachment with subretinal dense debris and no calcific mass. There was a retinal macrocyst superiorly. OCT revealed the fovea overlying subretinal dense, irregular debris with loss of the outer retinal layers and trace cystoid macular edema *(Figure 1D)*.

The differential diagnosis in a 2-year-old patient with exudative retinopathy includes a wide range of pathologies, including Coats' disease, retinal hemangioblastoma, vasoproliferative tumor, familial exudative vitreoretinopathy, facioscapulohumeral muscular dystrophy, retinopathy of prematurity sequelae, retinitis pigmentosa and some infections. Rarely does retinoblastoma display exudative retinopathy. Less-common causes include diabetes mellitus and hypertension. While the patient's history of prematurity with NICU admission might prompt concern for late sequelae of retinopathy of prematurity, the dilated fundus examination was less consistent as there was an absence of tractional elements of extraretinal fibrovascular tissue or vitreoretinal scarring. Instead, the presence of extensive retinal telangiectasia associated with retinal exudation, with no sign of retinal traction was most suggestive of Coats' disease. Given the absence of prior medical or family history, the clinical diagnosis of Coats' disease was established and the patient underwent laser photocoagulation and cryotherapy to the areas of telangiectasia.

On follow-up examination four months later, there was 60-percent resolution of the exudation, with temporal chorioretinal scarring, mild persistent subretinal fluid and residual telangiectasia along the posterior margin of the previous treatment temporally (*Figure 2A*). FA confirmed the presence of residual telangiectasia *(Figure 2B)*. A second round of therapy was then performed over these remaining telangiectasia.

On follow-up six months after the the second treatment, funduscopy revealed minimal macular exudation with a residual foveal gliotic scar and peripheral treatment scarring. FA confirmed inactive telangiectasia and a macular blocking defect from gliosis. OCT demonstrated the fovea draped over old exudation and an otherwise flat retina. No further intervention was performed, and the most recent follow-up 12 months after the second round of treatment showed complete resolution of the telangiectasia and macular exudation, with persistent foveal gliosis (*Figure 2C*).

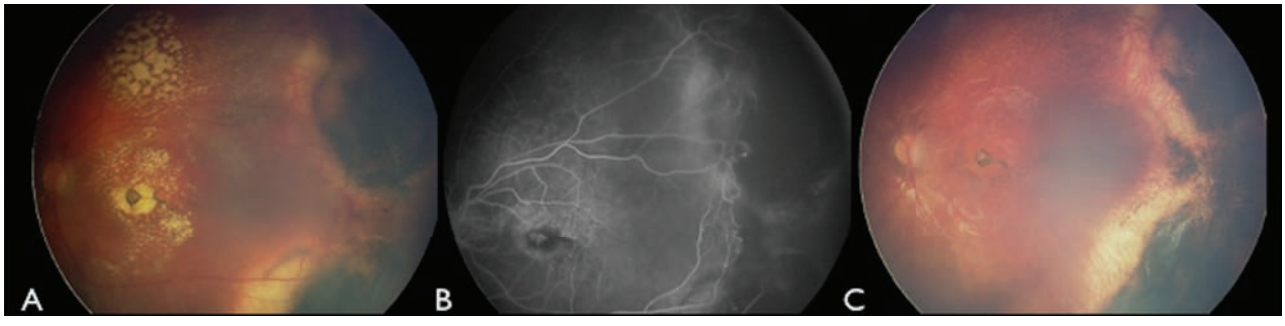


Figure 2. (A) Fundus photography of the left eye four months after first cryotherapy demonstrates partial resolution of the regions of retinal exudation, chorioretinal scarring in areas of cryotherapy and residual telangiectasia along the posterior margin. (B) Fluorescein angiography during the same visit highlights the residual telangiectasia adjacent to the chorioretinal scarring temporally. (C) Fundus photography at one year after treatment shows subfoveal gliotic scar, temporal chorioretinal scarring and resolution of the telangiectasia.

Discussion

Coats' disease was first described by George Coats in 1908 as unilateral retinal vascular abnormalities with retinal exudation, typically found in young males.[1] The definition has since been refined to findings of idiopathic retinal telangiectasia with intraretinal and/or subretinal exudation without evidence of vitreoretinal traction.[2,3] Coats' is rare and sporadic, and hasn't been linked to any systemic diseases. A one-year, prospective survey in the United Kingdom estimated a population incidence of 0.09 per 100,000.[4] This condition typically presents unilaterally in younger males: In a study of 150 patients with Coats' disease, 76 percent were males and 95 percent presented with unilateral findings. The median age at presentation was 5 years (age range: 1 month to 63 years).[3]

The most common initial presenting symptoms of Coats' disease included decreased visual acuity, strabis-

mus and leukocoria.[3] In the natural course of the disease, retinal telangiectasia and associated vascular abnormalities, including microaneurysms, arteriovenous communications and capillary dropout lead to extensive vascular leakage with subsequent subretinal fluid and exudation. Interestingly, while most telangiectasia are found temporally and anterior to the macula, exudation is often found more diffusely involving the periphery and post-equatorial retina.[3,5] Exudation in Coats' disease is often remote from the areas of telangiectasia and has a notable preference for the macula, forming a macular star.[2,3,5,6] As subretinal fluid progresses, retinal detachment can occur and may progress to total detachment.

