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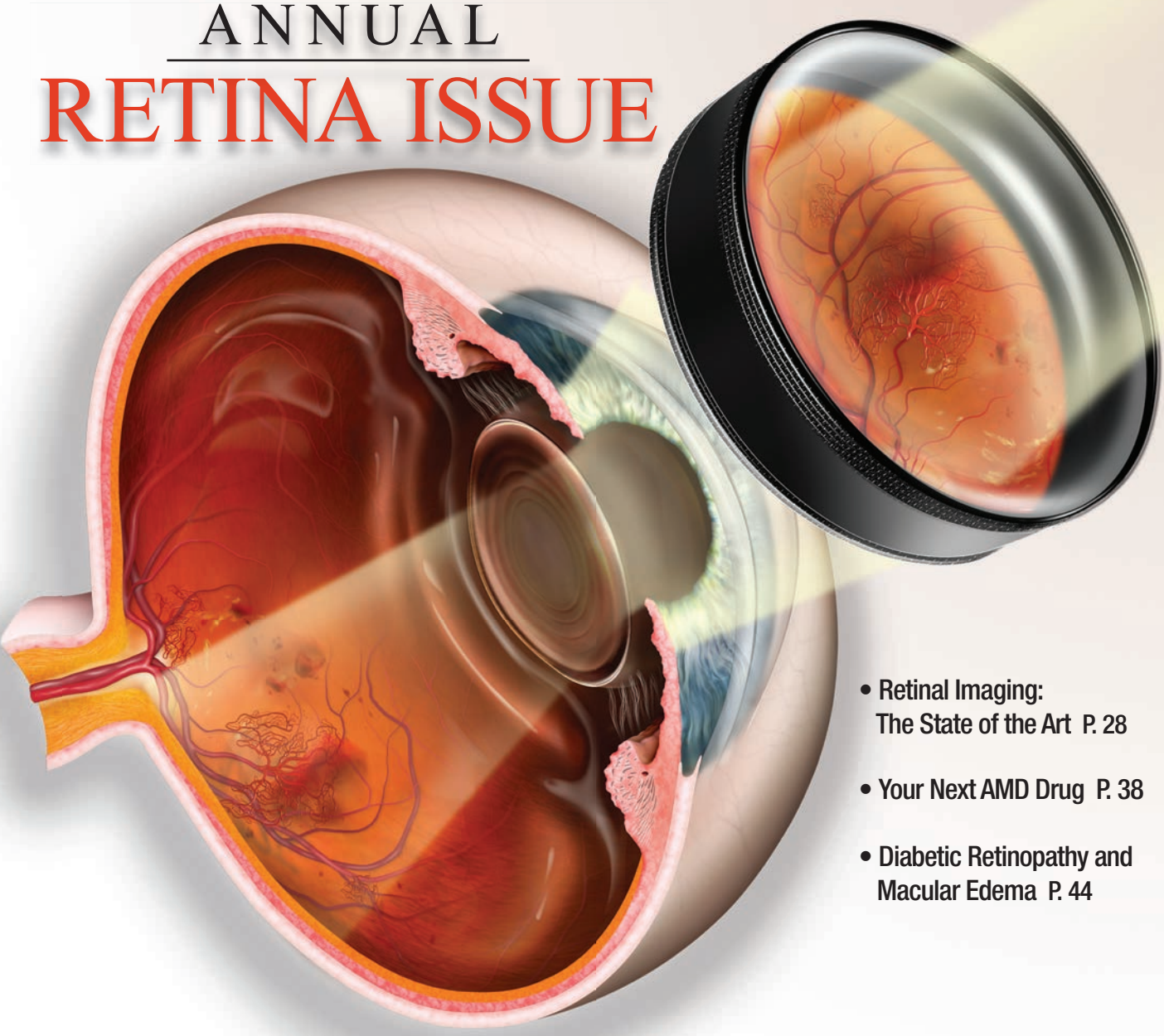

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REVIEW NEWS
Volume XXII • No. 8 • August 2015

A New Approach to Preserving Photoreceptors After RD

Researchers at the Massachusetts Eye and Ear/Harvard Medical School Department of Ophthalmology have taken a first step in solving the problem of preserving photoreceptor cells and avoiding irreversible vision loss in patients following retinal detachment.

Degeneration of photoreceptors is a primary cause of vision loss worldwide. Identifying the underlying causes surrounding photoreceptor cell death is paramount in order to develop new treatment strategies to prevent their loss. Retinal detachment and subsequent degeneration of the retina can lead to progressive visual decline due to photoreceptor cell death. Since photoreceptors are non-dividing cells, their loss results in irreversible visual impairment even after successful retinal reattachment surgery.

New research led by Kip M. Connor, PhD, a researcher and assistant professor of ophthalmology at Mass Eye and Ear, and colleagues analyzed innate immune system regulators in the eyes of human patients with retinal detachment and correlated their findings in an experimental model. They discovered that there was a significant increase in the immune system's alternative complement pathway following retinal detachment and that this pathway facilitated early photoreceptor cell death after injury. Injured photoreceptors lose important proteins that normally protect them from complement-mediated cell death, allowing for selective targeting by the alternative complement pathway. Additionally, by blocking the alternative complement pathway, through both genetic and pharmacologic means, photoreceptors were protected from cell death. "When photoreceptors in a detached retina were removed from their primary source of oxygen and nutrients, we found an increase in complement factor B, a key mediator of the alternative complement pathway that leads to photoreceptor cell death," says Dr. Connor. "For the first time these results provide evidence that the alternative complement pathway exacerbates photoreceptor cell death and that inhibition of the pathway is protective," said Kaylee Smith, a member of the Connor Lab and contributing author on the manuscript. Their findings were published *Science Translational Medicine*.

Today's state-of-the-art surgical techniques are highly effective at physically reattaching the retina, and if surgery is timely, a positive visual outcome often results. Even so, patients often complain of permanent vision loss accompanied by changes in color vision. "Studies in both humans and animal models have shown that photoreceptor cell death is induced as early as 12 hours after detachment, indicating that early intervention could potentially preserve photoreceptors and improve the visual function of patients who undergo reattachment surgery," says Dr. Connor. "Our research provides a new role for complement in retinal detachment, and suggests that inhibition of the alternative complement pathway may be good therapeutic target to prevent the initial photoreceptor cell loss.

"What makes this research so exciting is the potential impact it can have on our patients. Working closely with our colleagues in the clinic, we identified a challenging issue, went back to our laboratories to uncover a cause, and now have knowledge that may help us to develop therapies that will help to preserve our patients' vision."

Five Years After EHR Adoption, 41 Percent ROI

Switching to an EHR in 206 has netted one ophthalmology practice roughly $1.2 million over a five-year period, according to a new report published in July's *Ophthalmology*. Initially, the practice's costs increased due to the hiring of IT staff, software maintenance and scanning paper records. Eventually process changes driven by the EHR led to efficiencies that lowered the staffing needs related to medical records, transcription, billing, check-out and appointment scheduling. The system also acted as a revenue-driver by enabling EHR meaningful use incentive payments, increasing productivity in the later stages and making claims submission faster and more accurate. *(For a more extensive look at EHR in ophthalmology practice, see p. 60.)*

NEI Study: Microglia and RP

Microglia often play a beneficial role by helping to clear dead cells and cellular debris and protect the central

Ophthalmic Product Development Insights

Aki Tobaru, Hiro Matsuda, PhD, & Matthew Chapin • Ora Inc., Andover, Mass.

Tips for Doing Business and Collaborations in Japan

In prior columns we have discussed development strategies, financing and business issues related to developing new products, particularly geared towards the new entrepreneur. Global strategy is another important issue to consider early in business planning. As Japan is one of the top markets outside the United States, in this installment of Development Insights we will explore some elements related to Japanese business culture and customs that may be useful to consider as business and development relationships are sought after and formed in Japan.

There are many opportunities for entrepreneurs and start-up companies to explore global or regional partnerships with pharmaceutical and biotech companies in Japan, pursue assets and engage investors from within Japan, or try to bring products being developed in the United States into Japan. Historically there has in general been a significant lag between drug approvals in the two countries. Today, there is more focus on reducing that time-lag, which may involve engaging with global or regional Japanese partners early in the process. Japan is a unique country, with a culture different from any other. Here, we will focus on three key concepts: respect; formality; and long-term relationships. These customs tie together an underlying theme of respect and building trust, moving toward a long-term relationship that is important for the entrepreneur/developer who is forging a new relationship in Japan.

Respect

As in most, if not all cultures, respect is the ultimate form of acceptance and value, and is highly revered in Japan. Japanese respect others, and they respect seniority. One form of Japanese etiquette and respect best known outside of Japan is bowing. In the Japanese culture, bowing signifies greeting one another with respect. There are still many people in Japan, especially those of the older generations, who believe that they cannot trust those who do not greet properly, as it denotes lack of respect.

This concept is an important foundation to those looking to do business in Japan. For example, when visiting with a Japanese company, the first step should be for the main contact persons from both parties to greet each other, and continue with the exchange of business cards. As a nod to seniority, the main contact person from the host company should introduce the other members of the group, starting with the most senior personnel. During the meeting, the highest ranking person will likely make opening remarks, followed by his or her second-in-command, who will then begin the meeting. While the meeting is proceeding, conversation can take place as it plays out; however, great care should be taken to avoid interrupting any speakers. In Japan, this is considered one of the highest forms of disrespect to the speaker, and signals a lack of listening and understanding by the person who interrupts. Straightforward discussions are appropriate; however, it is recommended that you acknowledge points made by your Japanese partners before you introduce your ideas. This demonstrates that you were listening and respect their opinion, even if you have differing thoughts.

Formality

Japanese business always involves formality. While we are in a digital age with social networking, and this practice is certainly accepted by the Japanese, the preferred route of introduction, when possible and available, is through mutual friends. For Japanese, being formally introduced by a common connection is considered to be a more personal and professional route of introduction. This is particularly important when dealing with sensitive matters of a significant business deal, as a proper initial meeting is crucial for both parties and helps to kick off a successful project.

The exchange of business cards is considered a formal ritual. In the Japanese culture, offering a business card is quite personal, as it represents the "face" of the individual. Giving a business card is equivalent to providing someone with a significant amount of information about yourself. It is representative of the individual personally and professionally, and of the company. During a business card exchange, Japanese will present it with both hands, and prefer to receive business cards the same way, as it is a sign of respect. Additionally, the card should be delivered face-up and facing the recipient so he or she may read the card, with introduction of name and title. Finally, be sure to leave the card unmarked—it is not appropriate to write anything on a business card in front of the individual.

One fairly common mistake by made by foreigners surrounds the use of the word "san." Those unfamiliar with Japanese culture may believe that using san at the end of a first name is very polite and formal. However, san is rarely used in this manner among the Japanese. Among friends and colleagues in Japan, san is most commonly used at the end of an individual's last name. For those unaccustomed to Japanese formalities, the best way to show formality is to use a title such as doctor, mister or miss until the person indicates that you may use just his or her last name; and then it is appropriate to use the last name with san. Once you have established a friendship and valued relationship, the person may ask you to use his or her given name.

Another common mistake surrounding the use of san is its use to refer to your own colleagues. While in Japan, it is not commonplace to use san with last names when speaking about anyone in your company, including those that maintain higher positions. For example, you might say, "Our company president, Sato, believes that innovation is the key for our company." You simply refer to your own colleagues by their last name, which shows formality and politeness to others in Japan.

Specifically in the field of science or

academia, when meeting with professors and researchers at Japanese universities, it's proper etiquette to include doctor or professor with their last names. This demonstrates your respect for their accomplishments. Should a professor or researcher suggest that you call him by his last name, still use "sensei," meaning "teacher," accompanied by the last name. If he insists that you use his first name, it is then appropriate to use that name. It should be noted, however, that Japanese typically will not asked to be called by their first name until there is a sustained, long-lasting relationship. It's always safer to use "sensei" at the first meeting, and when they say that they prefer to be called by a first name, move forward accordingly.

Formality at meetings is common, and often can be misinterpreted. A very interesting example is nodding. Japanese business people tend to show politeness to the other party, and tend to nod, meaning that they listen well and understand, even at a negotiation table. However, Americans may interpret nodding to suggest agreement. This is very common mistake and can lead to misunderstandings. Therefore it is very important to ensure alignment and avoid misunderstanding, to confirm via written minutes or summary what both parties talked about, any decisions that were made, and action or follow-up items discussed.

Long-Term Relationships

The Japanese value relationships, so it is important to cultivate and build long-term relationships. Certainly, building a long-term relationship takes time and likely requires many interactions with one another. It is generally a good sign if an invitation to dinner is extended, and this is an important time for continuing to build the relationship with more casual conversation. Don't be afraid to engage in business talk and/or topics that were discussed earlier in the day. Japanese business people value honesty, and will appreciate it if you can honestly talk about what you need from the Japanese company.

If you are invited to a social networking event, consider yourself to be a valued partner. If you have been able to cultivate a relationship with a Japanese company to such an extent that you are invited to gatherings of this type, you can expect that your relationship is solid, and will benefit you as you begin to expand your network across Japan.

Corporate-wide relationship-building can be much tougher than at an individual level because it involves multiple people and moving parts. As with many development programs, there may be longer-term potential opportunity for a continued relationship beyond a single product or deal. In stereotypical "U.S. fashion," it is tempting to try to put several topics and objectives into one first deal or project discussion and figure it all out at once. While, of course, the desire for a long-term relationship is a good thing to show, the Japanese company may want to take a step-by-step approach and focus on the first item or product deal. It is important to respect the process and have patience for the benefit of the long-term relationship.

Trust and honesty are key components to creating such long-lasting relationships, and while this characteristic is not unique to Japan, be prepared for what is typically a longer process in Japan. The customs and formalities all relate to respect and building trust, which is ultimately what a successful long-term relationship can be based on.

Each country naturally has its own business manner and customary practices, and of course, you should value and respect all of them. It is always important for you to be dedicated to sound and clear science and good business practices, and be true to yourself without getting overly hung up with tradition and formal details. As you prepare, present and defend details of a project, don't lose sight of the end goal. As long as you always try to value respect, trust and integrity, Japanese business people will certainly prefer a friendly approach, open discussion and creativity that sparks long relationships that have value for everyone.

Mr. Chapin and Mr. Tobaru are with the Corporate Development group at Ora Inc. Ora provides a comprehensive range of product development, clinical-regulatory and product consulting for developers, investors and buyers; clinical trial services and regulatory submissions; and asset and business partnering support in ophthalmology. Dr. Matsuda is General Manager of Ora Japan KK, based in Japan. Ora Japan provides local support, consulting and clinical trial services to clients and partners for development in Japan and support for business collaborations between the U.S. and Japan. We welcome comments or questions related to this or other development topics. Please send correspondence to mchapin@oraclinical.com.

nervous system against infection. But a new study by researchers at the National Eye Institute shows that they also accelerate damage wrought by blinding eye disorders, such as retinitis pigmentosa. "These findings are important because they suggest that microglia may provide a target for entirely new therapeutic strategies aimed at halting blinding eye diseases of the retina," said NEI Director, Paul A. Sieving, MD. "New targets create untapped opportunities for preventing disease-related damage to the eye, and preserving vision for as long as possible." The findings were published in *EMBO Molecular Medicine*.

Research has shown links between RP and several mutations in genes for photoreceptors. In the early stages of the disease, rod photoreceptors are lost, causing night blindness. As the disease progresses, cone photoreceptors can also die off, eventually leading to complete blindness.

Lead investigator, Wai T. Wong, MD, PhD, chief of the Unit on Neuron-Glia Interactions in Retinal Disease at NEI, and his team studied mice with a mutation in a gene that can also cause retinitis pigmentosa in people. The researchers observed in these mice that very early in the disease process, the microglia infiltrate the outer nuclear layer, where they don't usually venture. The microglia then create a cup-like structure over a single photoreceptor, surrounding it to ingest it in a process called phagocytosis. Dr. Wong and his team caught this dynamic process on video. The whole feast, including digestion, takes about an hour.

In retinitis pigmentosa the researchers found that the microglia target damaged but living photoreceptors, in addition to dead ones. To confirm that microglia contribute to the degeneration process, the researchers genetically eliminated the microglia, which slowed the rate of rod photoreceptor

(continued on page 18)

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(610) 492-1008
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Managing Editor
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(610) 492-1024
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Senior Editor
Christopher Kent
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Chief Medical Editor
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Art Director
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Graphic Designer
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Business Offices
11 Campus Boulevard, Suite 100
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(610) 492-1000
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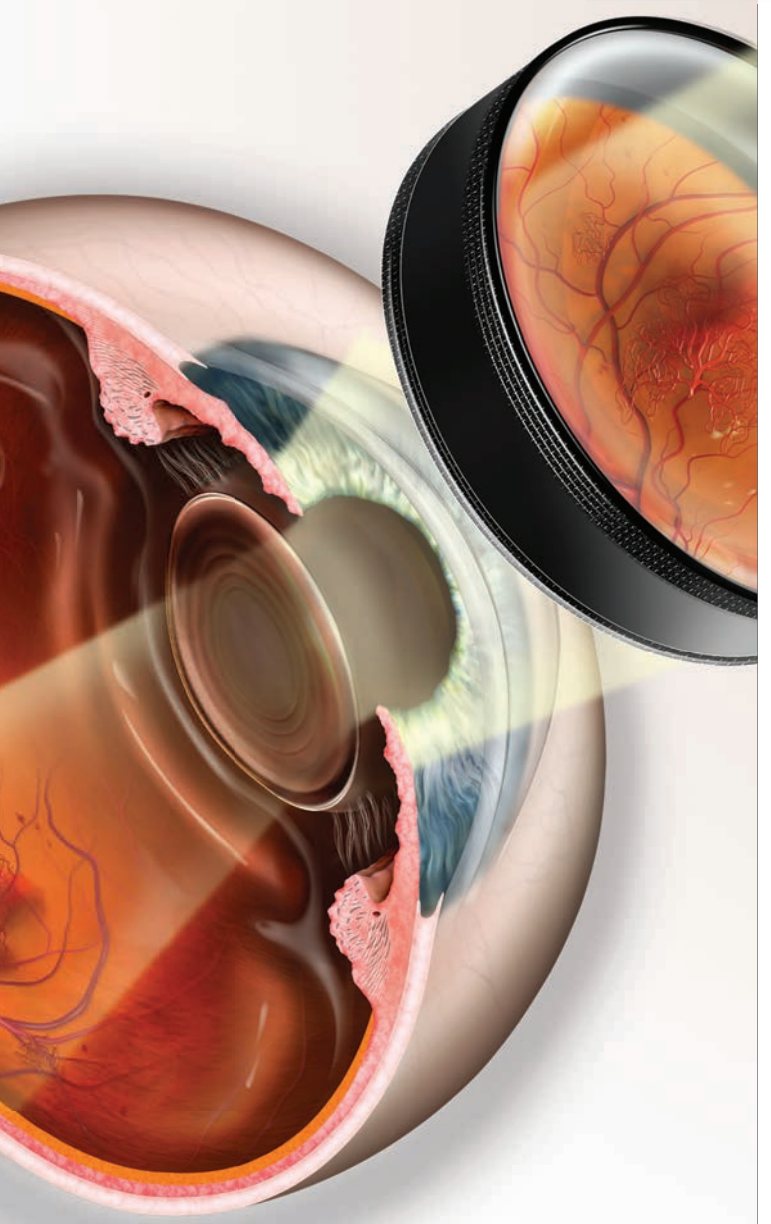

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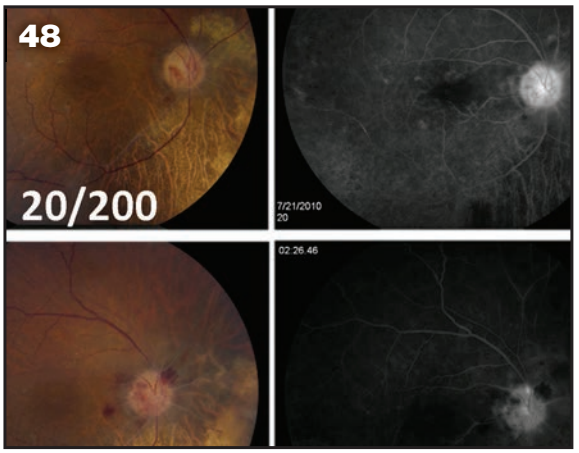

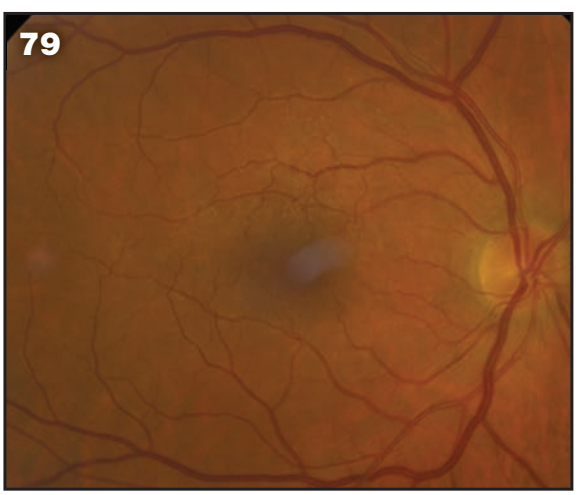

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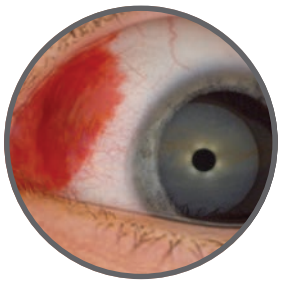

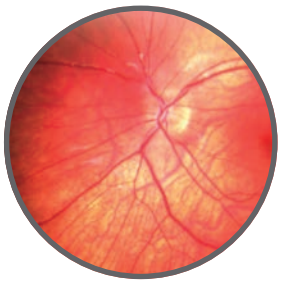

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Advances in Digital Retinal Photography

A look at the upgrades and add-ons that 2015 has brought to non-mydriatic retinal cameras.

Walter Bethke, Managing Editor

From screening for retinal pathology to acquiring images for use in telemedicine applications, non-mydriatic fundus cameras are a mainstay in the exam suite. In an effort to keep users on the cutting edge of retinal photography, companies constantly upgrade their camera systems and produce add-on hardware that increases their functionality. Here's a look at the latest upgrades and updates to non-mydriatic cameras that have arrived so far in 2015.

Kowa WX3D and Nonmyd 7

Both the WX3D and Nonmyd 7 cameras from Kowa received upgrades to their imaging systems in June, bringing them up to 24-megapixel resolution.

"The 24-MP resolution is particularly helpful when the imaging is in the macular area," says Kowa's Rick Torney, "since doctors are focused on catching abnormalities such as AMD in the macula area earlier. They need to be able to blow up that area a good deal, and doing that takes a lot of megapixels.