Coats' disease is primarily diagnosed clinically, though several diagnostic procedures can assist in unclear cases. Fluorescein angiography highlights telangiectasia with early hyperfluorescence, hypofluorescence of exudation, capillary dropout peripheral to telangiectasia, and mild hyperfluorescence of subretinal fluid and overlying retinal capillaries. Ultrasonography can be particularly helpful in advanced cases with total exudative retinal detachment. Subretinal fluid will typically be clear or with minor, noncalcific echogenicity from subretinal cholesterolosis. These findings are particularly helpful in differentiating Coats' from the solid mass with dense echoes of calcification seen in retinoblastoma. In unusual cases, cytological assessment of the subretinal fluid can show lipid-laden macrophages and cholesterol crystals.[3,7]

The progression of Coats' disease has been classified into five stages. Stage 1 involves only retinal telangiectasias. Stage 2 includes additional exudation, with further subclassification specifying extrafoveal exudation as 2A and intrafoveal exudation as 2B. In stage 3, additional exudative retinal detachment is noted with subclassification detailing partial and total retinal detachment as 3A and 3B, respectively. Stage 3A is further subclassified into extrafoveal and foveal partial detachment as 3A1 and 3A2, respectively. Stage 4 describes eyes with total retinal detachment and secondary glaucoma. In stage 5, end-stage disease has occurred with a blind, nonpainful or painful eye and total retinal detachment. In a review of 124 eyes, the following incidences across stages were noted: stage 1 (1-percent incidence); stage 2 (14 percent); stage 3 (68 percent); stage 4 (15 percent); and stage 5 (2 percent).[2] Recently, the subfoveal gliotic nodule has been found to be predictive of macular fibrotic scarring and poorer visual outcomes.[8]

The management of Coats' disease is stage-dependent. Stage 1 or early stage 2 disease with mild telangiectasias and only small amounts of exudation are either observed or treated with laser photocoagulation. Observation is especially considered in older patients where the disease is usually less aggressive. Also, spontaneous regression of Coats' disease has been described.[9,10] However, periodic follow-up should be maintained. In a retrospective study of 39 patients across two decades, there was a trend toward better final visual acuity in the second decade of life when eyes were treated more often and with a higher number of procedures, suggesting that a low threshold for treatment is best.[11] Appropriate treatment has been shown to anatomically stabilize or improve the eye in 76 percent of eyes.[2]

For stage 2 Coats' disease, treatment modalities include laser photocoagulation or cryotherapy directly to the area of telangiectasia.[2,12,13] Multiple treatments may be required, and areas of remote exudation often resolve with the telangiectasia. Both modalities may also be used in some cases of partial retinal detachment. In eyes with total retinal detachment, visual prognosis is considered poor[11,14] and the decision against intervention must be weighed against the risk of developing painful neovascular glaucoma. In two retrospective case reviews of advanced Coats' disease that were untreated, four of six and 18 of 25 patients progressed to neovascular glaucoma.[14,15] Considering this risk, vitrectomy with subretinal fluid drainage, intravitreal tamponade with silicone oil or gas, and concomitant cryotherapy or photocoagulation to the telangiectasia has been performed with variable success, with the goal of preventing development of painful neovascular glaucoma.[2,12,13,16] Others have used treatments such as intravitreal triamcinolone or repetitive laser photocoagulation directly to telangiectasia on the detached retina.[17,18] Enucleation may be required in advanced disease that has progressed to a blind painful eye with or without secondary glaucoma. For stage 5 disease, in the absence of pain, observation is advised.