"The main feature of the WX is one-shot stereo imaging," Mr. Torney adds. "It has two light pathways that allow two images taken non-mydriatically to come together in stereo. In the stereo view you get a 3-D view of the optic nerve and, after you've taken several of them, you can align them, stack them and then play them back in a video to see if a patient's glaucoma condition has progressed or swelling in the optic nerve head has decreased." Mr. Torney says capturing the stereo images in non-dilated pupils is possible in about 95 percent of patients, though in some patients, "they just have too small a pupil size."

The Kowa WX3D allows users to perform one-shot stereo imaging of the retina.

Mr. Torney says users of Kowa's older Nonmyd systems, such as those that used 2 or 5 MP, might be more inclined to upgrade to the higher resolution. "The real advantages would be for the people taking images in the 1-, 2- or 5-MP range," he says. "Going to 24 will make a difference for them. So, really, for the upgrade, the Nonmyd 2 MP and Nonmyd 7 MP are essentially the same; you put a different camera back on them to get the higher resolution. If the user had a WX, he could put the higher-resolution camera back on it now. However, there would be few who'd choose to go that route since the earlier WX cameras had 12-megapixel resolution, so going to 24 MP wouldn't be a huge advantage."

To upgrade the Nonmyd 7 camera system would involve purchasing a new computer that's able to run the Windows 7 operating system, the software and a new camera, and would cost between $4,500 and $5,500. If a user wanted to upgrade the WX to 24 MP, it would cost about $1,500 since he already has most of the necessary equipment. For information, visit kowa-usa.com.

An NSAID formulated to penetrate target ocular tissues

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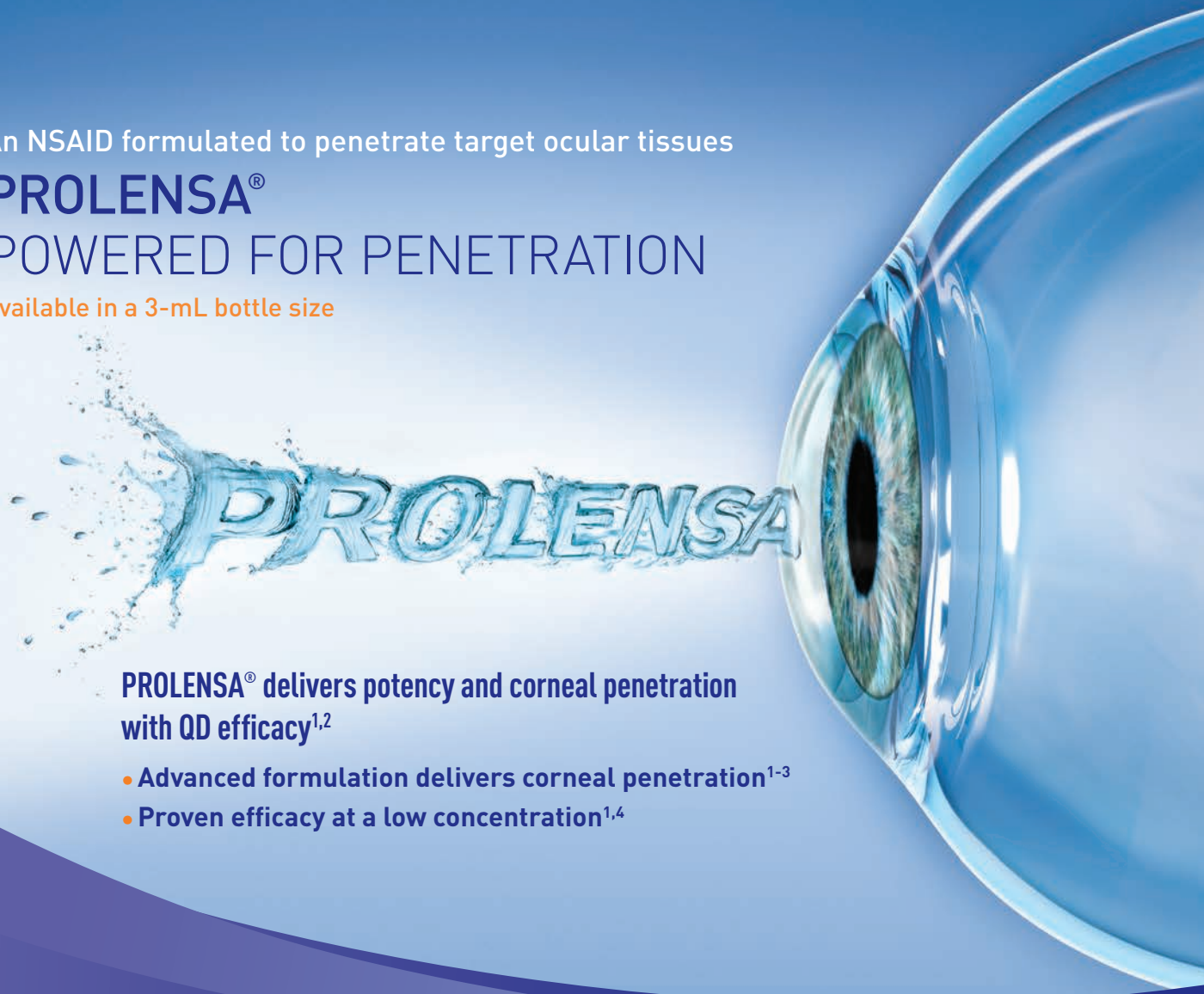


PROLENSA® delivers potency and corneal penetration with QD efficacy[1,2]

- **Advanced formulation delivers corneal penetration[1-3]**
- **Proven efficacy at a low concentration[1,4]**

INDICATIONS AND USAGE

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

IMPORTANT SAFETY INFORMATION ABOUT PROLENSA®

Warnings and Precautions

- Sulfite allergic reactions
- Slow or delayed healing
- Potential for cross-sensitivity
- Increased bleeding of ocular tissues
- Corneal effects, including keratitis
- Contact lens wear

Adverse Reactions

The most commonly reported adverse reactions in 3%-8% of patients were anterior chamber inflammation, foreign body sensation, eye pain, photophobia, and blurred vision.

Please see brief summary of Prescribing Information on adjacent page.

References: 1. PROLENSA® Prescribing Information, April 2013. **2.** Data on file, Bausch & Lomb Incorporated. **3.** Baklayan GA, Patterson HM, Song CK, Gow JA, McNamara TR. 24-hour evaluation of the ocular distribution of 14C-labeled bromfenac following topical instillation into the eyes of New Zealand White rabbits. *J Ocul Pharmacol Ther*. 2008;24(4):392-398. **4.** BROMDAY® Prescribing Information, October 2012.

BAUSCH + LOMB

PROLENSA®
(bromfenac ophthalmic solution) 0.07%

Brief Summary

INDICATIONS AND USAGE

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

DOSAGE AND ADMINISTRATION

Recommended Dosing

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

Use with Other Topical Ophthalmic Medications

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

CONTRAINDICATIONS

None

WARNINGS AND PRECAUTIONS

Sulfite Allergic Reactions

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

Slow or Delayed Healing

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

Potential for Cross-Sensitivity

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

Increased Bleeding Time

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

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

Keratitis and Corneal Reactions

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

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

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

Contact Lens Wear

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

ADVERSE REACTIONS

Clinical Trial Experience

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

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

USE IN SPECIFIC POPULATIONS

Pregnancy

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

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

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

Nursing Mothers

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

Pediatric Use

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

Geriatric Use

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

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis and Impairment of Fertility

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

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

Bromfenac did not impair fertility when administered orally to male and female rats at doses up to 0.9 mg/kg/day and 0.3 mg/kg/day, respectively (systemic exposure 90 and 30 times the predicted human exposure, respectively).

PATIENT COUNSELING INFORMATION

Slowed or Delayed Healing

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

Sterility of Dropper Tip

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

Concomitant Use of Contact Lenses

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

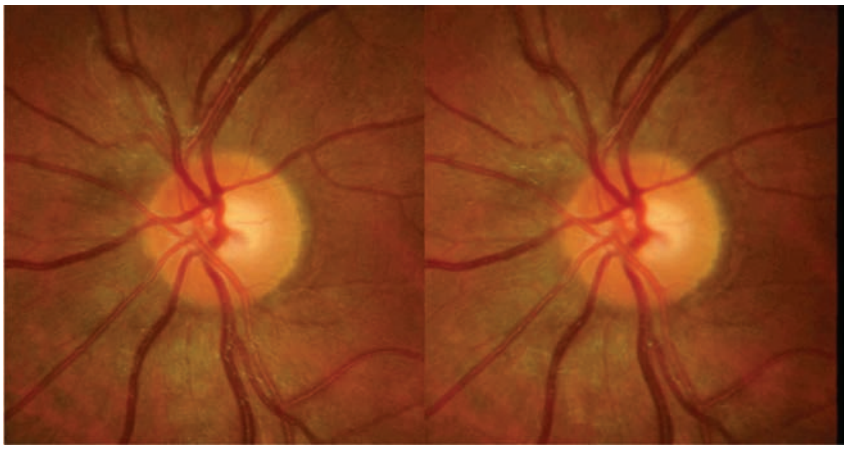
Concomitant Topical Ocular Therapy

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

Rx Only

Manufactured by: Bausch & Lomb Incorporated, Tampa, FL 33637
Under license from:
Senju Pharmaceuticals Co., Ltd.
Osaka, Japan 541-0046

9317600
US/PRA/14/0024



Stereo images of the optic nerve head taken by the Kowa WX3D can be "stacked" on top of each other and then played back as a movie to illustrate subtle changes over time.

Canon CR-2 AF

This is a new retinal camera that was just launched in late May, and is equipped with several features that may help users acquire better patient images.

Since many patients have issues that may make images appear less than ideal, such as early cataract, the CR-2 AF has a contrast-enhancement function. "Contrast enhancement examines the structures of the eye and then increases the contrast as needed," says Canon's Jim Laux. "This can allow the user to see such things as the edges of the veins and arteries more cleanly. As a corollary to this, the camera also provides auto exposure. It does this by reflecting an infrared signal off the back of the eye and using that exposure information to drive the camera settings to generate an optimal image. This means you don't need a highly skilled technician who, in the past, would have to bracket the exposure by changing the ISO and flash intensity to take different photos at different exposure levels in order to get the level of contrast the doctor wants. Because of this, the user can do more with less flash intensity, which avoids pupil shrinkage due to a bright flash or photophobia, and generally makes it more comfortable for the patient."

The camera also has a function called auto fundus, which is basically the camera's way of confirming it's got the fundus in sharp focus and is ready to begin shooting. "It works kind of like the way you used a microscope in biology class in high school," explains Mr. Laux. "When using a microscope to look at a slide, you'd start with the lowest magnification to get it semi-focused, and then increase it until the subject was in focus. Similarly, in the CR-2 AF, you begin with a split image of the eye in the camera. When the eye is focused, the upper and lower halves of the image come together and form a single picture. When that happens, the camera knows it's in focus and it automatically jumps to high magnification and moves the imaging to the back of the eye. This means the technician doesn't need to know when to push that button—it automatically takes him there. This is helpful because this can be where some of the stumbling occurs in image acquisition—if the patient suddenly moves and the user needs to go backward, you can press a button manually and do the rough alignment again, rather than having to go back to the very beginning of the whole process. Also, if a technician is a little uncomfortable determining if it's a good time to take the picture, he just looks at two small dots on the screen. When the dots are in a box on the screen and in focus, the camera automatically takes the picture because it knows it's in focus." The camera can get an image through pupils 2.7 mm in diameter or a bit smaller; it also comes with image management software that allows users to save high-resolution images for use in an electronic medical records system.

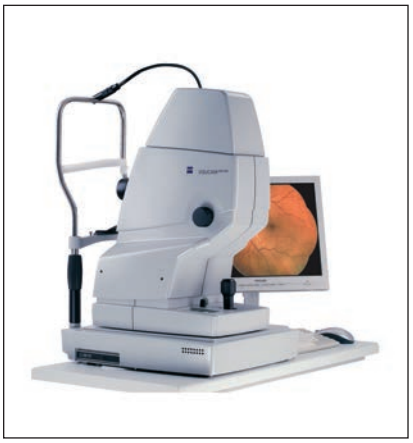
The Canon CR-2 AF's auto-exposure feature helps users get the right shot the first time.

The base price of the CR-2 AF is $15,450. For information, visit usa.canon.com.

Zeiss Visucam Pro NM

The Visucam Pro NM will now feature fundus autofluorescence, a function that, until now, was only available on the higher-end model of the Visucam.

"Fundus autofluorescence lets physicians see the condition of the RPE layer," says Zeiss' Sunny Virmani. "Certain parts of the retina will fluoresce in different ways based on their condition. In a normal retina, the fundus autofluorescence image would look like a black and white retinal image. However, if there's any activity going on in parts of the retinal pigment epithelium, they'll display as bright. The bright areas are an indication that those areas are



The Zeiss Visucam Pro NM now comes equipped with fundus autofluorescence.

in danger of dying. If there are any areas of geographic atrophy or RPE atrophy, they will look dark." Fundus autofluorescence also aids in the visualization of retinal detachment and central serous chorioretinopathy; the detection of hereditary dystrophies, such as Stargardt's and Best's disease; and the detection of changes due to hydroxychloroquine toxicity.

In addition to traditional non-mydriatic fundus photos and fundus autofluorescence, the Pro NM has autofocus, auto-flash and allows users to image the anterior segment.

For information on the Visucam Pro NM, visit zeiss.com.

Ezer EFC-5200/5200 FFA

Ezer, which distributes its cameras through U.S. Ophthalmic (Doral, Fla.), introduced two new cameras in June, the EFC-5200 and the 5200 FFA, with the main difference between the two being that the latter can perform fluorescein angiography, indocyanine green angiography and fundus autofluorescence.

Both cameras can shoot the retina through a 3.3-mm pupil, and have a nine-dot internal fixation target to use for creating mosaic images of the retina. "The 5200 FFA uses optical electromechanical integration to combine digital fluorescein fundus photography, digital video capture and image processing," says U.S. Ophthalmic's Henry Morales. "It's capable of displaying both the continuous, real-time, high-quality color fundus photography image as well as the fluorescein monochrome fundus video image. The color images and retinal fluorescence photos can then be stored and are available for image processing, report generation, lesion measurement, graphical editing and for use with electronic medical record systems."

For information on either camera system, visit usophthalmic.com.

Canon's Mr. Laux says the new features on fundus cameras remind him of the advances in prenatal ultrasound. "When my wife had our first child, the ultrasound was very basic," he says. "Now, however, these ultrasounds are more like pictures of the child. Fundus photography is similar. With signal processing, higher-resolution cameras and the way the image is handled after it's taken, retinal photography has become a more valuable tool." REVIEW

Non-mydriatic Retinal Cameras

Make and Model	Website
Canon CR-2 AF	usa.canon.com
Centervue DRS	centervue.com
Ezer/U.S. Ophthalmic EFC-5200	usophthalmic.com
Kowa WX3D/Nonmyd 7	kowa-usa.com
Nidek AFC-330	nidek.com
Optovue iCam	optovue.com
Topcon TRC-NW400	topconmedical.com
Carl Zeiss Meditec Visucam	zeiss.com

(continued from page 5)

death and the loss of visual function in the mice. Inhibiting phagocytosis with a compound had a similar effect. The microglia seem to ignore cone photoreceptors, which fits with the known early course of retinitis pigmentosa.

"These findings suggest that therapeutic strategies that inhibit microglial activation may help decelerate the rate of rod photoreceptor degeneration and preserve vision," Dr. Wong said.

What triggers microglia to go on this destructive feeding frenzy? Dr. Wong and colleagues found evidence that photoreceptors carrying mutations undergo physiological stress. The stress then triggers them to secrete chemicals dubbed "find me" signals, which attracts microglia into the retinal layer. Once there, the microglia probe the photoreceptors repeatedly, exposing themselves to "eat me" signals, which then trigger phagocytosis. In response to all the feasting, the microglia become activated. That is, they send out their own signals to call other microglia to the scene and they release substances that promote inflammation.

Other potential treatments for retinitis pigmentosa, such as gene therapy, are progressing, but are not without challenges. Gene therapy requires replacing defective genes with functional genes, yet more than 50 distinct genes have been linked to the disease in different families, so there's no one-size-fits-all gene therapy. A therapy targeting microglia might complement gene therapy because it's an approach that's independent of the specific genetic cause of retinitis pigmentosa, said Dr. Wong.

A clinical trial is already under way at NEI to see if the anti-inflammatory drug minocycline can block the activation of microglia and help slow the progression of retinitis pigmentosa. The trial is currently recruiting participants. For more information, see https://www.clinicaltrials.gov/ct2/show/NCT02140164. REVIEW

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What You Should Know About the VBPM

The Value-Based Payment Modifer is one of three "quality and cost" programs that may affect your practice reimbursements.

Q Does the Centers for Medicare & Medicaid Services intend to change the reimbursement structure for physicians?

A Yes. On January 26, 2015, CMS delivered a strong message to providers regarding future payments for the care they deliver. Several fact sheets and press releases, including "*Better Care, Smarter Spending, Healthier People: Paying Providers for Value, Not Volume*," describe new health-care payment models intended to improve health-care quality and reduce cost.

Q Is there a structure and timeline to this new payment system?

A The framework adopted by the Department of Health and Human Services categorizes how payments are made to providers under this initiative. The categories are:

- Category 1–fee-for-service with no link of payment to quality (*current system*);
- Category 2–fee-for-service with a link of payment to quality;
- Category 3–alternative payment models built on fee-for-service architecture; and
- Category 4–population-based payment.

The description for Category 2 indicates "*at least a portion of payments varies based on the quality and efficiency of health care delivery*." The majority of eye-care providers will fall into Category 2 with a small number in Category 3.

HHS expects to have 85 percent of Medicare fee-for-service payments in Category 2 or Category 3 by 2016 and increase this to 90 percent by 2018. HHS cites the immediate need for providers to make changes in day-to-day operations that will improve quality and reduce cost.

Q How does the Value-Based Payment Modifier fit into the new payment structure?

A The VBPM is a "shared savings" program and fits into Category 2. The Affordable Care Act mandated that CMS include cost and quality data in calculating physician reimbursements by 2015. The VBPM is a "quality and cost" program. It is the third quality program that affects reimbursements for individual eligible professionals and group practices. The other two programs are Physician Quality Reporting System and the Electronic Health Record programs. The VBPM links directly to the PQRS program and rewards or penalizes providers for the quality and cost of care provided. No registration or specific attestation for VBPM is required and no exemptions apply.

Q Who is included in the VBPM program?

A The VBPM program includes all eligible professionals. The Social Security Act defines eligible professionals and includes physicians and non-physician practitioners. Within eye care, they include: ophthalmologists; optometrists; osteopaths; physician assistants; nurse practitioners; anesthesiologists; CRNAs; and audiologists (for those eye-care practices that offer hearing services).

Q How is the cost component calculated?

A The cost composite score equally weighs two costs. The first cost is the *total* per capita cost for patients; it includes payments under Medicare Parts A and B. The second

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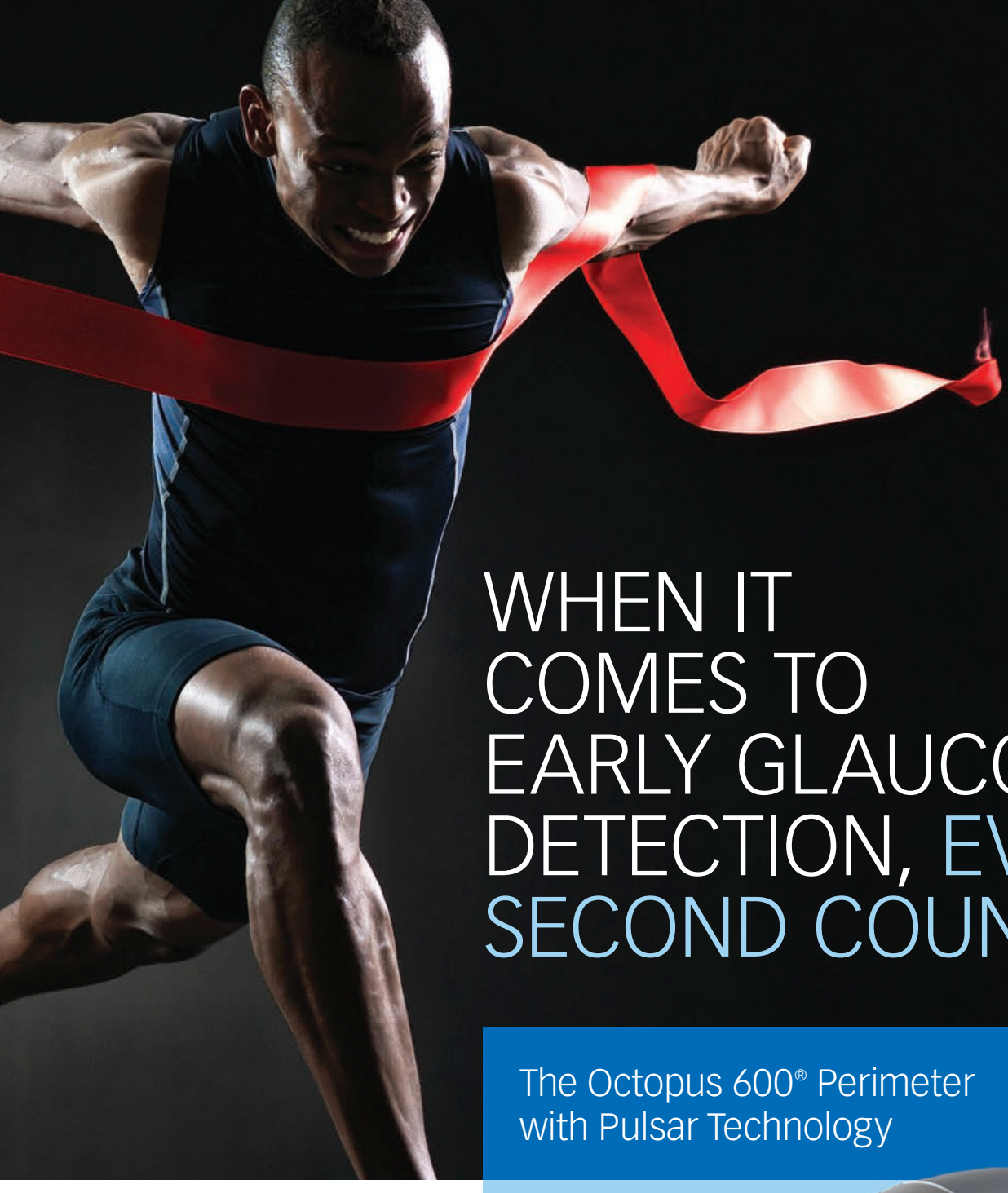

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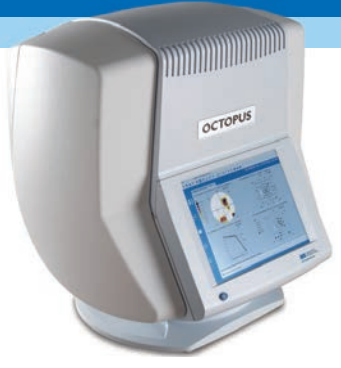

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cost is the per capita cost for beneficiaries with diabetes, coronary artery disease, heart failure and chronic obstructive pulmonary disease. The process used to assign the per capita cost per patient is the same process used to assign beneficiaries to Medicare Shared Savings Accountable Care Organizations. The majority of beneficiaries will be "assigned" to primary-care providers. However, it is possible that some will be assigned to specialty-care providers if the beneficiary received the majority of primary-care services from other eligible professionals.