The use of anti-VEGF has been proposed as an adjunctive therapy for Coats' disease.[11,19-22] VEGF has been found to be elevated in the disease[23] and a number of case series have described its use in Coats' with favorable results.[11,19,21,22,24] In one small series of 10 patients treated with intravitreal bevacizumab compared to 10 matched controls, all of the bevacizumab patients achieved full resolution of the disease, compared to eight out of 10 in the control group.[20] The effects of anti-VEGF therapy in Coats' disease remains under study, and there are several limitations associated with it: One small study noted the formation of tractional fibrosis (rarely seen in Coats' disease) in four out of eight patients treated with intravitreal bevacizumab.[24] The use of anti-VEGF in the pediatric population may also be of concern, given

REVIEW Advertising Index

REVIEW Resident Case Series

the potential for systemic effects in developing children with relatively small volumes of distribution. There is also the risk of mistakenly injecting a patient with undiagnosed retinoblastoma, leading to potentially catastrophic consequences.[25]

The outcome of Coats' disease is particularly stage-dependent. In a study of 124 treated eyes, post-treatment poor visual acuity of 20/200 or worse was found in zero percent of stage 1, 53 percent of stage 2, 74 percent of stage 3 and 100 percent of stages 4 and 5. Enucleation was required in 0 percent of stages 1 and 2, 7 percent of stage 3, 78 percent of stage 4 and zero percent of stage 5. Poor visual acuity was associated with post-equatorial or diffuse location of the telangiectasia, retinal macrocyst and failed resolution of subretinal fluid after treatment.[2] It's important to note that Coats' disease can recur. In a retrospective analysis performed over 25 years, there was recurrence of telangiectasia and exudation in six out of 86 eyes (7 percent) that had initially been treated with good control of the disease.[2]

In conclusion, Coats' disease is a rare, nonhereditary condition defined by idiopathic retinal telangiectasia with retinal exudation and without evidence of retinal or vitreal traction. This condition typically presents unilaterally in young males, and a high index of suspicion should be maintained in such patients presenting with leukocoria and/or decreased vision. REVIEW

1. Coats G. Forms of retinal diseases with massive exudation. Royal London Ophthalmology Hospital Reports;1908: 17:440-525.
2. Shields JA, Shields CL, Honavar SG, Demirci H, Cater J. Classification and management of Coats disease: The 2000 Proctor Lecture. Am J Ophthalmol 2001;131:5:572-583.
3. Shields JA, Shields CL, Honavar SG, Demirci H. Clinical variations and complications of Coats disease in 150 cases: The 2000 Sanford Gifford Memorial Lecture. Am J Ophthalmol 2001;131:5:561-571.
4. Morris B, Foot B, Mulvihill A. A population-based study of Coats disease in the United Kingdom I: Epidemiology and clinical features at diagnosis. Eye (Lond) 2010;24:12:1797-1801.
5. Egerer I, Tasman W, Tomer TT. Coats disease. Arch Ophthalmol 1974;92:2:109-112.
6. Ridley ME, Shields JA, Brown GC, Tasman W. Coats' disease. Evaluation of management. Ophthalmology 1982;89:12:1381-1387.
7. Eagle R. Eye Pathology: An Atlas and Text. Third ed. Philadelphia: Wolters Kluwer; 2017.
8. Daruich AL, Moulin AP, Tran HV, Matet A, Munier FL. Subfoveal nodule in Coats' disease: Toward an Updated Classification Predicting Visual Prognosis. Retina 2017;37:8:1591-1598.
9. Deutsch TA, Rabb MF, Jampol LM. Spontaneous regression of retinal lesions in Coats' disease. Can J Ophthalmol 1982;17:4:169-172.
10. Wolfe JD, Hubbard GB. Spontaneous regression of subretinal exudate in Coats' disease. Arch Ophthalmol 2006;124:8:1208-1209.
11. Ong SS, Buckley EG, McCuen BW, et al. Comparison of Visual Outcomes in Coats' Disease: A 20-Year Experience. Ophthalmology 2017;124:9:1368-1376.
12. London NJS, Shields CL, Haller JA. Chapter 56 - Coats Disease. In: Schachat A, ed. Retina (Fifth Edition). London: W.B. Saunders, 2013:1058-1070.
13. Mulvihill A, Morris B. A population-based study of Coats disease in the United Kingdom II: Investigation, treatment, and outcomes. Eye (Lond) 2010;24:12:1802-1807.
14. Haik BG. Advanced Coats' disease. Trans Am Ophthalmol Soc 1991;89:371-476.
15. Silodor SW, Augsburger JJ, Shields JA, Tasman W. Natural history and management of advanced Coats' disease. Ophthalmic Surg 1988;19:2:89-93.
16. Yoshizumi MO, Kreiger AE, Lewis H, Foxman B, Hakakha BA. Vitrectomy techniques in late-stage Coats'-like exudative retinal detachment. Doc Ophthalmol 1995;90:4:387-394.
17. Levinson JD, Hubbard GB. 577-nm yellow laser photocoagulation for Coats disease. Retina 2016;36:7:1388-1394.
18. Ghazi NG, Al Shamsi H, Larsson J, Abboud E. Intravitreal triamcinolone in Coats' disease. Ophthalmology 2012;119:3:648-649.
19. Lin CJ, Hwang JF, Chen YT, Chen SN. The effect of intravitreal bevacizumab in the treatment of Coats disease in children. Retina 2010;30:4:617-622.
20. Ray R, Barañano DE, Hubbard GB. Treatment of Coats' disease with intravitreal bevacizumab. Br J Ophthalmol 2013;97:3:272-277.
21. Villegas VM, Gold AS, Berrocal AM, Murray TG. Advanced Coats' disease treated with intravitreal bevacizumab combined with laser vascular ablation. Clin Ophthalmol 2014;8:973-976.
22. Zheng XX, Jiang YR. The effect of intravitreal bevacizumab injection as the initial treatment for Coats' disease. Graefes Arch Clin Exp Ophthalmol 2014;252:1:35-42.
23. He YG, Wang H, Zhao B, Lee J, Bahl D, McCluskey J. Elevated vascular endothelial growth factor level in Coats' disease and possible therapeutic role of bevacizumab. Graefes Arch Clin Exp Ophthalmol 2010;248:10:1519-1521.
24. Ramasubramanian A, Shields CL. Bevacizumab for Coats' disease with exudative retinal detachment and risk of vitreoretinal traction. Br J Ophthalmol 2012;96:3:356-359.
25. Avery RL. Extrapolating anti-vascular endothelial growth factor therapy into pediatric ophthalmology: Promise and concern. J AAPOS. 2009;13:4:329-331.