Q How will a provider be analyzed?

A The simple analysis of the program indicates that eligible providers successfully participating in the PQRS program and considered high-quality and low-cost providers will be eligible for a VBPM bonus. The VBPM applies at the Tax Identification Number level of an individual or a group practice.

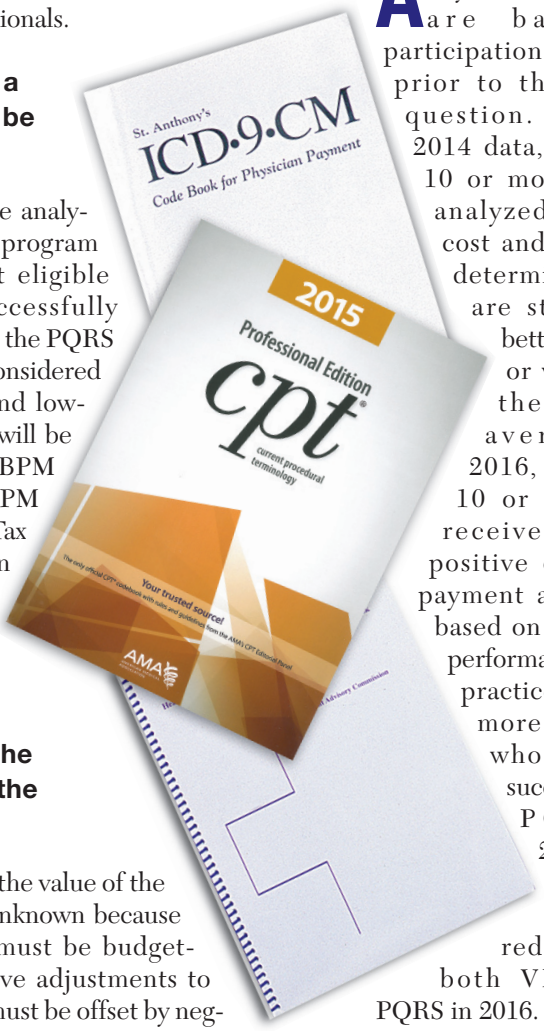
Q What is the value of the bonus?

A Currently the value of the bonus is unknown because the program must be budget-neutral; positive adjustments to those eligible must be offset by negative adjustments to others, and the bonus cannot be calculated until the end of the PQRS reporting period.

Reimbursement adjustments, both upward and downward, associated with the VBPM by CMS will be phased in from 2015 to 2017. Reimbursement adjustments affect only physician payments under the Medicare Physician Fee Schedule. It applies to Medicare paid amounts, so co-insurance amounts are not affected.

Q When do the payment adjustments begin?

A Payment adjustments are based on participation two years prior to the year in question. Utilizing 2014 data, groups of 10 or more will be analyzed on their cost and quality to determine if they are statistically better, the same or worse than the national average. In 2016, groups of 10 or more will receive either a positive or neutral payment adjustment based on their 2014 performance. Group practices of 10 or more providers who were not successful with PQRS in 2014 will be assessed a 2-percent reduction for both VBPM and PQRS in 2016.



In 2015, all providers are subject to the VBPM. Performance in 2015 affects reimbursements in 2017. Failure with PQRS in 2015 results in a 2-percent PQRS penalty and a 2- to 4-percent VBPM penalty, depending on the size of the practice, in 2017.

Q Is there an accessible report that contains practice-specific feedback associated with the VBPM?

A Quality Resource and Use Reports, also known as Physician Feedback reports, contain quality-of-care and cost performance rates on measures that will be used to compute the VBPM. To access your report, you can log in to the CMS Enterprise Portal with an Individuals Authorized to Access the CMS Computer Services (IACS) account. The 2013 reports are currently available; they provide information as to how you rate under the VBPM. The 2014 interim reports were released in April 2015 and contain cost information for 2014 but do not contain quality data.

Q Why are changes to the existing reimbursement model necessary?

A The existing fee-for-service methodology is not sustainable. According to the *2014 Trustee Report*, the Medicare Hospital Insurance Trust Fund will be depleted by 2030. Initiatives that move away from the fee-for-service method to alternative payment methods are the goal of HHS and private payers. The VBPM is one component of the new payment framework affecting the future of reimbursements. REVIEW

Ms. McCune is vice president of the Corcoran Consulting Group. Contact her at DMcCune@corcoranccg.com.

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CONTINUOUS THERAPEUTIC EFFECT THROUGHOUT SURGERY[1]

IMPORTANT SAFETY INFORMATION

OMIDRIA must be added to irrigation solution prior to intraocular use.

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

Systemic exposure of phenylephrine may cause elevations in blood pressure.

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

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

Use of OMIDRIA in children has not been established.

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

You are encouraged to report suspected adverse reactions to the FDA. Visit www.fda.gov/medwatch, or call 1-800-FDA-1088.

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NO EFFECT ON PHYSICIAN FEES OR HEALTHCARE SYSTEM[3,4]

INDICATIONS AND USAGE

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

Reimbursement information is based on Omeros data on file. Omeros does not guarantee reimbursement for any particular patient. Contact 1-844-OMEROS1 (1-844-663-7671) for more information about how to submit for OMIDRIA reimbursement.

References: 1. OMIDRIA [package insert]. Seattle, WA: Omeros Corporation; 2015. **2.** Omeros data on file. **3.** Federal Register, April 7, 2000, 65 FR. **4.** Kaiser Family Foundation analysis of the CMS Medicare Current Beneficiary Survey Cost and Use File, 2010. **5.** Lindstrom RL, et al. *Clin Ophthalmol.* 2014;8:1735-1744. **6.** Katsev D, Katsev C, Pinnow J. Intracameral ketorolac concentration after topical ketorolac administration prior to cataract surgery. Electronic poster session presented at: American Society of Cataract and Refractive Surgery. 2015 ASCRS-ASOA Symposium and Congress; 2015 Apr 17-21; San Diego, CA. Study sponsored by Omeros Corporation. **7.** Florio V, Cowan L, Prusakiewicz JJ, Bentley E, Waterbury LD. Ocular tissue distribution of ketorolac after administration of OMS302 to dogs during IOL replacement. Electronic poster session presented at: American Society of Cataract and Refractive Surgery. 2015 ASCRS-ASOA Symposium and Congress; 2015 April 17-21; San Diego, CA. **8.** Waterbury LD, et al. *Curr Med Res Opin.* 2006;22:1133-1140. **9.** Hovanesian JA, et al. *J Cataract Refract Surg.* 2015 [in press].

What you can expect with OMIDRIA®

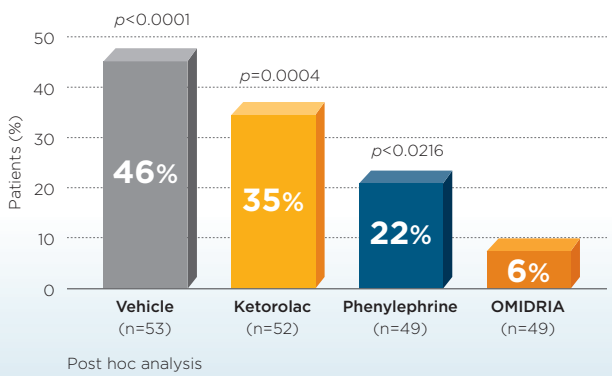
(phenylephrine and ketorolac injection) 1% / 0.3%

FDA-approved OMIDRIA is added to the irrigation solution used during cataract surgery and lens replacement for direct and continuous intracameral delivery of mydriatic and NSAID therapy.[1]

SUPERIOR TO PHENYLEPHRINE OR KETOROLAC ALONE*

In a phase 2b clinical trial, OMIDRIA was 4 to 6 times more effective in preventing pupil diameter of <6 mm than intracameral phenylephrine or ketorolac.[2]

Percent of patients with pupil diameter <6 mm at any time during surgery[2,*]

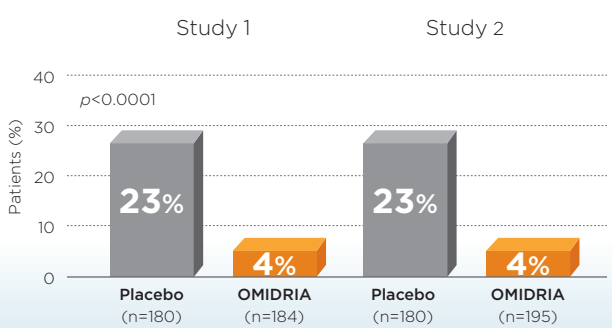


Post hoc analysis

CONSISTENTLY MAINTAINS PUPIL DIAMETER[2,5]

In pivotal phase 3 clinical trials (N=808) in which all patients received standard topical mydriatics preoperatively, OMIDRIA was superior to placebo across all assessments of pupil size. In fact, 96% of OMIDRIA-treated patients had pupil diameter ≥6 mm at the time of lens implantation.[1,2,5]

Pupil diameter <6 mm at start of lens implantation[2,5]



TOPICAL MEDICATIONS CAN WASH OUT[6]

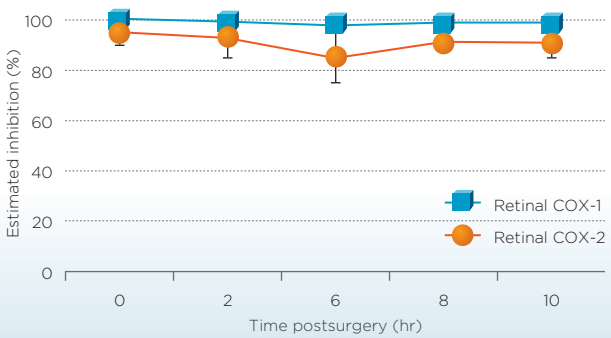
Topical ketorolac may not go the distance. In fact, in a study evaluating the presence of preoperative topical ketorolac at the end of cataract surgery:

100% of patients receiving **topical** ketorolac preoperatively had nominal or undetectable ketorolac levels at the end of the procedure.[6,†]

WITH OMIDRIA, NSAID LEVELS MAINTAINED THROUGHOUT SURGERY[1]

OMIDRIA is delivered in the irrigation solution continuously during surgery. In a study of conventional phacoemulsification and lens replacement performed with OMIDRIA in 20 canines, ketorolac levels measured throughout the structures of the eye were sufficient to ablate COX-1 and -2 pathways for at least 10 hours postoperatively.[7,8,‡]

Ketorolac tissue levels inhibited COX-1 and COX-2 pathways for at least 10 hours postoperatively[7,8]



OMIDRIA EFFECTIVELY REDUCES POSTOPERATIVE OCULAR PAIN[1]

In two pivotal phase 3 clinical trials[§] in which all patients received standard anesthetic agents preoperatively, patients treated with OMIDRIA were:

50% more likely to be pain-free up to 12 hours after surgery[9]

50% less likely to have moderate-to-severe pain[9] and...

30% less likely to use analgesics on day of surgery[9]

Have confidence in reimbursement across payers

The Centers for Medicare and Medicaid Services (CMS) granted pass-through reimbursement status to OMIDRIA. Under the Outpatient Prospective Payment System, pass-through products are paid separately by CMS.

- No co-payment in hospital outpatient departments (HOPDs)
- 20% co-payment in ambulatory surgery centers (ASCs)
  - Approximately 90% of Medicare Part B patients have some form of supplemental insurance, which covers co-payments

OMIDRIA is covered by **100% of Medicare contractors**

as well as by Medicare Advantage and commercial payers.

To ensure that patients under all payer types can benefit from OMIDRIA, Omeros is establishing a patient assistance program and a commercial co-payment program.

Positive effect on facility fees[3,4]

Following expiration of its pass-through status on December 31, 2017, OMIDRIA likely will be included in the bundled facility fees for cataract surgery. As a result, those fees will increase by an amount that correlates with the magnitude of OMIDRIA utilization during its pass-through status.

No effect on physician fees[3,4]

Payment to the surgeon for cataract surgery under Medicare's Physician Fee Schedule will be unaffected by the use of OMIDRIA or the pass-through payments related to OMIDRIA, now and in the future.

No effect on the healthcare system[3,4]

The pass-through regulation is budget-neutral to the healthcare system. To the extent that ophthalmic surgeons/facilities elect not to access pass-through payments, the funds set aside will be used by other specialties. Any remaining amount will be lost to the system.

Reimbursable across surgical facility types[3,4]

OMIDRIA is also on the Federal Supply Schedule and on 340B formularies. In partnership with ophthalmic surgeons and their teams, Omeros offers billing support services (1-844-OMEROS1) and is establishing an OMIDRIA-focused:

- **reimbursement hotline**
- **patient assistance program based on financial need**
- **co-payment program for commercial beneficiaries**

TO FIND OUT MORE ABOUT OMIDRIA, GO TO OMIDRIA.COM

IMPORTANT SAFETY INFORMATION

OMIDRIA must be added to irrigation solution prior to intraocular use.

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

Systemic exposure of phenylephrine may cause elevations in blood pressure.

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

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

Use of OMIDRIA in children has not been established.

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

You are encouraged to report suspected adverse reactions to the FDA. Visit www.fda.gov/medwatch, or call 1-800-FDA-1088.

INDICATIONS AND USAGE

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

* Randomized, double-masked trial using a 4-arm factorial design to show that OMIDRIA is superior to either agent alone.[2]

† Study of ketorolac levels in aqueous humor of 14 patients at the start and end of cataract surgery following multiday preoperative topical ketorolac administration.[6]

‡ Canine study assessing ketorolac levels in retina, choroid, ciliary body/iris, cornea, vitreous, lens capsule, and sclera samples following cataract surgery using OMIDRIA. COX-1 and COX-2 inhibition was estimated using IC50 values.[7,8]

§ Pooled analyses of post hoc analysis (Study 1) and secondary endpoint (Study 2).[9]

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

Retinal Imaging: The State of the Art

Christopher Kent, Senior Editor

Technology for scanning the back of the eye is outrunning our ability to treat—but probably not for long.

When it comes to imaging the retina, there's a kind of "catch-22" dance that takes place between new technology and clinical usefulness. New technology often results in the discovery of new information, but unless that information impacts the management of a treatable disease, clinicians are not motivated to purchase and use the technology. Yet without the data generated through clinical use, practical connections to treatable disease can't be demonstrated.

Somehow, despite this awkward situation, new technologies continue to be developed, and—in large part thanks to clinical trials—many do eventually become clinically relevant. Here, four retina experts share their experience with current retinal imaging technologies and discuss how several new technologies in the pipeline may impact clinical care.

The OCT Factor

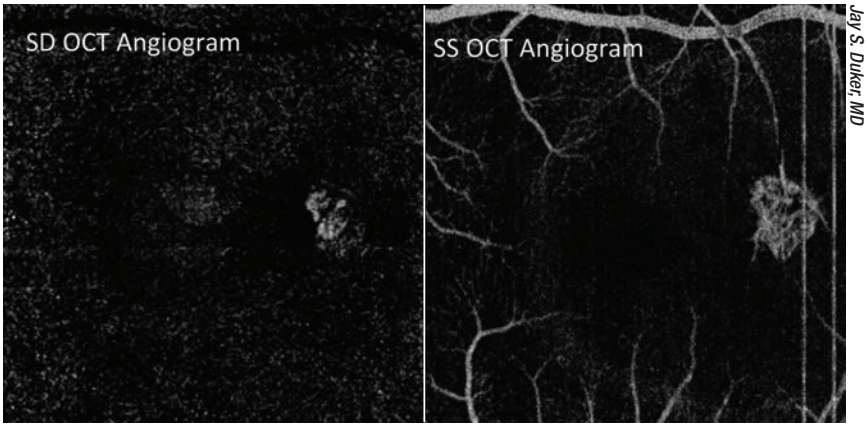
"By far, the most important clinical utility for imaging in retinal practice is to help us diagnose and manage disease," says Jay S. Duker, MD, director of the New England Eye Center and professor and chair of the department of ophthalmology at Tufts Medical Center and the Tufts University School of Medicine in Boston. "The primary imaging tool used in retinal practice today is optical coherence tomography. One of the reasons OCT is so ingrained in clinical practice right now is that the treatment paradigms for diseases like wet macular degeneration, diabetic macular edema and retinal vein occlusion are all based around the presence and quantification of abnormal collections of fluid in or under the retina. For the past 10 or 15 years we've been able to treat abnormal retinal fluid with medications—first cortisone, now anti-VEGF drugs. We need to be able to tell if our therapies are working. If we didn't have medical treatments that improve fluid leakage in the macula rapidly and measurably, OCT wouldn't be nearly as popular.

"Beyond that, OCT helps us to make diagnoses," he continues. "There are certain diseases that we've come to recognize from OCT scans. The problem at the moment is that not all of those diseases are treatable. For example, I've done a lot of research on choroidal thickness and morphology. But if you ask how many times imaging the choroid changes my diagnosis or my management of patients, the answer is rarely. In contrast, we use OCT to measure fluid in the retina about 40 times a day."

Today, several types of OCT are available (although not all are available in the United States), and several more are in the pipeline. "Ultra-high-resolution OCT refers to OCT with an axial resolution less than 3 µm," says Dr. Duker. "There are three ways to increase OCT resolution. First, axial resolution is inversely proportional to the bandwidth of the light source, so increased axial resolution can be achieved with improved broadband light sources, using any type of OCT system. Second, higher resolution can be achieved by increasing pixel density; to do that, you generally need a faster system. The third way to increase resolution is by oversampling. This means scanning the same area multiple times, very rapidly; any difference between the scans is noise, which the software eliminates.

"There are also three major ways OCT images are created," he continues. "They relate to different ways of detecting reflectance patterns. The first is time-domain, which has been in clinical practices since 2002 and is still in clinical use. In retinal practice that type of OCT has largely been supplanted by spectral-domain systems, available since about 2006. Because there are no moving parts, spectral-domain systems are faster than time-domain. Spectral-domain OCT has become the standard for most retinal specialists at this point.

"Swept-source OCT is an even faster way of detecting those reflection patterns," he says. "The typical time-domain system runs at 400 A-scans per second. Clinically available spectral-domain systems run from 20,000 to 70,000 A-scans per second. A swept-source system made by Topcon (not available in the United States) runs at 100,000 A-scans per second. And we have an investigational swept-source system in our office that runs at 400,000 A-scans per second, built by James G. Fujimoto at the Massachusetts Institute of Technology."



Jay S. Duker, MD

The longer wavelength used in swept-source OCT makes it better able to visualize the choroid than spectral domain OCT. Above: angiograms showing choroidal neovascularization.

Swept-source vs. Spectral

"Swept-source OCT uses a longer wavelength than spectral-domain," notes Philip Rosenfeld, MD, PhD, professor of ophthalmology at Bascom Palmer Eye Institute in Miami and the University of Miami Miller School of Medicine. "The longer wavelength is capable of better penetration into the choroid, and it's able to scan at a faster speed. With increased speed and penetration the choroid can be visualized with greater clarity, compared with spectral-domain technology."

Dr. Duker agrees. "With spectral-domain there's an effect called sensitivity roll-off," he says. "That means the deeper you image, the worse the signal-to-noise ratio. Swept-source OCT doesn't have that problem."

Dr. Rosenfeld says he believes this is the greatest advantage of this imaging technology. "The holy grail for macular degeneration is what's happening to the choriocapillaris," he notes. "It's a thin, microvascular layer right under the retinal pigment epithelium. We believe macular degeneration is a disease of the photoreceptor-retinal pigment epithelium-choriocapillaris complex. We've been able to look at the photoreceptors using OCT and adaptive optics; but we haven't really been able to study the RPE well in high resolution, and until now, no one has been able to visualize the choriocapillaris. Professor Fujimoto has a paper coming out suggesting that changes in the choriocapillaris may be some of the first vascular changes that we'll see in the progression of macular degeneration. Once we come up with a therapy, particularly for dry macular degeneration, we're going to be looking at the choriocapillaris to see whether these therapies are having a beneficial effect."

Dr. Rosenfeld points out that the differences between the specific instruments are more complicated than simply whether the technology is spectral-domain or swept-source. "Different instruments are using different algorithms to analyze the signals they detect," he explains. "All the companies are trying to show that their algorithms are better than their competitors'. But it's becoming clear that it's not just the algorithm that matters; it's also the design of the instrument using it. The only way to determine that one is better than the other will be to test that instrument on a particular disease and see which instrument generates the best images that are relevant to that disease and clinical practice."

SriniVas R. Sadda, MD, president and chief scientific officer of the Doheny Eye institute, and the Stephen J. Ryan-Arnold and Mable Beckman endowed chair and professor of ophthalmology at the University of Cali-

The Shifting Purpose of Retinal Imaging

Steve Charles, MD, FACS, founder of the Charles Retina Institute in Memphis, Tenn., notes that the purpose of retinal imaging has changed in recent years as treatments have evolved. "In the past, our goal was to find a lesion using angiography or OCT and then target that with some destructive form of energy, laser or photodynamic therapy," he says. "Feeder-vessel therapy is an example of that approach. That's what I call visualization-based anatomic or structural targeting.

"That approach served to eliminate some problematic tissues or vessels, but it wasn't very effective," he continues. "Now, we do molecular targeting using drugs such as ranibizumab and aflibercept. Those work incredibly well and have virtually no side effects. Consider Protocol T, comparing anti-VEGF agents for diabetic retinopathy, recently released by DRCR.net. Anti-VEGF therapy can be considered molecular targeting; it works phenomenally well when managing diabetic retinopathy. It is also incredibly effective for macular degeneration, retinal vein occlusion or retinopathy of prematurity. So the idea of using imaging for targeting or sub-group classification doesn't reflect the reality of today's treatments."

Dr. Charles notes that imaging companies and their physician advocates still promote the idea that it's crucial to locate problematic ischemic areas, vascular leakage or neovascularization with better and better images. "It's become an imaging ritual," he says. "That's part of the philosophy behind wide-field angiography—to locate ischemic areas in the periphery and ablate them with targeted laser photocoagulation. The reality is, this doesn't impact outcomes. That's not the direction things are moving."

—CK

fornia, Los Angeles, specializes in the evaluation of new imaging hardware and technologies; he runs a software engineering lab that develops new algorithms to analyze images automatically, and also runs an ophthalmological image-reading center. He notes that the advantages of swept-source OCT over spectral-domain are only incremental. "Spectral-domain represented a massive jump from time-domain, in terms of resolution and speed, which added a wealth of additional information about the retina and deeper structures. Having said that, though, I think swept-source is an important advance."