xiidra® (lifitegrast ophthalmic solution) 5%

Rx Only

BRIEF SUMMARY:
Consult the Full Prescribing Information for complete product information.

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

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

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

ADVERSE REACTIONS
Clinical Trials Experience
Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in clinical studies of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. In five clinical studies of dry eye disease conducted with lifitegrast ophthalmic solution, 1401 patients received at least 1 dose of lifitegrast (1287 of which received lifitegrast 5%). The majority of patients (84%) had ≤3 months of treatment exposure. 170 patients were exposed to lifitegrast for approximately 12 months. The majority of the treated patients were female (77%). The most common adverse reactions reported in 5-25 % of patients were instillation site irritation, dysgeusia and reduced visual acuity. Other adverse reactions reported in 1% to 5% of the patients were blurred vision, conjunctival hyperemia, eye irritation, headache, increased lacrimation, eye discharge, eye discomfort, eye pruritus and sinusitis.

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

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

USE IN SPECIFIC POPULATIONS
Pregnancy
There are no available data on Xiidra use in pregnant women to inform any drug associated risks. Intravenous (IV) administration of lifitegrast to pregnant rats, from pre-mating through gestation day 17, did not produce teratogenicity at clinically relevant systemic exposures. Intravenous administration of lifitegrast to pregnant rabbits during organogenesis produced an increased incidence of omphalocele at the lowest dose tested, 3 mg/kg/day (400-fold the human plasma exposure at the recommended human ophthalmic dose [RHOD], based on the area under the curve [AUC] level). Since human systemic exposure to lifitegrast following ocular administration of Xiidra at the RHOD is low, the applicability of animal findings to the risk of Xiidra use in humans during pregnancy is unclear.

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

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

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

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

NONCLINICAL TOXICOLOGY
Carcinogenesis, Mutagenesis, Impairment of Fertility
Carcinogenesis: Animal studies have not been conducted to determine the carcinogenic potential of lifitegrast.
Mutagenesis: Lifitegrast was not mutagenic in the *in vitro* Ames assay. Lifitegrast was not clastogenic in the *in vivo* mouse micronucleus assay. In an *in vitro* chromosomal aberration assay using mammalian cells (Chinese hamster ovary cells), lifitegrast was positive at the highest concentration tested, without metabolic activation.
Impairment of fertility: Lifitegrast administered at intravenous (IV) doses of up to 30 mg/kg/day (5400-fold the human plasma exposure at the recommended human ophthalmic dose (RHOD) of lifitegrast ophthalmic solution, 5%) had no effect on fertility and reproductive performance in male and female treated rats.

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.

Patented: please see https://www.shire.com/legal-notice/product-patents
Last Modified: 01/2018 S33769

xiidra® (lifitegrast ophthalmic solution)5%

MAKE XIIDRA YOUR FIIRST CHOICE

When artificial tears aren't enough, consider prescribing Xiidra for symptomatic Dry Eye patients.

Proven to treat the signs of inferior corneal staining in 12 weeks and symptoms of eye dryness in 12, 6, and as little as 2.

Xiidra helped provide symptom relief from eye dryness in some patients at week 2—and a measurable reduction in signs of inferior corneal staining in just 12 weeks. Consider Xiidra to help your Dry Eye patients find the relief they've been waiting for.

Check it out at Xiidra-ECP.com

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

Indication

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

Important Safety Information

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

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

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

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

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

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

Shire