Dr. Sadda says that his group has worked with a prototype swept-source OCT device from Carl Zeiss Meditec in the past, and more recently with a Topcon swept-source OCT unit as part of an approved research protocol. "You get a deeper penetration with swept-source, and looking at the choroid is pretty spectacular," he says. "There may be other applications, such as imaging tumors, where swept-source has such an advantage over spectral-domain that will help it gain traction."

Is More Detail Better?

The more advanced versions of OCT definitely make it possible to see finer details of the retina and its layers. But how much of an advantage is that to the clinician?

"From a clinical utility standpoint, it's hard to show that one version of OCT is better than the other for most clinical situations," says Dr. Duker. "As already noted, the number-one use for OCT in retinal practice today is measuring fluid in or under the retina, and you can do that even with a time-domain system. Image quality is definitely better with spectral-domain, which is the reason most retina specialists in the United States now use spectral-domain, but around the world there are still more time-domain systems in use than spectral-domain."

Dr. Duker notes that better resolution and depth has some current benefits, depending on your purpose. "It's well-known that there's a very good correlation between nerve fiber layer thickness and glaucoma," he says. "And, it may turn out that ganglion cell layer thickness correlates well with visual field findings. But it's less clear that measuring other layers of the retina will help us to better manage retinal disease. There are examples where it appears that measuring the ganglion cell layer may help us manage certain neuro-ophthalmic diseases, and we've always been interested in measuring the outer retina—the photoreceptors—because that's the source of our vision. However, measuring the photoreceptors is still problematic because the photoreceptor layer is hard to quantify it when it's abnormal; the software has a hard time correctly segmenting the layers.

"Of course, we can still do a qualitative assessment," he adds. "We can judge the general appearance of a scan. For example, we may look at the external limiting membrane in a scan and see that the layers are disrupted, which will probably correlate to poor visual function. But without a way to quantify that, its usefulness is limited."

Dr. Sadda also acknowledges that simply getting a sharper picture may not be a major benefit in the clinic today. "We need to have data that's compelling, that says seeing this new level of detail will transform our clinical management," he notes. "Unfortunately, you only get data like that if you're able to use these kinds of technologies in well-designed clinical trials, but to do that they have to be somewhat time-efficient and broadly available." He notes that with some of the new technologies in the pipeline, that's not the case—at least so far.

OCT angiography

"The biggest thing that's happening in OCT right now is OCT angiog-

Discover Strength in efficacy

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

Choose EYLEA® (aflibercept) Injection from the start

Learn about EYLEA at EYLEA.us/ro

INDICATIONS AND IMPORTANT SAFETY INFORMATION

INDICATIONS

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

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

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

ADVERSE REACTIONS

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

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

EYLEA®
(aflibercept) Injection
For Intravitreal Injection

TARGETED SCIENCE

REGENERON

05/2015
LEA-0760

EYLEA® (aflibercept) Injection For Intravitreal Injection

BRIEF SUMMARY OF FULL PRESCRIBING INFORMATION

For complete details, see Full Prescribing Information.

1 INDICATIONS AND USAGE

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

2 DOSAGE AND ADMINISTRATION

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

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

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

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

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

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

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

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

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

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

3 DOSAGE FORMS AND STRENGTHS

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

4 CONTRAINDICATIONS

EYLEA is contraindicated in patients with

- Ocular or periocular infections
- Active intraocular inflammation
- Known hypersensitivity to aflibercept or any of the excipients in EYLEA. Hypersensitivity reactions may manifest as severe intraocular inflammation

5 WARNINGS AND PRECAUTIONS

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

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

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

6 ADVERSE REACTIONS

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

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

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

A total of 2711 patients treated with EYLEA constituted the safety population in seven phase 3 studies. Among those, 2110 patients were treated with the recommended dose of 2 mg. Serious adverse reactions related to the injection procedure have occurred in <0.1% of intravitreal injections with EYLEA including endophthalmitis and retinal detachment. The most common adverse reactions (≥5%) reported in patients receiving EYLEA were conjunctival hemorrhage, eye pain, cataract, vitreous floaters, intraocular pressure increased, and vitreous detachment.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

8 USE IN SPECIFIC POPULATIONS

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

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

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

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

17 PATIENT COUNSELING INFORMATION

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

REGENERON

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

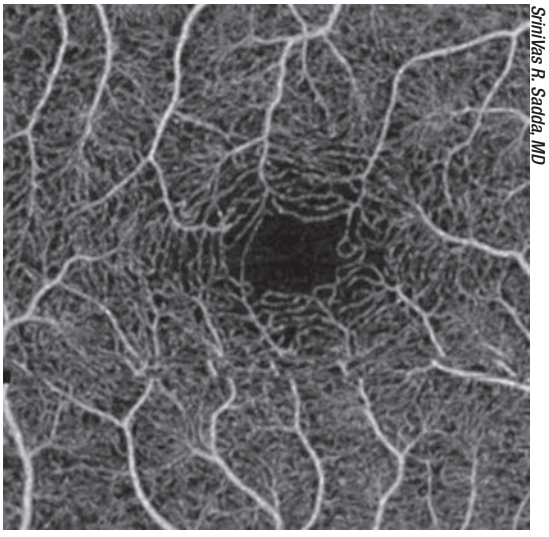
U.S. License Number 1760

Issue Date: March 2015
Initial U.S. Approval: 2011

Regeneron U.S. Patents 7,070,959; 7,303,746; 7,303,747; 7,306,799; 7,374,757; 7,374,758; 7,531,173; 7,608,261; 7,972,598; 8,029,791; 8,092,803; 8,647,842; and other pending patents.

LEA-0721

raphy," says Dr. Duker. "Using OCT with either spectral-domain or swept-source systems, we're now able to create a 3-D representation of the retinal and choroidal vasculature. OCT instruments designed to do this image the same area rapidly and repeatedly; then the software uses the multiple images to eliminate the 'noise.' The only thing left changing between the images will be the blood flow. The machine can then use that information to create a 3-D outline of the retinal vessels. The advantage of this approach is that you can get beautiful images—in some cases, better quality than fluorescein angiography—without a dye injection, in about three seconds."



SriniVas R. Sadda, MD

An OCT angiography scan of a normal subject obtained using a prototype swept-source OCT (not FDA-approved).

"We'll not only be able to see the retinal microvasculature better than we can with fluorescein, but also the choroidal microvasculature, as clearly as we can see it using indocyanine green angiography—perhaps more clearly—without the use of any dyes," adds Dr. Rosenfeld. "We often talk about multimodal imaging—using different techniques such as OCT, autofluorescence, infrared and color imaging. OCT angiography introduces a new term: multidimensional imaging. You can get a 3-D reconstruction of the back of the eye and also look at the change in blood flow by repeating the scans over and over in a very short period of time. That adds the fourth dimension: time. Of course, we're really just beginning to learn about this imaging strategy."

"The clinical relevance of this is something we're trying to figure out now," he adds. "The nice thing about OCT angiography is you can do this intense image analysis but you still have the conventional OCT B-scans to look at, too, so you get the best of both worlds with a single scan pattern."

"The current version of this technology does have several disadvantages," notes Dr. Duker. "First, you need a machine that images rapidly; most machines in current practice will not be able to be retrofitted for this purpose. Second, because there's no dye injection, there's no dye leakage. Dye leakage from abnormal vessels is something that we're interested in looking at in most—though not all—cases. Third, the field of view is very small. In fluorescein angiography, the trend has been to do very wide-field angiograms up to 110 degrees to look at non-perfusion in the retinal periphery. OCT angiography can only image the macula in 3 x 3-, 6 x 6- or 9 x 9-mm cubes. And the larger the area you image with OCT angiography, the more noise you have, and the worse the signal-to-noise ratio. So, you lose image quality."

Dr. Rosenfeld agrees that the current form of OCT angiography has limitations. "Right now we can only get really high-resolution, detailed angiographic images in the central macula," he says. "We get the best images if we scan a 3 x 3-mm area. Fujimoto's instrument can generate beautiful images at 6 x 6 mm; but retina specialists using OCT angiography instruments are just focusing on diseases that impact the central macula, such as diabetic macular edema, wet macular degeneration and macular telangiectasia type II, or MacTel2. MacTel2 is a bilateral disease that only affects the central macula. Since we don't currently have a treatment for MacTel2, this technology is just helping us to better understand the disease and its progression. But once we come up with treatments—and there is a clinical trial going on now with an implant from Neurotech—this technology will let us determine whether there's a change in the microvasculature, without having to perform fluorescein angiography at every visit."

Where OCTA Is Headed

Dr. Rosenfeld points out that conventional OCT was in a position similar to the current state of OCT angiography, back in 2001. "Back then, our group conducted the Phase I and II clinical trials of ranibizumab" he says. "We were the first ones to incorporate OCT into a trial of this type, using it to follow the changes in the retina that occurred within 24 to 48 hours of treatment. Back then everyone was saying we needed to repeat fluorescein angiography every month just to see what was going on. But the data from our studies showed unambiguously that OCT was all we needed to manage patients with wet macular degeneration. We got a lot of push-back for saying this, and it took about three years before using OCT became the standard of care.

"We're at the same stage right now with OCT angiography," he notes. "We don't know how it's going to be used in clinical practice. Some people think that with wet macular degeneration patients we're going to be following the neovascular lesions, even when they're not leaking, to see if the

lesion changes shape and complexity. We could end up treating based on the shape of the neovascular complex, rather than based on leakage and vision loss. People are now designing clinical trials to test this premise. Similarly, some people think we're going to be following the microvasculature in patients with diabetes. Richard Rosen from New York has developed an algorithm that allows you to quantify the capillaries in the central macula. He skeletonizes the images so he can come up with a quantitative evaluation of the ischemic areas. He thinks we're going to be following these areas of ischemia, and if they change in size, we're going to start treatment—before vision is affected and fluid accumulates in the macula. Maybe he's right; maybe not. Those clinical trials are under way, and similar hypotheses are being tested relating to vein occlusion.

"The advantages of OCT angiography go beyond simply increasing speed or resolution," says Dr. Sadda. "We don't do fluorescein angiography on every patient today because it's invasive—we have to inject dye. OCT angiography can be obtained when you're getting an OCT on the patient anyway. So doctors may eventually perform OCT angiography on virtually every patient that comes into the clinic, just because it's so easy to get. With that much data, we'll start to learn new things, and new applications are likely to arise.

"But right now, it's still a technology that's in its infancy," he adds. "There are still lots of artifacts in the data, and things we don't fully understand. For example, we're still learning how to best view and interpret the images. Should we be looking at them as movies? Should we be looking at the B-scans, as well as the *en face* images? We need careful studies looking at repeatability and the impact of artifacts when interpreting these images. I think OCT angiography will eventually become a key part of our clinical practice, but right now it's a work in progress."

Dr. Duker notes that no machine capable of doing this is currently available in the United States. "The Avanti from Optovue is OCTA-ready," he says. "The hardware is Food and Drug Administration-approved, but the software is not, as of today. The Avanti is available worldwide and more than 300 units are in use. Meanwhile, all the other major OCT companies are working on this technology. I think this will be the next big thing in OCT, and it will be integrated into the next generation of OCT machines."

Adaptive Optics

"Adaptive optics is an optical imaging system that eliminates higher-order aberrations," explains Dr. Duker. "It can be applied to any imaging device. You can use adaptive optics on a camera, a scanning laser ophthalmoscope or on OCT, where it allows us to do things such as imaging the cone mosaic in an *en face* image.

> *For now, adaptive optics is a niche technology."*
> *—Steve Charles, MD*

"However, there are four problems with using it in retinal practice," he says. "First, measuring the cone mosaic doesn't really help us; so far, we're not able to treat patients who have photoreceptor loss. As a result, the cone mosaic is not of clinical utility at present. Second, this technology has a very narrow depth of field. So, if you're trying to measure the cone mosaic and there's a little bit of fluid that has shifted some of the cones up or down, they may fall outside the depth of field you're measuring and appear to be missing. Third, when applying this technology to OCT, which several research labs are doing, the processing takes a long time. Fourth, the technology is quite expensive. For all of these reasons, it hasn't caught on commercially."

Dr. Sadda concurs. "The reason OCT has been so transformative is that it's quick; thus, it's compatible with the speed of clinical practice," he says. "Wide-field imaging can also be done quickly. In contrast, some technologies such as adaptive optics have instruments that are not as robust and may require a lot of time to use or need regular maintenance."

Steve Charles, MD, FACS, founder of the Charles Retina Institute in Memphis, Tenn., agrees that adaptive optics technology has limited usefulness. "This technology has no role in the clinic or operating room unless you're part of a clinical trial involving gene therapy or cell-based therapy for hereditary retinal degenerative disease," he says. "As soon as the retina has any structural distortion—epimacular membrane, vitreomacular traction, a macular hole, subretinal fluid or macular degeneration—the retinal structure changes and the rods and cones aren't pointing in the direction they're supposed to point. Cones and rods reflect 30 dB less light back to your adaptive imaging system if they're off-angle, so if you use adaptive optics to monitor any of the aforementioned diseases, it will appear that the rods and cones are missing in many areas. They're not missing—they're just not pointed toward the light you're directing into the eye.

"So for now, adaptive optics is a niche technology," he says. "It's great for improving resolution in conditions that involve only apoptosis with no structural distortion, especially genetically driven conditions like retinitis pigmentosa, cone degeneration or

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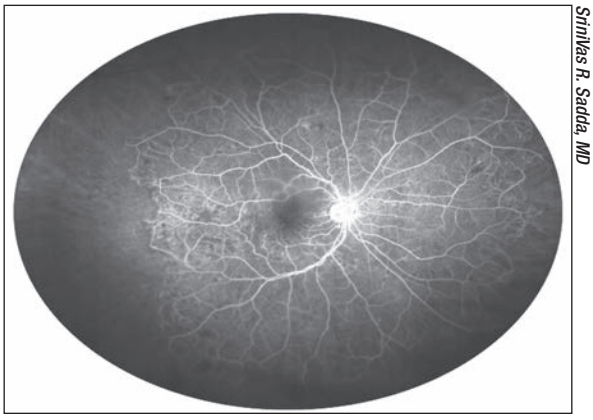
Stargardt's disease. However, treatments for these conditions are a ways down the road. In the meantime, adaptive optics won't help to answer clinical questions such as: Does this patient have a macular hole? Should I operate? Was my surgery successful? Does the patient need an injection of an anti-VEGF compound? Answering these questions calls for more traditional imaging approaches."



Srinivas R. Sadda, MD

Optos ultrawidefield fluorescein angiogram from a patient with a retinal vein occlusion. Note the extensive non-perfusion in the retinal periphery.

Will adaptive optics eventually become clinically useful? "It may very well," says Dr. Duker. "But two things will have to happen for adaptive optics to catch on clinically. First, it has to be fast and reproducible; second, it has to help us address a clinical problem. Once we have treatments that help us restore photoreceptors to health, or prevent the loss of photoreceptors in a disease like dry macular degeneration, that's when we'll need a device that measures the photoreceptors and can tell us if our therapy is working."

Intraoperative Imaging

"Imaging in the operating room is in its infancy, and it's not yet proven that there is an advantage to it for retinal surgery," notes Dr. Duker. "The femtosecond lasers used in cataract surgery have OCT integrated into them to measure the depth of the cornea and the anterior chamber. I think having imaging integrated into the microscope oculars or via a heads-up display [for retinal surgery] will be a reality in the future, but right now it's investigational and unproven."

Dr. Charles is concerned about the value of today's OCT systems during retinal surgery. "The problem is that the axial resolution of OCT right now is such that you cannot image the internal limiting membrane," he explains. "What people often assume to be the ILM is actually just the first reflective surface on the retina. The ILM itself is 3-µm thick and transparent. The axial resolution of OCT today ranges from 5 to 8 µm, so even in an ideal viewing situation, it can't possibly image the actual ILM.

"Retinal surgeons need to peel off the ILM," he continues. "So if OCT can't visualize it, what's the point of having OCT in the operating room? On the other hand, if you put a stain like brilliant blue in the eye, you can see the ILM beautifully during surgery. OCT is very useful in the office, but that doesn't mean it will be useful in the operating room. Just because it's great to have a swimming pool in your backyard doesn't mean you should put one in your car."

Wide-field OCT

"There's another OCT technology that has great potential—wide-field OCT imaging using swept-source technology," says Dr. Rosenfeld. "This will allow us to get a 12 x 12-mm scan of the back of the eye. I think it's going to replace conventional fundus imaging, although for now that remains to be proven."

Dr. Rosenfeld notes that some surgeons remain unconvinced of the value of wide-field imaging, but he points out that in this case "wide-field" is a relative description. "Here, we're talking about a 12 x 12-mm area that encompasses the macula," he says. "We're not talking about imaging the far periphery. I think everyone understands the benefit of getting a good macular image, like a conventional photographic image of the back of the eye."

Dr. Sadda has also done a lot of work with wide-field imaging (in the broader sense). "A lot of our imaging technologies over the past few decades have focused on evaluating the macula and the area around the optic nerve—the posterior pole of the eye," he notes. "But there's a great deal of information beyond the posterior pole that's relevant to diseases like diabetic retinopathy and macular degeneration. Now we have technology like the Optos device that allows us to capture images that extend all the way out to the retinal periphery. That's also been quite transformative. We've learned that there's a lot of pathology out there that we were missing that may be relevant to various diseases, not just diabetic retinopathy and macular degeneration but also retinal vein occlusions, inflammatory diseases and hereditary disorders. We've learned that there can be large areas in the periphery that have no retinal blood flow, something we didn't recognize before. So I think the next step will be to develop a wide-field OCT platform allowing us to take OCTs out to the retinal periphery."

Dr. Rosenfeld notes that how much clinicians will benefit from OCT information about the far periphery remains to be determined. "My colleagues who study diabetes, vein occlusion, inflammatory diseases and even macular degeneration tell me

(continued on page 59)

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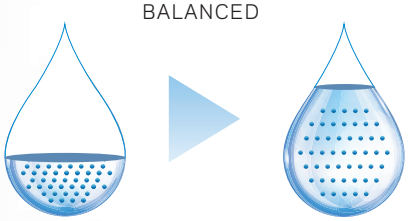

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Reference: 1. Research in dry eye report of the Research Subcommittee of the International Dry Eye WorkShop (2007). *Ocul Surf.* Apr 2007; 5(2): 179-193.

Meet Your Next AMD Drug

Walter Bethke, Managing Editor

A review of the AMD drugs furthest along in the approval process.

Drugs designed to inhibit vascular endothelial growth factor in patients with wet age-related macular degeneration have revolutionized treatment—but physicians and researchers alike think there is room for improvement. This improvement might consist of a therapy that enables ophthalmologists to reduce the number of injections patients need, a modality that yields better vision results or even one that might finally have an effect on geographic atrophy. With this in mind, here's a look at the current results from the drugs leading the charge, the four agents that have either begun their Phase III AMD trial or have announced that such a trial is imminent.

Fovista

Retina experts view Ophthotech's anti-platelet-derived growth factor drug Fovista as the furthest along the road to approval for the treatment of exudative AMD, with its Phase III trial already under way. It's designed to work alongside an anti-vascular endothelial growth factor drug such as ranibizumab.

Wills Eye Hospital's Richard Kaiser, MD, describes where Fovista fits in as a therapy, based on the way in which wet AMD develops. "The theory is that there are two types of cells recruited into a choroidal neovascular membrane," he says. "These are endothelial cells and pericytes. The recruited pericytes bind to the outer walls of the endothelial cells, stabilizing the lesion and limiting the effect of anti-VEGF therapy as the lesion becomes more mature."

Dr. Kaiser's colleague at Wills, Sunir Garg, MD, says it's for these advanced lesions that Fovista may be useful. "Anti-VEGF agents do a good job of causing the choroidal neovascular membrane to stop leaking, bleeding and growing," Dr. Garg says. "However, anti-VEGF doesn't do a good job of getting the vessels to regress, especially after the choroidal neovascularization has matured. If we are able to treat wet AMD of very recent onset with anti-VEGF agents alone, they will work really well. However, the more typical AMD patient presents with a more mature choroidal neovascular membrane in which anti-VEGFs help, but they don't get the abnormal blood vessels to disappear.

"Anti-PDGF agents such as Fovista work through a different mechanism," Dr. Garg continues. "As blood vessels mature, pericytes surround and stabilize them. Fovista weakens the pericytes, which allows the anti-VEGF agent to act on more of the vessels,

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which will hopefully get more of the lesion to regress to a greater extent than it would with anti-VEGF alone."

In terms Fovista's effectiveness, the latest data that's available is from the drug's Phase II trial. In the three-armed, prospective, controlled trial, researchers randomized 449 patients with exudative AMD to a 0.3-mg dose of Fovista combined with Lucentis, a 1.5-mg dose combined with Lucentis or Lucentis alone.[1] The company reports that the 1.5-mg treatment arm gained a mean of 10.6 letters at 24 weeks compared to a gain of 6.5 letters for the Lucentis monotherapy patients, a difference that was statistically significant (p=0.019). They add that, for treatment endpoints such as visual gains greater than three, four and five letters and final vision of 20/40 and 20/25 or better, the results favored the 1.5-mg Fovista combination treatment arm. Also, using masked readers and in a retrospective subgroup analysis, Ophthotech reports that patients receiving the 1.5-mg combination therapy showed a greater mean change of neovascularization area in two subgroups for which that data was available at baseline and 24 weeks.

Ophthotech has three Phase III studies planned, two of which are currently under way.[2] The inclusion criteria are as follows: patients age 50 or over; active subfoveal CNV secondary to AMD; and the presence of subretinal hyper-reflective material on optical coherence tomography. The exclusion criteria are as follows:

- any prior treatment for AMD in the study eye prior to the day-one visit, except oral supplements of vitamins and minerals;
- any intravitreal treatment in the study eye prior to the first visit;
- any intraocular surgery or laser within three months of entry, and any prior laser in the macular region, regardless of indication;
- subjects with subfoveal scar or subfoveal atrophy; and
- diabetes mellitus.

The trials' structures will be similar to the Phase II trials. In the Fovista+Lucentis trial, 622 patients will be randomized to either combination therapy with 1.5-mg Fovista and 0.5-mg Lucentis or a sham Fovista injection combined with 0.5-mg Lucentis. They'll be treated for two years, but the primary endpoint, mean change in acuity, will be evaluated at 12 months.

In the other Phase III Fovista combination trial that's recruiting patients, 622 patients will be randomized between two groups. The first group will receive Fovista and either 1.25-mg Avastin or 2-mg Eylea. The second group will receive sham Fovista combined with either Avastin or Eylea.

"The Phase II studies theoretically showed that anti-PDGF could bring about regression of the choroidal neovascular membrane, which wasn't seen in any anti-VEGF study," Dr. Kaiser says. "Stripping the pericytes may cause lesions to actually regress as opposed to remaining a fibrovascular, static lesion. The Phase II data was encouraging, so that's why they're doing the Phase III trials."

Lampalizumab

As daunting as it's been to find a treatment for wet AMD, dry AMD has proven to be even tougher, with no known treatment aside from the support of AREDS vitamins. Now, however, Phase III trials have begun on Roche's lampalizumab, which demonstrated an effect on geographic atrophy in dry AMD in Phase II trials. If the late-stage trials are successful, it would be the first approved therapy for dry AMD. The Phase III trials are about to start.

According to Roche, lampalizumab is an antigen-binding fragment of a humanized, monoclonal antibody directed against the enzyme known as complement factor D. Complement factor D is a rate-limiting enzyme involved in the activation of the alternative complement pathway, a part of the immune system. Genetic polymorphisms as well as hyperactivity of the ACP have been implicated in the development of AMD, including GA.

The MAHALO Phase II trial of lampalizumab was the springboard for the larger-scale Phase III trials. In it, 129 patients were divided into two sham-injection groups (monthly, n=21; bimonthly, n=21) and two treatment groups who received lampalizumab 10 mg monthly (n=43) or bimonthly (n=44). Treatments lasted 18 months.

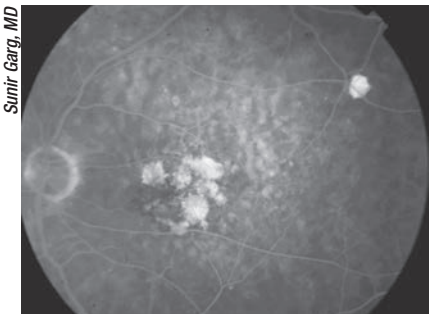
In the Phase II study, an analysis of the change in GA size, the primary outcome measure, showed a 20.4-percent reduction in mean change from baseline with a p-value less than a prespecified significance level of 0.2. There was no significant change in the rate of atrophy growth in the bimonthly patients.[3]

Dr. Garg says one particular finding of MAHALO helped shape the structure of the Phase III trials. "The other thing they're looking at in the lampalizumab trials has to do with the fact that, in MAHALO, there was a genetic biomarker, complement factor I, which seemed to correlate with the patients' response to the drug," he says. "In MAHALO, patients with the complement factor I biomarker had a 44-percent reduction in progression compared to the 20.4-percent in the overall trial. So, in Phase III, the researchers want to see if the geographic atrophy in patients with this biomarker progress differently and/or respond differently to the drug than patients who don't have this biomarker. This is one of the first instances in our field in which a patient's genetic biomarker may help predict response to a medication. It could be one of our first forays into personalized medicine."

Even though the treatment slowed the rate of progression but didn't cause the atrophy to regress, Frank Holz, MD, director of the eye clinic at the

University of Bonn in Germany, says its effect can still be beneficial. "In many areas of medicine, if there is no cure or improvement in something, then the next best goal is to slow progression," he says. "We're used to that in glaucoma, and it's a common theme in oncology. Of course, we'd prefer something that restores vision, but to save the life of the foveal tissue for a longer period of time in order to preserve good central vision is still of high clinical impact."

Lampalizumab will be studied in two identical, double-masked, randomized, prospective Phase III trials named Chroma and Spectri. Each will enroll approximately 936 patients and will compare a 10-mg dose of the drug given via intravitreal injection every four or six weeks to sham injections. To test the results in complement factor I, 188 biomarker-positive and 124 biomarker-negative patients each will be enrolled in the sham, lampalizumab q4w and lampalizumab q6w groups in each study. The primary endpoint is the rate of GA progression, which will be evaluated at one year.



Sunir Garg, MD

If approved, Lampalizumab would be the first treatment for geographic atrophy.

Abicipar

Though patients' vision is at the forefront of companies' research into AMD treatments, reducing the frequency of injections has also emerged as a priority, since doing so would reduce the treatment burden for patients. It's the twin goals of improved vision and a less-frequent dosing schedule that drive the current research of abicipar pegol for the treatment of wet AMD. In early July, Allergan began enrolling patients in the Phase III study of the drug as part of its partnership with the Swiss biotech firm Molecular Partners.

Abicipar is from a class of drugs known as DARPins. "DARPins are highly potent therapeutic proteins that we've developed here at Molecular Partners," says Christian Zahnd, MD, PhD, chief executive officer of the company. "They're derived from a natural class of binding proteins called ankyrin and repeat proteins, which nature has evolved to specifically attach to other proteins in a way similar to antibodies. We used our molecular library to identify a DARPin that's highly potent for neutralizing VEGF, abicipar. Specifically, it blocks several splice variants of VEGF-A from binding to its receptor, similar to what Lucentis does. However, abicipar is a pegylated DARPin, so it carries a polyethylene tail. The reason for this is to provide a longer intravitreal half-life. Its longer half-life in the vitreous is proposed to lead to a longer duration of action and thus less-frequent dosing for patients." In preclinical testing at Molecular Partners, Dr. Zahnd says that, in a rabbit model, abicipar had a vitreous pharmacokinetic duration of action of six days, compared to three days and 4.5 days for ranibizumab and aflibercept, respectively.

Though the abicipar Phase II REACH study wasn't powered to show statistical significance, it showed enough positive trends in efficacy to give Allergan and Molecular Partners the confidence to go ahead with Phase III. In REACH, 25 patients were randomized to abicipar 1 mg, 23 to abicipar 2 mg and 16 to ranibizumab. All patients received doses at the start of the trial and then at four and eight weeks. Ranibizumab patients received additional doses at 12 and 16 weeks, while abicipar patients got sham injections at those visits. Everyone was followed for 20 weeks.

After 16 weeks, mean acuity improvement was 8.2 letters for abicipar 2 mg, 6.3 for abicipar 1 mg and 5.33 letters for ranibizumab. After 20 weeks, which was 12 weeks after the last abicipar injection and four after the last injection of ranibizumab, acuity improvement from baseline was nine letters for abicipar 2 mg, 7.1 for abicipar 1 mg and 4.7 letters for ranibizumab. Two patients in the abicipar 2-mg group and three in the 1-mg group experienced inflammation.

Dr. Zahnd says the inflammatory reaction is being addressed. "The inflammation rate in REACH was at around 10 percent, which was still too high," he says. "After significant improvements of the manufacturing process for Phase III, it's expected that inflammation is under control."

Abicipar's Phase III program will consist of two trials, CEDAR and SEQUOIA, each recruiting around 900 patients. In each trial there will be three arms. The first arm will consist of abicipar 2-mg injections on day one, week four and week eight, followed by injections every eight weeks through week 96. The second arm will be abicipar 2-mg injections on day one, week four and week 12, with injections every 12 weeks through week 96. The third arm, the control, will consist of ranibizumab injections on day one and then every four weeks until week 96.

Squalamine Lactate

The anti-angiogenic drug squalamine lactate (Ohr Pharmaceutical) has gone through a couple of iterations over the years, and its current form is a topical drop. As its treatment protocol is currently configured, the drop is to be administered b.i.d. in combination with Lucentis injections in the hope that it will boost visual acuity gains and/or reduce the number of anti-VEGF injections a patient needs. Ohr recently

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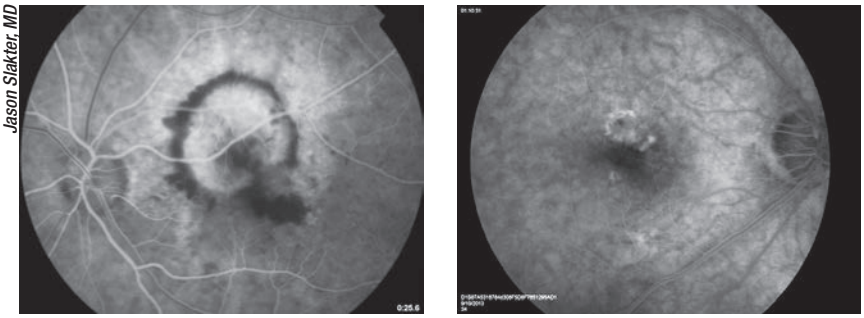
completed the Phase II trial of squalamine and, though it didn't decrease the number of Lucentis injections (the primary endpoint), the company says the drug showed enough potential to increase visual acuity gains vs. Lucentis alone that a Phase III trial is warranted and will start this year.

Squalamine lactate is described as a small-molecule, anti-angiogenic agent that acts against aberrant neovascularization by inhibiting multiple protein growth factors, including VEGF, PDGF and basic fibroblast growth factor. "In order for VEGF, PDGF and bFGF to exert their negative effects, they bind to the receptor and signal intracellular actions that cause leakage, vascular growth, scarring and all the other things we've come to expect from neovascular diseases," says Jason Slakter, MD, Ohr's chief medical officer. "When you apply squalamine it reaches the back of the eye and is taken up into the endothelial cells. There, it binds to a molecule called calmodulin and pulls it away from the inside of the receptors, silencing the receptor activity."

The most recent results with squalamine are from the Phase II trial, named IMPACT. In IMPACT, 142 patients with wet AMD were randomized between two groups: squalamine drops b.i.d. combined with Lucentis as-needed and a group receiving placebo drops plus Lucentis as-needed. Everyone got an initial dose of Lucentis.

In a modified intent-to-treat population with lesions containing classic CNV that consisted of 37 squalamine+Lucentis patients and 28 Lucentis-only patients, Ohr reports that the former group showed visual acuity gains.[4] In the combination-therapy group, patients gained a mean of 11 letters, vs. a mean gain of five letters with Lucentis alone, a difference the company says was clinically meaningful. In addition, 44 percent of the combination patients gained three or more lines of vision at nine months, vs. 29 percent in the Lucentis monotherapy group. Also, 22 percent of the combination patients gained four or more lines and 14 percent gained at least five lines at nine months, compared to 7 percent and 7 percent, respectively, for the Lucentis monotherapy group. In the overall population, though, with either classic-containing or occult-only lesions, Ohr says the mean gain was just 7.8 letters for the combination group and 5.3 for Lucentis.



Jason Slakter, MD

Two different eyes from the squalamine IMPACT study. Though they differ greatly in appearance, they would both be classified as classic-containing lesions.

Dr. Slakter says the Phase II results will help design a Phase III study. "From a regulator's standpoint, it doesn't matter what your primary endpoint was in Phase II," he says. "It only matters what it is in Phase III. What's more important is that you have a valid endpoint to pursue for approval. From the point of view of regulators, it's all about vision. The fact that we didn't find a difference in the number of injections but did show a robust effect in visual outcomes allows us to sit back and say, 'Great, now we have the capability to design and execute a Phase III study with a high likelihood of success based on a visual acuity endpoint.' "

In terms of the better results occurring in predominantly classic lesions, that finding set Ohr researchers on a new course. "We carefully analyzed the data based on emerging information," Dr. Slakter explains. "When you look at the type of vessels that might be more affected by the combination of an anti-VEGF and an agent that's going to inhibit something such as PDGF, the occult vessels may be more likely to be affected by this combination.

"So, instead of rushing forward with a Phase III trial based on a group of patients with classic-containing lesions, we went back and looked at how the size of the occult neovascularization component made a difference in the outcome," Dr. Slakter adds. "We found that, if you look at eyes with occult CNV at baseline of less than 10 mm^2, or four disc areas in size, you get a very dramatic difference in outcome with the combination treatment: an 11-letter mean gain in vision vs. a six-letter gain for Lucentis alone. What's more, we actually had a larger group of patients who met this occult size criteria compared to those with predominantly classic lesions: three-quarters of the patients vs. 50 percent. We're now in the process of finalizing what our patient population will be in Phase III. Though we haven't fully defined this population yet, we believe that occult size may be one of the most important factors in determining it." REVIEW

Dr. Kaiser has a financial interest in Ophthotech and Dr. Holz is a consultant to Roche. Dr. Garg receives research support from Genentech and Allergan. Dr. Slakter is employed by Ohr Pharmaceutical.

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DR-Related DME: Treatment Update

Michelle Stephenson, Contributing Editor

Laser treatment is still the treatment of choice for many patients with non-center-involving edema.

Two anti-VEGF agents have recently been approved by the U.S. Food and Drug Administration for the treatment of diabetic retinopathy in patients with diabetic macular edema. For diabetic retinopathy patients with center-involving edema, anti-VEGF agents are now the first-line treatment. For those with non-center-involving edema, laser treatment is still often used.

Anti-VEGF Agents

For years, laser was the treatment of choice; however, studies have shown that it is not the most effective treatment, and it can cause damage to the eye. "During the past 10 years, anti-VEGF injections have become the standard of care for diabetic macular edema, mainly as a result of multiple clinical trials that have shown increased vision and better anatomic outcomes," says Tom Stone, MD, who is in practice in Lexington, Ky. "Today, we have several agents that we can choose from, including Avastin, Lucentis and Eylea. All of these work very well in most patients."

In a study conducted in Sydney, Australia, researchers compared ranibizumab alone, ranibizumab combined with laser, and laser monotherapy.[1] In this study, 345 patients with visual impairment due to diabetic macular edema were randomized to one of the three treatments. Ranibizumab alone (plus sham laser) was given for three months and then on an as-needed basis. Laser was given at baseline and then as needed.

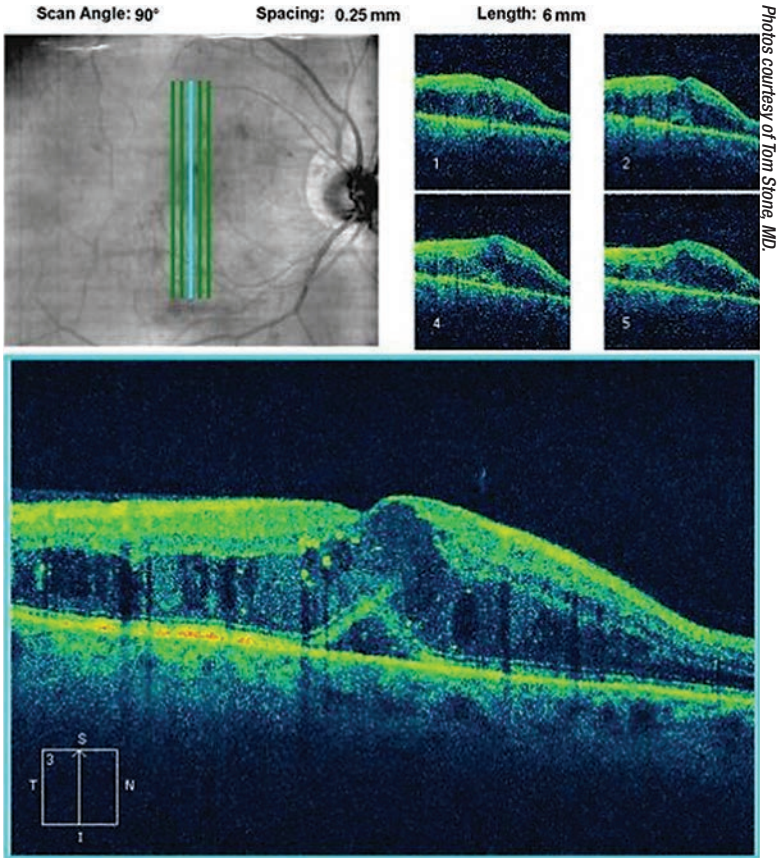
The study found that ranibizumab alone, as well as ranibizumab combined with laser, were superior to laser alone in improving the mean change in best-corrected acuity letter score from the baseline visit to months one through 12 (+6.1 for ranibizumab alone, +5.9 letters for combination therapy, and +0.8 letters for laser alone).

In February, Lucentis (ranibizumab injection, Genentech) 0.3 mg became the first eye medication to be FDA-approved for the treatment of diabetic retinopathy in patients with diabetic macular edema. Lucentis was previously approved by the FDA to treat diabetic macular edema and macular edema secondary to retinal vein occlusions. It is also approved to treat wet age-related macular degeneration.

For patients with diabetic retinopathy, Lucentis is meant to be injected into the eye once a month and used along with appropriate interventions to control blood sugar, blood pressure and cholesterol. The safety and

efficacy of Lucentis to treat diabetic retinopathy with diabetic macular edema were established in two Phase III trials involving 759 participants who were treated and followed for three years.[2] In these two studies, participants being treated with Lucentis showed significant improvement in the severity of their diabetic retinopathy at two years compared to patients who did not receive an injection.

The most common side effects include conjunctival bleeding, eye pain, floaters and increased intraocular pressure. Serious side effects include endophthalmitis and retinal detachments.



Photos courtesy of Tom Stone, MD.

Figure 1. Optical coherence tomography image of diabetic macular edema.

In March, the FDA approved Eylea (aflibercept injection, Regeneron) for the treatment of diabetic retinopathy in patients with DME. Eylea's safety and efficacy to treat diabetic retinopathy in patients with diabetic macular edema were evaluated in 679 participants in two clinical trials where participants were randomly assigned to receive Eylea or macular laser photocoagulation.[3] At week 100, participants being treated with Eylea showed significant improvement in the severity of their diabetic retinopathy compared to patients who did not receive Eylea.

The most common side effects were conjunctival bleeding, eye pain, cataracts, floaters, increased intraocular pressure and vitreous detachment. Serious adverse reactions include endophthalmitis and retinal detachments.

A third anti-VEGF, Avastin (bevacizumab, Genentech), is not approved for this use, but has been used off-label to treat these patients.

"In patients who have central-involving macular edema, the first-line treatment of choice is an anti-VEGF," says David S. Boyer, MD, who is in practice in Beverly Hills, Calif. "In patients who present with vision that is 20/40 or better, all three drugs [Avastin, Lucentis and Eylea] seem to provide excellent results at reducing vision loss. Patients who have 20/50 or worse vision may want to start with bevacizumab until insurance clearance is obtained; however, the efficacy of Eylea has been clearly demonstrated in these patients."

A recent study conducted by the Diabetic Retinopathy Clinical Research Network has found that intravitreal injections of all three drugs improved vision in eyes with center-involved diabetic macular edema, but the relative effect depended on baseline visual acuity.[4] When the initial visual loss was mild, there were, on average, no apparent differences among study groups. At worse levels of initial visual acuity, Eylea was more effective at improving vision. This study was conducted at 89 sites and included 660 adults with DME involving the macular center. Patients received intravitreous aflibercept at a dose of 2.0 mg (224 participants), bevacizumab at a dose of 1.25 mg (218 participants), or ranibizumab at a dose of 0.3 mg (218 participants). Injections were administered as often as every four weeks.

Patients' mean visual-acuity letter scores were evaluated. Scores ranged from 0 to 100, with higher scores indicating better visual acuity. As an example, a score of 85 is approximately 20/20. From baseline to one year, study participants' mean visual-acuity letter score improved by 13.3 with aflibercept, by 11.2 with ranibizumab and by 9.7 with bevacizumab. However, while aflibercept demonstrated the greatest improvement, it was not clinically meaningful, because the difference was affected by the eyes with worse visual acuity at baseline. Just more than half of patients (51 percent) had an initial visual-acuity letter score between 78 and 69 (equivalent to approximately 20/32 to 20/40), and, in these patients, the mean improvement was 8.3 with ranibizumab, 8.0

with aflibercept and 7.5 with bevacizumab. Additionally, when the initial visual-acuity letter score was less than 69 (approximately 20/50 or worse), the mean improvement was 18.9 with aflibercept, 14.2 with ranibizumab and 11.8 with bevacizumab. No significant differences in the rates of serious adverse events, hospitalization, death or major cardiovascular events were observed among the groups.

Although anti-VEGF injections are effective in many patients, they do not achieve visual improvement in all eyes. "It is still not clear how long we should treat a patient with an anti-VEGF agent before switching to another agent if there is no vision or OCT improvement," Dr. Boyer says. "Also, if we decide to switch agents, it is not clear whether to switch to another anti-VEGF or switch to a steroid. All ophthalmologists have their 'magic number' at which they switch and what they do when they switch. Many people today start treatment with Eylea, because of its success in drying the retina and overall improvement of vision in newly diagnosed patients. After three treatments, if there is not a good response, we may consider adding a steroid to the Eylea treatment or just using a steroid."

Steroids

If a steroid is needed, several options are available. "Triesence works fairly well," Dr. Stone says. "More recently, there seems to be more clinical acceptance of patients to Ozurdex, which tends to cause fewer pressure problems."

Dr. Boyer notes that "first-line steroids include Ozurdex, which is FDA-approved, and Kenalog, which is not FDA-approved."

The disadvantage of these steroids is that they wear off after a few months. "Finally, there is a new Iluvien injection, which is a three-year steroid implant. It was only FDA-approved a few months ago, so we are just gaining experience with it," Dr. Stone says.

Dr. Boyer adds that Iluvien (fluocinolone acetonide intravitreal implant, Alimera Sciences) will have a place in the treatment of patients who don't have a pressure rise after being treated with a steroid and in patients who are going to have cataract surgery or have had cataract surgery. "Iluvien may be able to provide long-term benefit for some of our patients for two years or more with one injection in the office. Its exact place will be determined by the market," he explains.

Iluvien was approved by the FDA in September 2014 for the treatment of diabetic macular edema in patients who have been previously treated with a course of corticosteroids and did not have a clinically significant rise in intraocular pressure. Two Phase III pivotal clinical trials were conducted to assess the safety and efficacy of Iluvien in the treatment of diabetic macular edema. Patients were randomized to receive high-dose Iluvien, low-dose Iluvien or control treatment. In these two studies, a total of 376 patients received Iluvien and 185 patients were in the control group. The primary endpoint for efficacy was the difference in the percentage of patients whose best-corrected visual acuity improved by 15 or more letters from baseline on the ETRDS eye chart at month 24 between the treatment and control groups. Based on the results at month 24, only the low-dose treatment group data were examined at month 36.

The first trial demonstrated statistically significant therapeutic effects in 28.9 percent at month 30 and 28.4 percent at month 33 of Iluvien patients gaining 15 or more letters, compared to the control group, in which less than 17 percent of patients gained 15 or more letters. At month 36, the therapeutic effect was maintained (28.4 percent of patients gained 15 or more letters compared to 18.9 percent of the control group).

Results from the second trial were similar. The percentage of Iluvien patients gaining 15 or more letters over baseline was 33.9 percent at month 30, 29.6 percent at month 33 and 29 percent at month 36 compared to the control group, which had less than 18 percent of patients gaining 15 or more letters.

In these two trials, Iluvien demonstrated a statistically significant effect at week three, and this effect was maintained throughout the 36 months, with 28.7 percent of Iluvien patients and 16.2 percent of control patients having an improvement in BCVA of 15 letters or more over baseline at month 24, 31.4 percent compared with 15.1 percent at month 30, and 28.7 percent compared with 18.9 percent at month 36.

Laser Treatment

In patients with non-center-involving edema, laser treatment may be the best option. "Laser treatment is still used in patients who have non-central-involving edema where areas of leakage are far enough away from the foveal area that treatment can be applied without any damage or any potential damage in the future to the foveal areas," Dr. Boyer says.

A study conducted by the DRCR.net examined the visual acuity and anatomic changes from baseline to 12 months after modified ETDRS-style (focal/grid) photocoagulation in eyes with non-center-involved, clinically significant macular edema.[5]

The study included 22 eyes of 22 patients who had 12 months of follow-up. Among these patients, medical visual acuity letter score remained within one letter of baseline over 12 months. Additionally, the median central subfield retinal thickness decreased by 10 µm, the median total

(continued on page 74)

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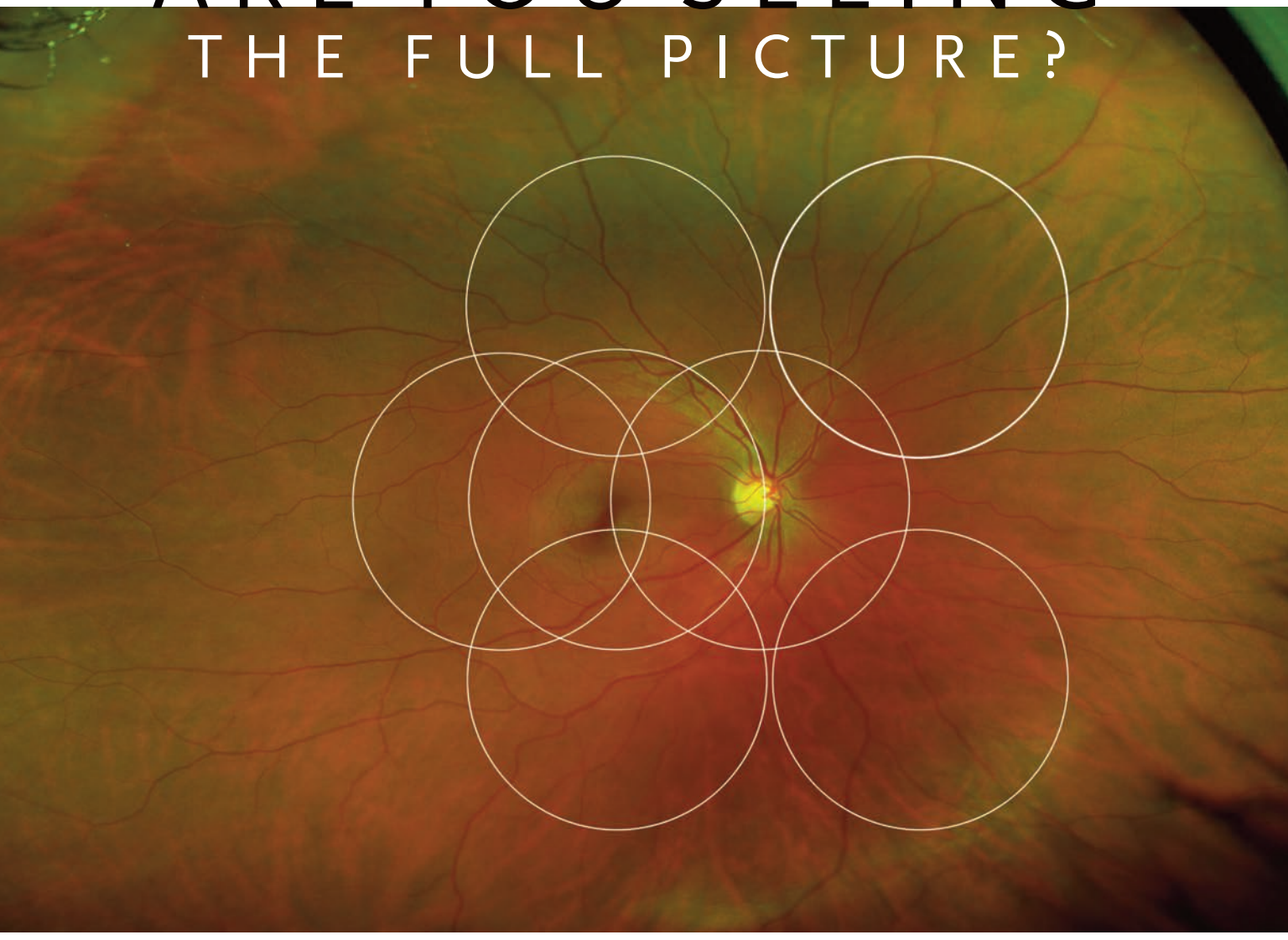

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2, 3 Data on file


Radiation Retinopathy: Treatment Strategies

The diagnosis and management of this condition are evolving, and choosing the right combination of treatments is critical.

Josh Wallsh, BS, Don Pham, BS, Jerry Shields, MD, Robert Johnson, MD, and Ron P. Gallemore, MD, PhD

Radiation retinopathy remains a common cause of blindness in patients following treatment for malignancies in or around the orbit. The most common setting is following radioactive plaque brachytherapy for choroidal melanoma. Some patients initially have excellent vision following successful management of the melanoma, but proceed to lose their vision after succumbing to RR. Herein, we review the current treatment strategies used for this disorder and future directions for the field.

Mechanism and Classification

Radiation retinopathy is the result of delayed loss of endothelial cells and pericytes along with capillary closure following radiation exposure from external beam radiation, gamma knife radiotherapy, proton beam radiation and—most commonly—plaque brachytherapy.[1-5] The effects at the cellular level and the clinical findings resemble those of diabetic retinopathy and, hence, a similar classification scheme has evolved.[6] Nonproliferative radiation retinopathy (NPRR) findings include retinal hemorrhages; cotton wool patches; exudates; telangiectasia; and macular edema. Proliferative radiation retinopathy (PRR) presents with neovascularization of the disc or elsewhere with or without vitreous hemorrhage.[7-11] Another classification scheme is similar to that for retinal vein occlusion: ischemic and nonischemic.[12] Each classification

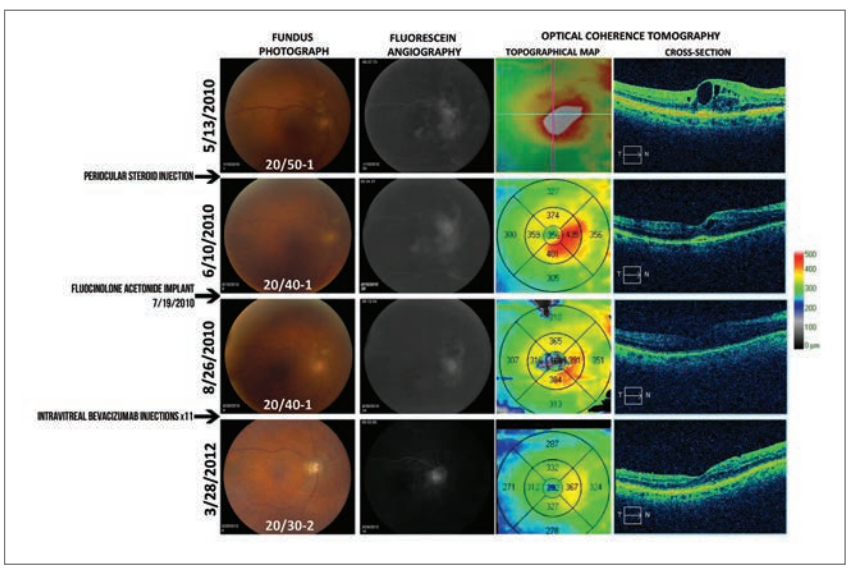

Figure 1. A 68-year-old patient was initially treated with periocular corticosteroid injections and only responded transiently, so he was treated with the extended-release fluocinolone acetonide implant. This only partially resolved his radiation retinopathy; therefore, it was combined with repeated intravitreal bevacizumab injections. He demonstrated an improvement in imaging and, following cataract extraction, realized an improvement in vision. Eventual pars plana Ahmed valve placement was required to manage corticosteroid-induced glaucoma in July 2012.

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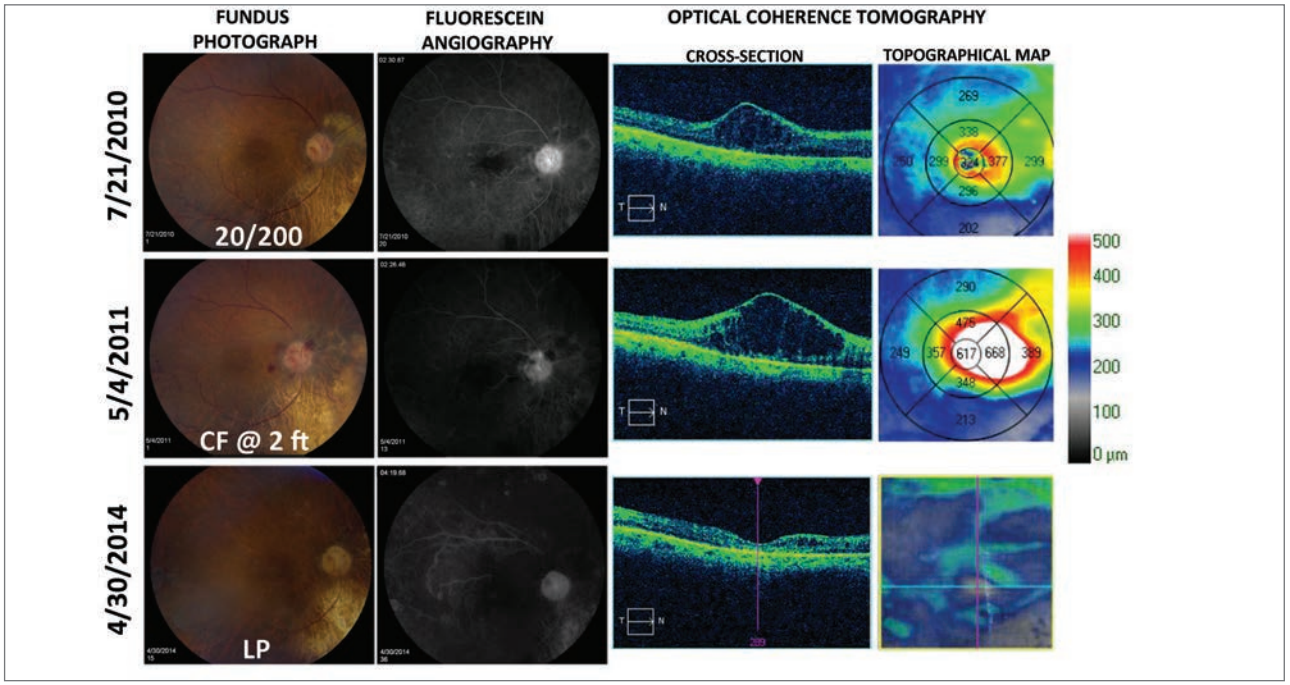

Figure 2. A 70-year-old patient with radiation retinopathy receiving multiple panretinal photocoagulation treatments from 7/21/2010 to 5/4/2011 with persistent leakage noted on fluorescein angiography. He was subsequently switched to monthly intravitreal bevacizumab injections and received this treatment from 5/24/2011 until 1/15/2013. He has since required no treatments, with improvement on fluorescein angiography from 4/30/2014.

scheme appears to have prognostic and therapeutic implications and, as discussed below, we use both. Other classification schemes have also been proposed, including the Finger classification of radiation retinopathy,[13] radiation maculopathy classification scheme[14] and Augsburger's radiation fundopathy scheme. The radiation maculopathy classification scheme utilizes fluorescein angiography to delineate ischemic and nonischemic maculopathy; grades radiation macular edema based on optical coherence tomography findings; and proposes the application of the Early Treatment Diabetic Retinopathy Study definition of clinically significant macular edema to radiation macular edema. This multi-modality approach to classifying radiation retinopathy should prove to be useful when studying treatment protocols. It has been reported that within five years of plaque therapy for uveal melanoma 42 percent of patients may experience NPRR and 5.8 to 8 percent PRR.[4,5] These conditions may be diagnosed anywhere from one month to 15 years post-radiation treatment, but are most frequent between six and 36 months.[9] An increased risk of RR has been associated with younger age at onset, closer proximity to the optic disc or fovea, thicker tumors, those associated with retinal detachments, non-dome shaped tumors and comorbidities such as diabetes or hypertension.[4,15-17] Radiation optic neuropathy can also be seen following brachytherapy with a prevalence of 23 percent and 53 percent after five and 10 years, respectively, further complicating treatment.[18]

Treatments

Laser photocoagulation. As noted, RR mimics other retinal vascular diseases. Strategies to treat RR, therefore, have centered on treatments for diabetic retinopathy and retinal vein occlusions. In the past, the only strategies used for the management of RR were focal photocoagulation for NPRR-related macular edema and pan-retinal photocoagulation (PRP) for PRR and ischemic RR.[19-22] James L. Kinyoun, MD, studied 42 eyes with NPRR—19 treated with focal photocoagulation and 23 untreated—with a decrease in mean visual acuity noted in both groups. However, the photocoagulation group visual acuity decreased less (from 20/40 to 20/100) compared to the non-treatment group (20/50 to 20/200).[23] Similar to diabetic retinopathy, advanced cases of RR can lead to proliferative disease resulting in retinal, disc or iris neovascularization, vitreous hemorrhage, neovascular glaucoma and tractional retinal detachment.[11,24,25] To assess the effectiveness of PRP in patients with PRR, Dr. Kinyoun treated 23 patients with PRP and compared to five who went untreated. The PRP cohort

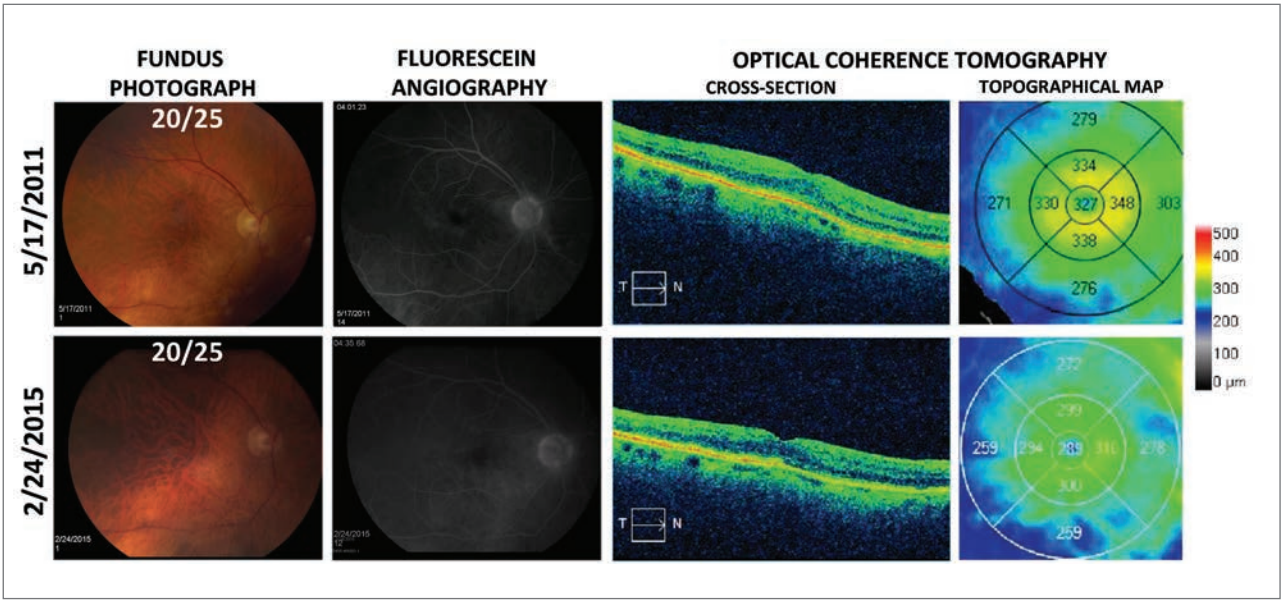

Figure 3. A 79-year-old initially treated with monthly intravitreal bevacizumab injections for approximately two years with a single application of panretinal photocoagulation. She has subsequently been maintained on a treat-and-extend protocol while maintaining her vision at 20/25 nearly four years later. Fundus photograph, fluorescein angiography and optical coherence tomography demonstrate pre-treatment and most recent images.

on average lost fewer lines of vision (20/189 to 20/357) when compared with the untreated cohort (20/170 to 20/1,371).[23] Carlos Bianciotto, MD, and colleagues reported resolution of PRR in 63 (66 percent) patients following PRP.[4] We recommend a course of PRP laser in high-risk cases or with early signs of RR, often combined with other adjunctive therapies as discussed below.

Triamcinolone acetonide injections. Given the upregulation of inflammatory mediators seen in RR, intavitreal corticosteroid injections have been used for management of RR. While no clinical trial has examined intravitreal corticosteroid treatment in the setting of RR, comparable research has been performed in the setting of diabetic retinopathy. In the study, intravitreal triamcinolone acetonide was compared to laser treatment for the management of diabetic retinopathy.[26] Results of this study, and its subsequent follow-up study,[27] were unclear as to the efficacy of IVTA on diabetic macular edema as compared to laser treatment in the long term. Carol Shields, MD, and colleagues treated 31 patients diagnosed with RR with a single IVTA injection and appreciated stable or improved visual acuity in 91 percent (n=20) and 45 percent (n=14) of patients after one and six months, respectively. In addition, these patients demonstrated an improvement in mean foveal thickness on optical coherence tomography from 471 µm at baseline to 207 and 292 µm at one and six months, respectively.[28] This response to IVTA may only be transient, and additional injections are commonly required within a year of the first treatment.[29]

Similarly, in clinical practice, we have found IVTA to be effective only in the short-term for managing RR. The risk of complications, such as cataract formation and corticosteroid-induced glaucoma, and the inadequate long-term effectiveness have limited our use of IVTA. However, periocular corticosteroid injections should also be considered, as this has been shown to lower the risk of macula edema and vision loss in RR.[30] We have used this in select cases *(See Figure 1)*.

Anti-vascular endothelial growth factor. The microvascular changes related to RR may be driven by the release of vascular endothelial growth factor in response to ischemia, similar to the mechanism seen in diabetic retinopathy.[31] With this in mind, the treatment of RR has turned to intravitreal anti-VEGF injections such as bevacizumab (Avastin, Genentech),[32-35] ranibizumab (Lucentis, Genetech),[36] pegaptanib (Macugen, Pfizer)[37] and aflibercept (Eylea, Regeneron). Use of intravitreal pegaptanib was reported in a single case review demonstrating an improvement in vision following a single injection after failed laser photocoagulation.[37] Similarly, multiple case reports have demonstrated an improvement in visual acuity associated with bevacizumab therapy.[32,33] Although no randomized controlled studies have assessed this treatment, multiple retrospective studies have been published.[34,35] In 2007, John Mason, MD, and colleagues studied 10 patients treated with a single bevacizumab injection, demonstrating a vast improvement

in foveal thickness (mean decrease of 198 µm) and only mild mean visual acuity improvement (from 20/100 to 20/89) after six weeks.[34] Paul Finger, MD, (2008) treated 21 patients with a mean of 3.8 (one to seven) intravitreal bevacizumab injections over a mean of 7.8 (two to 18) months with at least stabilization of visual acuity in 86 percent of eyes.[35] In the only published study of ranibizumab injections, Dr. Finger and Kimberly Chin, MD, performed a prospective trial of 10 eyes treated monthly with ranibizumab injections. At the end of the one-year study, mean central foveal thickness improved by 95 µm and mean visual acuity improved by 0.7 letters.[36]

We have found intravitreal anti-VEGF injections to be effective in the majority of cases in the management of macular edema associated with RR, but find that an aggressive treat-and-extend protocol must be followed with continued maintenance therapy in most cases. Undertreatment may lead to ineffective management of RR and, in some high-risk patients, prophylactic treatment may even be required. Figure 2 demonstrates a patient from our practice who, following PRP laser, was treated monthly with intravitreal bevacizumab for cystic macular edema. While the treatment effectively managed the edema, the patient went on to develop ischemic radiation retinopathy as well as radiation optic neuropathy and further vision loss.

Periodic injections of bevacizumab and ranibizumab may be needed to show a decrease in macular edema and retinal hemorrhages. Like diabetic macular edema and exudative macular degeneration, monthly treatments appear to be required long-term to achieve good outcomes.[35,38] Larger randomized controlled trials are currently under way to determine the efficacy of anti-VEGF therapy in reducing the symptoms of radiation retinopathy.[39,40] Figure 3 demonstrates a patient from our practice maintained with aggressive monthly intravitreal bevacizumab injections, up until a very recent transition to a treat-and-extend protocol. This approach has sustained her 20/25 vision.

Corticosteroid implants. For recalcitrant RR cases we have utilized intravitreal corticosteroid implants with both the surgically performed fluocinolone acetonide implant (Retisert, Bausch + Lomb) and the dexamethasone implant (Ozurdex, Allergen). These provide similar downregulation of cytokines and decrease in capillary permeability witnessed with other corticosteroid therapies, but in a time-released capsule allowing for upwards of six months of therapy. Multiple case reports

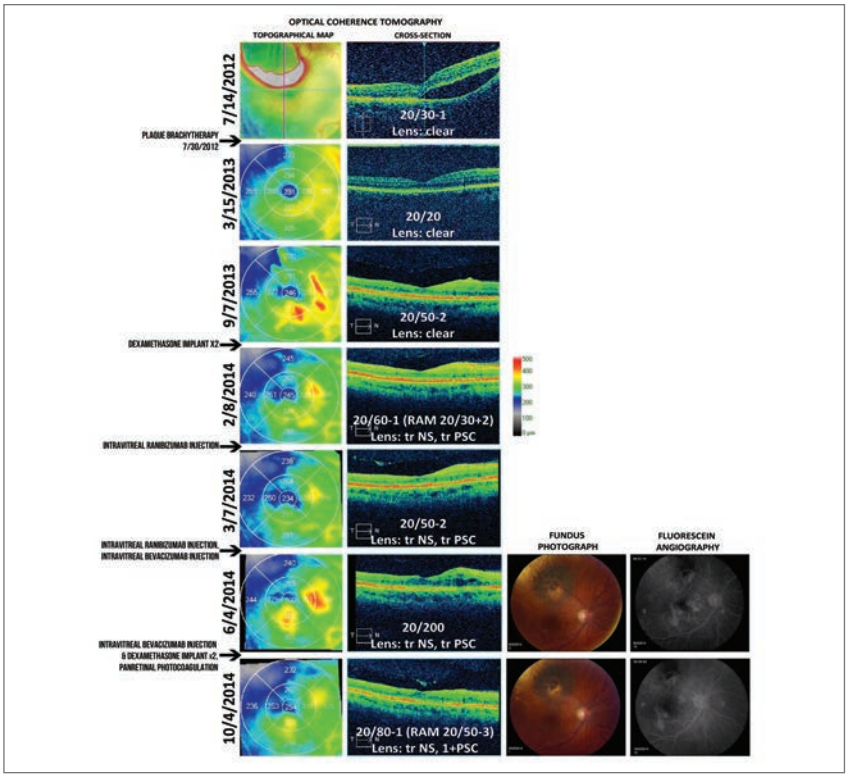

Figure 4. A 32-year-old patient initially had an excellent response to plaque therapy (89 Gy) for choroidal melanoma with resolution of subretinal fluid and improvement in vision. She subsequently developed radiation retinopathy and was treated with two intravitreal dexamethasone implants due to concerns associated with pregnancy. After delivery she received a series of anti-VEGF injections, both bevacizumab and ranibizumab. Initially, she responded well to all these treatments, but then developed tachyphylaxis. She subsequently underwent combination therapy with two treatments of combined intravitreal dexamethasone implant plus intravitreal bevacizumab injection, with resolution of edema and recovery of vision.

have demonstrated improvements in macular edema in refractory cases of RR treated with dexamethasone implants; however, visual acuity results have been varied.[41-43] While cataract formation and corticosteroid-induced glaucoma remain concerns, the long-term efficacy of the implants and the more sustained levels of corticosteroids appear to provide better results for patients. Figure 4 illustrates the use of the dexamethasone implant in a 32-year-old pregnant female with radiation retinopathy following brachytherapy for choroidal melanoma. This treatment approach was selected given the risk of anti-VEGF therapy during pregnancy. A prompt reduction in edema was achieved; however, vision decreased by a line following cataract development. Eventually a combined approach was required for this patient, which will be discussed below. With the fluocinolone acetonide implant, patients must be aware that two additional surgeries (cataract extraction and glaucoma valve placement) may ultimately be required.

We have had remarkable results recovering excellent vision using these strategies for patients who are willing to pursue the treatments required to achieve the best outcome. Figure 5 demonstrates the remarkable anatomical response to two fluocinolone acetonide implants placed 16 months apart, experienced by a 43-year-old female following brachytherapy for a peripapillary choroidal melanoma five years prior. She was initially managed with sectoral panretinal photocoagulation followed by a series of bevacizumab injections and several dexamethasone implants. The effects were not sustained and she did not tolerate the injections well due to anxiety and post-injection discomfort. Vision recovered from as low as count fingers to 20/100 and stabilized at 20/200 without further intervention two years out from her second fluocinolone acetonide implant.

Combination therapy. A combinatorial approach may be effective for recalcitrant cases. By taking a multidirectional approach and attacking more of the factors that may play a role in retinopathy, including prostanoids and VEGF-family proteins, several investigators have reported improvement following combination corticosteroids and anti-VEGF drug injections.[44,45] In our practices, we have found this combined approach to be effective for patients with RR resistant to monotherapy. An example is shown in Figure 1. This patient required management with periocular corticosteroid injections, fluocinolone acetonide implant and multiple intravitreal anti-VEGF injections. However, he required both cataract extraction and glaucoma valve placement (for corticosteroid-induced glaucoma, which developed following fluocinolone acetonide implantation). Similarly, Figure 4 demonstrates a patient that developed tachyphylaxis to anti-VEGF injections and was switched to combination intravitreal dexamethasone implant and bevacizumab injection with dramatic improvement in edema and vision.

Alternative Treatments. The advent of the strong topical corticosteroid difluprednate ophthalmic (Durezol, Alcon) has allowed for the topical management of certain cases of NPRR. Combining topical difluprednate with a topical non-steroidal

anti-inflammatory drug and carbonic anhydrase inhibitor forms a triple therapy that can be efficacious in treating cases of mild macular edema secondary to RR.

There have been a few reports of patients developing choroidal neovascular membranes associated with RR.[46,47] Sophie Bakri, MD, and Paul Beer, MD, noted that the use of verteporfin photodynamic therapy in such patients with CNV secondary to RR resulted in improved macular edema and visual acuity; therefore, they applied PDT to three patients with RR not associated with CNV. All three patients were noted to have a considerable decrease in hard exudates along with improvement or stabilization of visual acuity.[48] There has been no further follow-up research reported regarding the use of PDT in the setting of RR, and this option carries little promise as it was found to be ineffective in the management of diabetic macular edema.

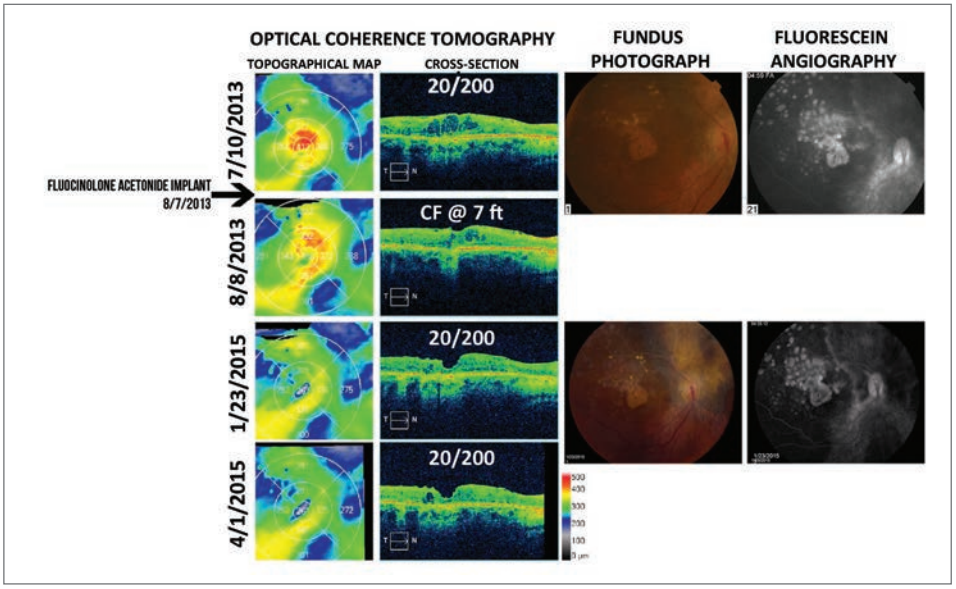

Figure 5. A 43-year-old patient who had received multiple intravitreal bevacizumab injections and intravitral dexamethasone implants without resolution of her macular edema, as demonstrated on optical coherence tomography topographical map and cross-section. Following fluocinolone acetonide injection she was noted to have considerable improvement in macular edema over the subsequent 1.5 years without further treatment required to maintain this improvement.

Oral pentoxyphylline (Trental, Sanofi-Aventis), a phosphodiesterase inhibitor that may reduce inflammatory mediators as well as improve perfusion via improved RBC flexibility, has been proposed, with little data to date.[49] PDT has also been used for "tumor consolidation"[50] and is thought to reduce tumor inflammation and mediators. Drugs like amifostine that sop up free radicals may be of theoretical benefit in preventing the development of RR when used concurrently with radiotherapy, and an animal study supports the effect of this drug in particular.[51] To date, there are no human trials on amifostine for RR; however, its scavenger ability has been demonstrated to be effective as protection against radiation damage to soft tissues in head and neck cancer without providing similar protection to the tumor.[52] This differential response by normal and neoplastic tissue is theoretically due to differences in alkaline phosphatase activity, pH and vascularity, which allow increased conversion of amifostine to its active metabolite in normal tissue.[53] Silicone oil placement at the time of or prior to brachytherapy has also been utilized as prophylaxis with three patients followed for 10 to 24 months who did not develop RR during that time.[54] In a case-control series, Tara McCannel, MD, PhD, and Colin McCannel, MD, demonstrated the development of abnormal macular findings in significantly fewer patients with silicone oil placement prior to brachytherapy compared to control.[55] There is also a report of hyperbaric oxygen therapy for the management of radiation optic neuropathy with apparent efficacy in some cases.[56]

Nutritional supplementation. There is growing evidence that the xanthophylic carotenoids, lutein and zeaxanthin, are beneficial in the management of other retinopathies including retinopathy of prematurity and diabetic retinopathy.[57] Their role in RR remains to be explored but, in theory, select supplementation may be beneficial. Excessive nutrient supplementation carries risk as well, and in the absence of randomized controlled studies, no guidelines can be set forth. In patients with RR and findings of macular degeneration, an AREDS II supplement is recommended. In others, lutein at 10 mg per day and zeaxanthin at 2 mg per day may be reasonable in the absence of contraindications such as the use of warfarin, allergies to said supplements, or vitamin A deficiency.

Radiation retinopathy remains a difficult-to-manage complication of radiation therapy without a single ideal treatment approach. Depending on the circumstances, the aforementioned treatment options all provide varying degrees of efficacy. In our practices, we have found the most benefit in a combined approach

utilizing multiple modalities over the course of treatment. Employing this approach seems to provide better maintenance of visual acuity and macular thickness than would be anticipated by repeated use of any single treatment alone. REVIEW

Dr. Gallemore is the founder and director of the Retina Macula Institute and Research Center, Torrance, Calif., and an assistant clinical professor at Jules Stein Institute, UCLA School of Medicine. Contact him at rongallemoremd@gmail.com.

Mr. Wallsh is a research associate at the Retina Macula Institute and Research Center and student at Albany Medical College, Albany, N.Y. Mr. Pham is a research associate at the Retina Macula Institute and Research Center, Torrance, Calif. Dr. Shields is the director of the Ocular Oncology Service at Wills Eye Hospital and professor of ophthalmology at Thomas Jefferson University, Philadelphia. Dr. Johnson is in private practice at West Coast Retina and is a clinical professor of ophthalmology at California Pacific Medical Center, San Francisco.

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RISC and Reward with Inhibitory RNAs

A new understanding of ribonucleic acid's activity in cells may lead to breakthroughs in ophthalmic treatment.

Mark B. Abelson, MD, CM, FRCSC, FARVO, and Connie Slocum, PhD, Andover, Mass.

Information flow is fundamental to all biological systems, an attribute that helps us understand the nature and function of a cell, an organ or an organism. A central dogma of that flow is that it's directional: The genetic code is deciphered from DNA to RNA intermediates, and finally to the structural and metabolic proteins from which we're built. But a flaw in this orderly arrangement became clear by the end of the 20th century, as we began to understand that those RNA intermediates carry the informational flow in both directions, as messenger RNA translated into protein and as regulators of gene expression in the form of microRNAs and interfering RNA.[1] This month, we'll look at the timeline of RNAi development and consider what the future may hold for this singular therapeutic modality.

Two Decades of RNAi

The process of RNA interference was comprehensively described by Andrew Fire, PhD, and Craig Mello, PhD,[2] in the late 1990s, and the significance of this discovery was instantly recognized. Drs. Fire and Mello were awarded the 2006 Nobel Prize in medicine, and before that prize was even announced, Sirna Therapeutics had initiated a Phase I clinical trial for treatment of age-related macular degeneration with an interfering RNA targeting the type 1 vascular endothelial growth factor receptor.[3] While that trial yielded encouraging data, it didn't progress.[4] Despite this, the potential for this treatment approach was validated and efforts to develop small interfering RNAs as a therapeutic platform for a host of ophthalmic conditions have accelerated over the past decade.

Theoretically, a targeted siRNA has the potential to provide treatment for any human disease by interfering with disease-associated genes in a sequence-specific manner.[5] Designing small RNA fragments to interfere with mRNA in the cytoplasm has the added theoretical benefit of inhibiting the downstream synthesis of targeted pro-

The ABCs OF RNAs

mRNA	messenger RNA	Single-strand encoding for individual protein
tRNA	transfer RNA	Converts mRNA triplets into amino acids
rRNA	ribosomal RNA	Forms complex for protein translation
siRNA	small, interfering RNAs	Synthetic (exogenous) RNA used to direct gene expression
miRNA	micro RNA	Hairpin or double-stranded endogenous RNA, processed to smaller fragments for RNAi
RNAi	RNA interference	Process by which small RNAs regulate gene expression

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teins.[6] This new therapeutic magic bullet was of particular interest for targeting genes that had traditionally been considered "undruggable" by other methods, such as small molecules.[6,7]

The discovery of RNAi as a potential therapeutic modality led to an era filled with bidding wars for RNAi intellectual property and publication of a number of controversial findings in high-profile journals. Early efforts to exploit RNAi technologies did not live up to their hype, and thus a period of general backlash and financial restrictions ensued.[8] After great initial promise came a series of disappointments followed by a steady progress to therapeutic success. Many of the therapeutics in the clinical pipeline now benefit from the scientific rationale derived from the historical trial-and-error of earlier RNAi therapeutic efforts, so we may have reached a second phase of therapeutic progress, with a growing number of RNAi therapies currently in various phases of clinical trials.[6] Despite the mothballing of Big Pharma RNAi programs in the past, it seems that it is more of a question of when, rather than whether, RNAi therapeutics will reach their potential as a unique and valued treatment modality.[8]

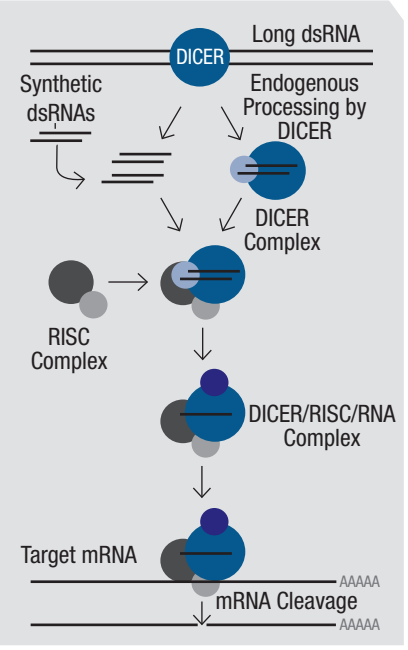
MicroRNAs, DICER and RISC

The endogenous process of transcribing genetic signals from DNA to RNA, and ultimately expressing proteins, is an evolutionarily conserved, multistep pathway that involves tissue-specific microRNAs and a series of enzyme complexes that drive the regulatory process. The miRNAs are trimmed to size by a specific ribonuclease called DICER and then paired with a target mRNA in a multiprotein RNA-induced silencing complex called RISC.[5] The complexity of this cellular apparatus serves to underscore the importance of miRNAs as regulatory molecules.[9] In the eye, miRNAs are increasingly used as biomarkers of disease states, and have been specifically linked to a host of ocular conditions. In the cornea, recent reports identify specific miRNAs that may participate in cellular events of wound healing.[10,11] By examining up- and downregulation of miRNAs associated with specific states, it's been possible to identify new mechanisms underlying both healthy and pathologic healing processes.

It's at this point in the endogenous gene regulatory process that therapeutic siRNAs enter. Whether generated by DICER or introduced exogenously, short, 18- to 25-nucleotide RNA duplexes assemble into the RISC and the double-stranded siRNA is separated, resulting in a single RNA strand coupled to RISC. The resulting RISC/RNA strand complex identifies and cleaves complementary host mRNA, thereby preventing translation and selectively silencing gene expression.[7] Although longer, double-stranded RNA has the potential to be delivered therapeutically, it is generally accepted that siRNA technology offers the best combination of specificity, potency and versatility as a therapeutic.[12]

Since siRNA must reach the cytosol of the cell to trigger RNAi, chemical modifications are required to bring siRNA to its site of action without inducing adverse effects,[7] and to minimize recognition by the innate immune system.[5] The potential for RNAi formulations to activate innate immunity was a significant hurdle for the early efforts to develop RNAi therapies.[8] This issue has been largely circumvented by a combination of chemical modifications to the introduced RNA and by alterations in RNA structural design. In addition, newer siRNAs incorporate principles that ensure proper strand selection, avoid partial hybridization to non-target mRNAs, and thus minimize potential off-target gene silencing.[7]

The Path to RNA Interference



Double-stranded RNAs (dsRNAs) are processed into siRNA duplexes by the enzyme DICER. These short, dsRNAs are subsequently unwound and assembled into the RISC, which can direct RNA cleavage and translational repression using antisense strands from either endogenous or exogenous dsRNAs.

SiRNA and Ocular Disease

Early efforts to apply siRNA therapeutics to ocular conditions targeted retinal degenerative diseases due to the number of conditions with limited successful therapeutic options and difficulty in formulating topical application of siRNA therapy that will be stable and penetrate the ocular surface. These studies faced the same difficulties that all retinal drugs do: physical barriers; rapid clearance; and heterogeneous disease etiology. The isolated compartment of the eye, however, provides advantages for siRNA delivery compared to other tissues and organ systems in that the siRNA can be directly delivered.[13] While most siRNA programs to date have delivered therapeutics by direct intravitreal injection,[5] opportunities for new delivery methods are likely to impact the future suc-

Trials of RNAi-based Therapies

Company	Drug Name	Gene Target	Disease Target	Delivery Method	Clinical Status*
Opko Health	Bevasiranib (Cand5)	VEGF	wet AMD	intravitreal injection	Phase III – terminated
Allergan	Sirna-027 (AGN211745)	VEGFR1	AMD	intravitreal injection	Phase II – terminated
Quark Pharmaceuticals	PF-655, others	RTP801	AMD	intravitreal injection	Phase II – completed
			DME	intravitreal injection	Phase II – completed
Quark Pharmaceuticals	QPI-1007	caspase-2	NAION	intravitreal injection	Phase II/III pre-recruitment
			AACG		Phase II – ongoing
Sylentis	SYL040012	ADRB2	POAG	topical	Phase IIb – recruiting
			ocular hypertension		Phase I – complete
Sylentis	SYL1001	TRPV1	ocular pain	topical	Phase Ib – recruiting
			dry-eye syndrome		Phase II – recruiting

*from clinicaltrials.gov, 11 June 2015

cess of siRNA in the eye.

The first clinical application of RNAi-based therapy was in 2006 by the intravitreal injection of a siRNA, Cand5, targeting vascular endothelial growth factor for the treatment of AMD.[4] Although Cand5 showed initial promise in clinical trials, it was terminated in Phase III for its lack of efficacy.[14] By 2011, two additional siRNAs had been evaluated by direct intravitreal administration for their treatment of retinal degenerative diseases in humans. Sirna-027 [sic] was also designed to target the VEGF pathway by silencing the VEGF receptor. Like Cand5, Sirna-027 was studied in trials for the treatment of AMD but was terminated in Phase II. An additional siRNA, PF-655, also developed for the treatment of AMD, was made to silence RTP801, a propriety gene target owned by Quark Pharmaceuticals.[7]

Silencing the synthesis of the apoptotic protein, caspase-2 is another target for siRNA-mediated ocular therapeutics. In animal models, QPI-1007 has been shown to provide ocular neuroprotection through preservation of retinal ganglion cells.[12] QPI-1007 has successfully completed Phase I studies for the treatment of non-arteritic ischemic optic neuropathy, and is also being evaluated in Phase II for acute, primary angle-closure glaucoma.

Another avenue for the application of siRNA for ocular disease therapy comes from Sylentis. The siRNA SYL040012 was developed as a therapy for primary open-angle glaucoma; it's designed to inhibit the synthesis of the β2-adrenergic receptor, ADRB2.[6] In contrast to previous siRNA therapies that are delivered by intravitreal injection, SYL040012 is the first RNAi therapeutic to be administered as a topical formulation. SYL040012 is currently being assessed in a Phase IIb clinical trial for POAG.

The newest siRNA to enter clinical development, SYL1001, is also from Sylentis. SYL1001 targets the gene TRPV1 that encodes the receptor for capsaicin, the active ingredient in chili peppers. The gene product of TRPV1 is a key component of nociceptive sensory nerve endings, and silencing of this receptor via siRNA will be evaluated for the treatment of ocular pain associated with dry-eye syndrome in a Phase Ib study.

The Future of siRNA Therapies

Despite the $2.5 to $3 billion that was invested in RNAi therapeutics from 2005 to 2008, we have yet to see such a therapy come to market.[8] A huge barrier to successful siRNA therapeutics has been their intracellular delivery, which significantly impacts their clinical efficacy. siRNAs are large and negatively charged, so they must be chemically modified or formulated to promote tissue distribution and cellular uptake. It is likely that future siRNA therapeutics will be designed with new drug delivery systems that

will have a profound impact on improving the therapeutic outcomes for ophthalmic applications. One group of researchers has recently predicted that nanocarriers may be this delivery system, due to their reported ability to increase drug bioavailability while reducing side-effects and the need for repeated intraocular injections.[5] Until then, there remains hope that products in development can demonstrate appropriate safety and efficacy. Despite its early promise, developing therapeutics that employ the siRNA platform has resembled swimming upstream, but recent success may indicate that going against the flow may ultimately be worth the risk. REVIEW

Dr. Abelson is a clinical professor of ophthalmology at Harvard Medical School. Dr. Slocum is a medical writer at Ora Inc.

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(continued from page 36)

that wide-field imaging is revealing new information," he says. "I don't think it can be discounted. Wide-field imaging in some diseases is almost certain to be helpful. This should be particularly true for ocular tumors in the far periphery. It's possible that ultra-wide-field swept-source OCT could even replace ultrasound as the best way to follow ocular tumors."

What the Future Holds

It seems clear that OCT-based technologies hold tremendous promise for retina management. "OCT has revolutionized the way we care for patients," says Dr. Rosenfeld. "A few months ago I had color fundus images done, as well as autofluorescence and infrared reflectance images. It was torture! But with OCT, you don't even have to be dilated, and you can do a scan in three or four seconds. It's a remarkable technology, and patients rarely complain. Most important, you can repeat it as often as you like. It's fast, and it's not painful."

Dr. Sadda notes that many doctors still make mistakes when imaging the retina with current OCT technology. "One common error is to look at the thickness maps alone—the automatic data that comes from the device—and simply assume it's correct," he says. "Those maps can be erroneous because it's very hard for the software to calculate retinal thickness accurately when you have disease disrupting the various retinal layers. For that reason it's important to look at the individual B-scans and the data that underlies the quantitatively derived data. And of course, there are other artifacts, such as conjugate image artifacts, that can also be misleading. This is the reason we have training course at the Academy and other meetings. Even with the current OCT technology, there's still a lot to learn."

Most retina specialists are currently using swept-source OCT; more advanced versions of OCT are not yet available in the United States. However, that will change in the years ahead. Should a clinician be thinking about upgrading? "If I was in the market for a new OCT device, and I could buy a swept-source OCT, what would be the disadvantage?" asks Dr. Sadda. "As long as I have normative data to use for comparisons when following my patients, which will presumably exist when these devices are cleared, then the only advantage spectral-domain might have over swept-source OCT would be cost. I think swept-source is the future of OCT devices."

"OptoVue has a spectral-domain instrument that seems to have a head start in the marketplace," notes Dr. Rosenfeld. "The company has placed hundreds of their instruments in the hands of retinal specialists around the world. But other companies, including Carl Zeiss Meditec, Heidelberg, Nidek and Topcon, are also developing these instruments. Heidelberg and Nidek are developing spectral-domain-based technology, but Topcon and Zeiss have swept-source instruments that are being tested in clinics right now. So, there's an open competition going on for the hearts and minds of the vitreoretinal community. We should see a huge transformation in the marketplace over the next year. A number of instruments should get FDA approval, so there will be lots of competition." REVIEW

Dr. Rosenfeld has received research grants in collaboration with Carl Zeiss Meditec; Dr. Duker receives research support from Carl Zeiss Meditec and OptoVue. Dr. Sadda has received research support from and served as a consultant to Carl Zeiss Meditec and Optos. Dr. Charles has no financial ties to any products or technologies mentioned.


EHR and Glaucoma: Perfect Together?

Despite some downsides, electronic records have practical advantages—especially if you're managing glaucoma.

Joel S. Schuman, MD, Pittsburgh

The switch to electronic health records is seen by many as—at best—a mixed blessing. In addition to the challenges that come with any kind of sweeping change, using EHR can be more time-consuming than using paper charts, and it comes with some pitfalls that don't exist with the traditional system. On the other hand, it offers some significant benefits—and some of those benefits are of particular use to those of us who manage glaucoma.

Here, I'd like to discuss what some surveys are showing about doctors' reactions to implementing EHR; review some of the benefits and downsides of using EHR; and highlight a few of the reasons EHR can be advantageous when managing glaucoma.

Reacting to Change

Recent surveys conducted by the American Academy of Ophthalmology provide a sense of where ophthalmologists stand in terms of adopting EHR. In 2013, 1,500 Academy members were surveyed about this; 500 replied. A third of the responding practices said they already had EHR; 15 percent had implemented EHR for some of their doctors or were in the process of implementation; and another third planned to implement EHR in the next couple of years. Of the doctors already using EHR, half were satisfied or extremely satisfied with their system. Forty-two percent reported stable or increased overall productivity; 20 percent reported that overall costs were stable or had decreased. Half of those using EHR said they would recommend their EHR to fellow ophthalmologists.

These numbers are hardly overwhelming, but most ophthalmologists might find them surprisingly positive. Even I was a little surprised that this many people were happy with their EHR systems, for the simple reason that they are a part of practice that doctors love to hate. However, if you ask physicians who have made the switch to EHR whether they'd be willing to go back to paper charts, only a small number say yes.

The data suggest that the answer to that last question changes over time as people get used to working with EHR. The longer a doctor has used EHR, the less likely it is that he'll be willing to switch back to paper charts. In 2010, for example, a survey was done here at the University of Pittsburgh Medical Center. In that survey, about 30 percent of the people who had been using UPMC's chosen outpatient system (EpicCare) for less than three months said they'd prefer to return to paper charts. But among those who had used the system for six months, the number dropped to 15 percent. The percentage was the same at one year, but by two years, it dropped to 5 percent.

Here at UPMC, we've looked at the acceptance of electronic records across our entire system. (UPMC encompasses 20 hospitals with about 3,500 employed physicians and more than 60,000 employees overall; it's a $12 billion-a-year global health enterprise.) In 2010 and 2011 we surveyed a random subset of our doctors and support staff. We found that about 70 percent of those surveyed thought EpicCare was an effective tool that gave good access to test results; that result didn't change a year later. Asked whether the system was more accurate than paper charts, whether the switch had contributed

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positively to the patient's care, and whether it made prescribing easier, 55 to 60 percent said yes in 2010; that rose about 10 percentage points by the following year. However, only about 40 percent agreed that the system improved communication, and only 15 percent felt that it increased their confidence in the data. Those numbers did not change between 2010 and 2011. (We'll talk about the probable reason for those answers shortly.)

Earnings Impact

We also looked at return on investment, using data from a four-year longitudinal study with a six-year follow-up. The four-year study looked at a fixed group of clinicians—people who were already in a stable practice—for the two years before implementation of the EHR, which took place in 2006, and then two years post-implementation. Our purpose was to look at the impact of implementing an ambulatory EHR in an academic ophthalmology practice, based on clinical productivity measures that could be quantified.

We found no difference in average number of office encounters per month between pre-implementation and post-implementation. *(See charts, p. 62.)* There was an intentional drop in office encounters during the period of implementation itself, but then the numbers came right back up within a month of implementation; implementing EHR had no effect on volume. The same was true six years out; volumes were stable.

We also looked at charges and work relative value units, or wRVUs. The charges were unchanged from two years before to two years after implementation *(see chart, p. 64)*, and there was no difference in charges per office encounter per faculty per month. The same thing was true six years later in 2014—there was no significant difference.

One advantage some electronic records programs have when managing glaucoma is the ability to show multiple parameters onscreen at once, and how they've changed over time. Some programs can also graph multiple parameters simultaneously, making it easy to see whether your patient is stable or getting better or worse. The graphs can also show when an intervention took place *(see sample, above)* or highlight the period of time when the patient was on one particular medication for comparison to other periods.

One area in which we did find change was testing; we found more testing was being billed after implementation of EHR than before. Prior to implementation the numbers for testing were flat (from 2004 to 2006). After implementation there was a big rise in testing. Then, from 2008 to 2014, we found no change. We think the reason for this is not that more testing was being done, but that more testing was being captured and billed for. When doctors have to fill out a paper superbill, they may forget to bill for some of the tests. Maybe they didn't complete their interpretation of the results. With the EHR, every test is captured, and the system forces you to complete your interpretation. (For the record, the unchanged rate of income per office encounter did not reflect the change in testing income.)

EHR Downsides

Managing patients using EHR does have some drawbacks:

• ***It can be more time-consuming for the physician.*** About half of the physicians surveyed at UPMC felt that using EHR added a couple of hours to the workday. This is true, in part, because EHR forms require more extensive input than traditional paper records. However, 30 percent said there was no change, and about 10 percent thought it was actually more efficient and took less time than paper charts.

My experience has been that it does add time to the workday. Probably the biggest reason for this is that the electronic record requires you to provide much more information than you would provide in a traditional paper chart. Also, in a paper chart you can abbreviate things or use your own shorthand; that's a lot faster than providing every piece of information the EHR system is asking for.

However, it's worth noting that the extra work time people notice when using EHR may be offset—at least a little—by the fact that when you're done, you're done. At the end of

the day, when you close the charts, that's it; you've completed all of your required tasks. Among other things, the letters to referring physicians are done; they go out the same day or the next day. (Academic medical centers have typically been notorious for the lag between a patient being seen and communication with the referring physician. On the other hand, not every referring physician is thrilled to receive a five-page letter that's filled with information the physician wasn't looking for.)

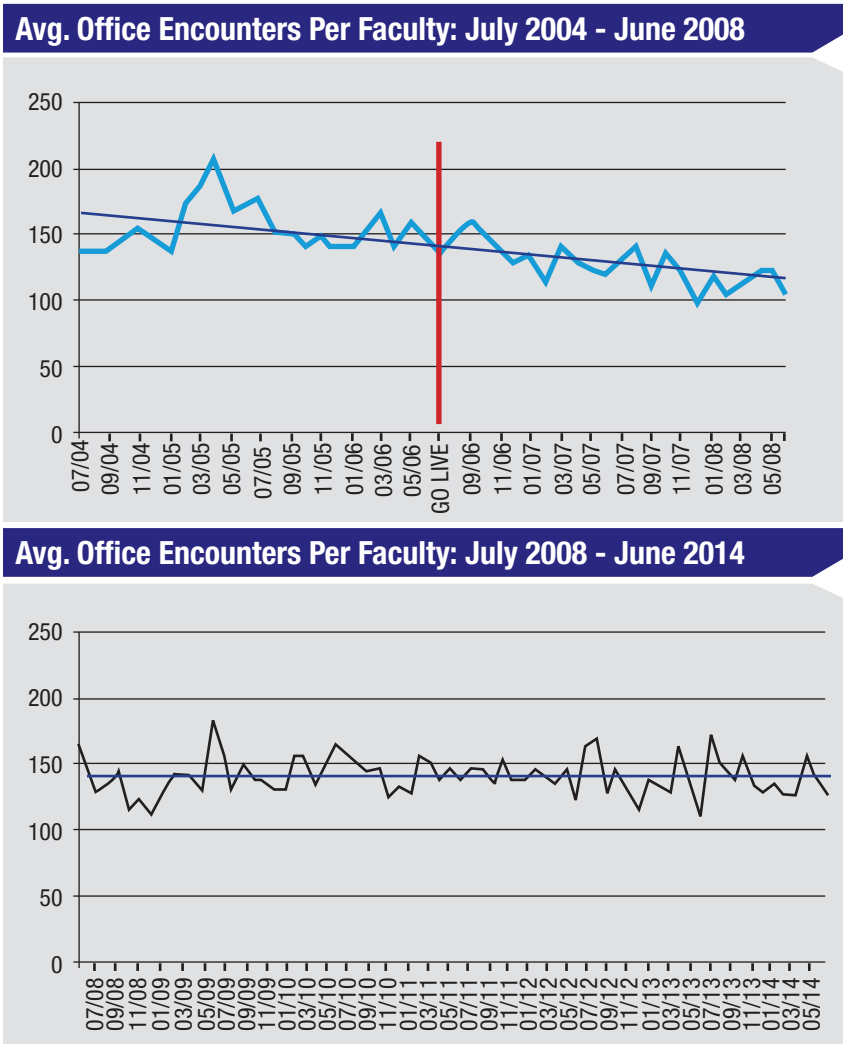
• ***It's harder to manage images.*** For ophthalmologists, one of the biggest problems with EHR is storing and retrieving images, such as scans, photographs and visual fields. Because many systems don't provide an easy way to do this, many doctors are using one system for text and another system for images. Sometimes the image system integrates with the text system; sometimes it doesn't.

Another side to the issue of managing images is that many of us like to draw what we're seeing. I used to draw what I saw on gonioscopy, and draw the optic nerve; I don't do that any more because it's just too cumbersome to do on a computer. However, not being able to create a drawing is somewhat offset by the fact that I have photos, OCTs and visual fields that I can access immediately. They usually give me the information I would have gotten from a drawing. (Plus, the information is presented in a more standardized and objective way.)

• ***Accuracy of chart information isn't guaranteed.*** Based on my own experience with this system, I'd say that electronic records can be a very effective tool. However, I wouldn't say the patient data is more accurate. Incorrectly entered data can and does occur. Also, the carry forward function may lead to the inclusion of outdated information. The carry forward function can speed up data entry, but you need to make sure that you change the relevant parameters to reflect your patient's current status.

• ***Some systems require multiple log-ins.*** People are often annoyed by having to log in over and over again to access different programs. (Our system includes a tap-and-go feature that circumvents most of this. It saves us a lot of time during the day.)

• ***Interference with patient interaction.*** Perhaps the most common objection to EHR is having to type information into the computer during the patient visit. The more time we spend typing, the less time we're interacting with the patient. I think this is a tremendous waste of time for a doctor, so I use a scribe; some of the other physicians here at UPMC do the same. Scribes make things go much faster and allow you to interact directly with the patient throughout the visit, as opposed to sitting behind



Data from two studies at the University of Pittsburgh Medical Center looking at the impact of implementing an ambulatory EHR system in an academic ophthalmology practice. The first, four-year study looked at clinicians who were in a stable practice for two years before and after implementation. The data showed no difference in average number of office encounters per month between the pre-implementation and post-implementation periods, except for an intentional drop in office encounters during the period of implementation. (The numbers came back up within a month.) At six years out, volumes were still stable.

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a monitor typing. Of course, there's some cost associated with having a scribe in the room, but we have found that it increases your productivity enough that that the increase in patient volume far exceeds the cost of the scribe.

EHR Benefits

Despite the drawbacks listed above, the advantages EHR offers to the patient and physician are significant:

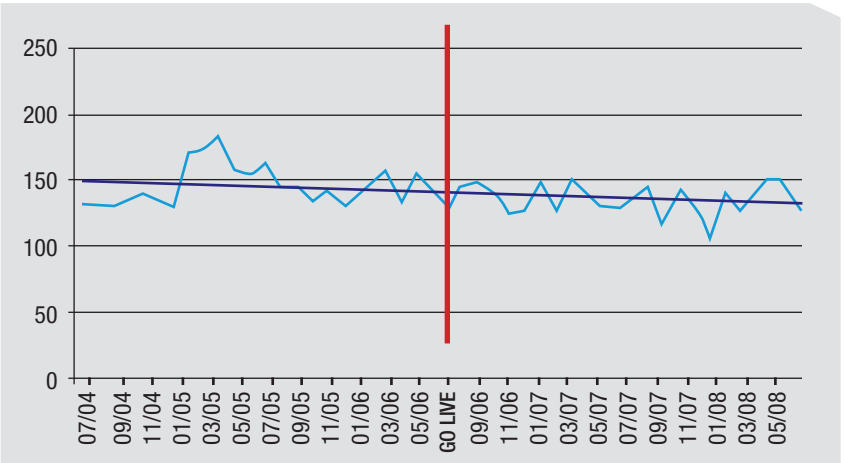
• ***No more lost charts.*** Many large practices have about a 10-percent rate of not being able to locate the patient's chart when the patient shows up. That's not an issue when you're using electronic records.

• ***Remote access to records.*** With EHR you can access a patient's record from anywhere in the world. That means you can address a problem your patient is having even if you happen to be in Mexico, Europe or Asia.

• ***Electronic management of prescriptions.*** This is a huge bonus for the patient and the physician. For example, when you enter in the name of a drug you want to prescribe, the system can tell you whether or not that drug is in the patient's formulary. This prevents follow-up phone calls from the pharmacy saying, "You prescribed this, but the patient's insurance won't pay for it. What else can the patient take?" You'll know if there's a problem while you're still with the patient.

• ***More complete information about the patient.*** If your EHR is connected to a larger health system, the electronic record may contain all of the other physician information that has been entered regarding a given patient. That gives you a sense of the overall health of the patient and also helps to guide your prescribing (assuming the list of medications is up-to-date, which isn't guaranteed, thanks to human error). For example, if the patient is taking an oral beta-blocker, there's no point to prescribing a topical beta-blocker. It's very helpful to have that clinical information at your fingertips.

Avg. wRVUs Per Office Encounter Per Faculty: July 2004 - June 2008



Another study at the University of Pittsburgh Medical Center looked at charges and work relative value units two years before and after EHR implementation. Charges were unchanged before and after implementation, and the same thing was true six years later.

• ***Notes are legible and easy to locate.*** The notes in a chart are always easy to read, standardized and in the same place. I can't tell you how many times during my training and as a fellow and faculty member I would look in a chart and be unable to decipher the prior notes. (This was true sometimes even if I had written the prior notes myself!) So having the information in a typed or graphical form, and being able to find it at a glance because you know where everything is on the electronic form is a big plus. Also, in the operating room the postoperative notes are usually templated and standardized, so they're quick and easy to do.

• ***Patients can access their records.*** EHR technology also has a few profound advantages for the patient. One of those is giving patients the ability to get their own test results and medical history remotely at their convenience; that includes information about their allergies, medications and health problems, as well as lab and test results.

This is empowering for the patient. At the same time, it reduces the power of the physician a little, because the patient is in control of her own information. It's something of a brave new world for us as doctors, because the patient can take that information and go anywhere. Of course, that doesn't include digital records such as visual fields—so far. But some countries already have medical systems that make all of that available to patients, and I predict that will happen here within a few years.

• ***Easier doctor-patient communication.*** EHR makes it easy for the patient to communicate with the physician and the physician's office online. Patients can schedule, confirm and cancel appointments; they can exchange secure messages with the physician; they can request a prescription renewal; they can get their eyeglass prescription automatically; they can even have an online e-visit with a physician to address some common conditions.

Benefits: Managing Glaucoma

Because of issues that are unique to managing glaucoma, EHR is

particularly advantageous:

• ***It can help monitor adherence***. EHR can tell you whether and when the patient's prescription was filled, which gives you a hint regarding the patient's adherence to therapy. You wouldn't be able to easily get that information any other way.

• ***It can present and graph multiple parameters and how they've changed over time.*** One feature of some EHR systems (including ours) is so useful as to be considered disruptive technology—particularly if you're treating glaucoma. Our system includes a program called Synopsis that allows us to see all of the discrete parameters that we're tracking, over time, on-screen, all at once. We can look at different tests results obtained at different times and compare them directly. That means we can look at the visual field data from a series of visits; we can also look at visual fields and OCT data at the same time, allowing us to look for correspondence in structure and function. Even better, it allows us to graph up to four of those parameters simultaneously. *(See example, p. 61.)* In addition to graphing IOP over time, you can look at nerve fiber layer thickness and visual field index or mean deviation. This makes it easy to see whether or not your patient is stable or getting better or worse, and whether you have the IOP under good control.

The graphs can also show when interventions took place and what medications the patient was on during a given period, as well as when they stopped using a given medication. In our program, if you hover over a medication with the mouse, it highlights the period of time when the patient was on that medication. That makes it easy to compare what happened on different medications. When the patient was on timolol, this was the pressure; when the patient was on latanoprost, this was the pressure; on Simbrinza, this was the pressure. This program gives us information at a glance that in the old days we'd have to go thumbing through the chart to identify, and it gives it to us in a way that could not be presented on paper. We have the ability to compare different parameters on the fly.

It's much easier for patients to understand a visual presentation than a verbal description.

Furthermore, we can link the text and image systems so that the patient's test images come up automatically when you open that patient's text-based chart. This is a big advantage, because the fewer steps you have to take to see what you need to see, the better.

This is one example of a disruptive technology that can be a part of EHR that enables the physician to provide better patient care. And it's something you can only do with the help of a computer.

• ***It helps with patient education***. Adherence is always a problem when managing a silent, often asymptomatic disease like glaucoma. EHR can help by making it easy to show the patient the problem on-screen and show how your interventions are impacting it. Seeing this on-screen can help motivate patients to make the effort to follow your instructions.

For example, I can show patients the trend of their IOP over the past two, five or 10 years, and what medications they were on during that time. I can even show them what was happening to their visual field and retinal nerve fiber layer during that time, although to avoid confusion I may just show the patient how the IOP changed and what effect each intervention and medication had. If the patient has a glaucomatous abnormality such as a nerve fiber layer loss or visual field defect, I can call up the OCT and visual field with a click of the mouse and show the patient exactly where the abnormality is. (Many programs highlight the abnormal area in red.) It's much easier for patients to understand a visual presentation than a verbal description. That helps the patient understand why we're using a certain medication, and it may even help encourage compliance.

Note: When graphing or comparing multiple results over time it's important to remember that you may need to eliminate some results from the series you're comparing or graphing. If you're following a glaucoma patient over time and the patient had a bad day for some reason, or there was something wrong with the test at one visit, you can eliminate that test data from the series. More important, if the patient had a surgical intervention during the follow-up period, you can eliminate the test results from before the surgical intervention. If you fail to do that and you compare the results from the beginning, the patient will appear to be on a downward slope, simply because the surgical intervention changed the patient's trajectory. It's important to check for this, because even in academic medical centers you don't always get the correct tests included in the analysis.

Another thing to remember is to manually store any part of the exam that isn't automatically captured by the EHR system. In our case, I always store the statistical-analysis portion of the visual field printout so that I can see what's happened over time with the patient, instead of just comparing one field to the next. Our system doesn't do this automatically;

we have to upload the image into the image storage and retrieval system. However, there is a system called Forum, made by Carl Zeiss Meditec, that allows you to send the visual field information and the OCT information from their machines into a single database on a server; it acquires the data, as well as the image. It also allows you to remove confounding testing data from the database. I'm not sure if any other systems offer this option, but having software that will integrate the data and allow you to selectively include certain data points in the analysis makes data analysis much less cumbersome.

A Step in the Right Direction

Overall, I believe EHR is better both for the doctor and the patient, and that's especially true when managing glaucoma. A good system will allow you to evaluate your patient's progress over time much more easily than you could with a paper chart, showing the data graphically and interactively; it will let you interpret tests in a more intuitive fashion and compare structure and function, looking at tests of both simultaneously, without having to flip pages. It can be a great tool for patient education; it makes prescribing easier and prevents corrections because a drug wasn't on the patient's formulary; it lets you know if a patient hasn't filled a prescription; and it makes it much easier for the patient to get hold of information and communicate with you. You'll definitely be tracking tests better than you were with pen and paper; the system will capture all the tests that were done and help ensure that you get paid for your work.

Using EHR is a different experience than using paper charts, and it can be slightly more cumbersome. But for somebody taking care of patients with glaucoma, a good EHR system is a boon in so many ways that the advantages far outweigh the annoyances and disadvantages. REVIEW

Dr. Schuman is Distinguished Professor, The Eye and Ear Foundation Endowed Chair in Ophthalmology and chairman of the department of ophthalmology at the University of Pittsburgh School of Medicine, professor of bioengineering at the University of Pittsburgh and director of the UPMC Eye Center. He receives royalties for intellectual property related to OCT licensed by MIT and MEEI to Zeiss; he otherwise has no financial interest in any product discussed in this article.

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The Link to a New Refractive Procedure?

Surgeons are perfecting the use of corneal collagen cross-linking for the treatment of refractive errors.

Walter Bethke, Managing Editor

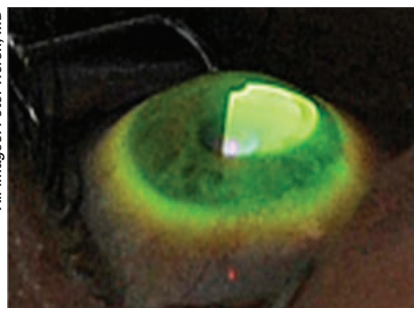
The therapeutic modality known as corneal collagen cross-linking has intrigued surgeons for several years now, as it's shown potential for stabilizing some corneas that may have been on the road to corneal transplants without such treatment. Recently, researchers outside of the United States and one of the companies behind several cross-linking devices, Avedro, have begun investigating the ability of cross-linking to create a refractive change in corneas that are otherwise healthy. Here's a look at what they've found so far.

PiXL

The technique and technology being investigated by Avedro is known as photorefractive intrastromal cross-linking, or PiXL; it uses the company's KXL II device, which features an active eye tracker.

Teaneck, N.J., surgeon Peter Hersh, MD, who is on the medical advisory board for Avedro, says the treatment needs both the energy to make the tissue alteration and the ability to put the energy in the proper place. "What PiXL does is take advantage of the fact that when you make isolated focal or topography-guided changes in corneal biomechanics, it can change the corneal shape and give a refractive outcome," he explains. "The equipment needs to have the ability to change treatment sizes, powers and patterns, as well as the ability to have an eye tracker so it can put the treatment in the right position.

"PiXL can be approached in a couple of ways," Dr. Hersh continues. "First, in irregular corneas and those with keratoconus, a surgeon can treat the cone itself, or treat the corneal topography, so to speak, by doing a focal application over the cone. Typically, this is a graded application, meaning there's more UV energy delivered right over the cone, and it gradually grades out or blends as you move away from the tip of the cone. You can take this concept a step further: If you focally treat the center of the cornea with customized patterns, you can get correction of modest amounts of myopia, hyperopia and astigmatism." Dr. Hersh says PiXL treatments usually use higher levels of energy delivered centrally than are used in standard cross-linking. "For instance, where it's standard to use 5.4 mJ for cross-linking, we are looking at doubling or tripling this in a graded pattern for the treatment of irregular cornea PiXL patients and refractive PiXL patients," he avers. "We don't know what powers are optimal yet, but that's the thinking."



All images: Peter Hersh, MD

One application for PiXL involves applying it on the cone in keratoconus patients.

John Kanellopoulos, MD, of Athens, Greece, has used PiXL in some patients so far in his practice and describes the myopic protocol: "The light profile is a very small-diameter beam of 4 mm placed at the corneal apex with a very high level of UV light at the magnitude of 15 mJ and a fluence of 45 mW/cm^2," he says. "And it uses a riboflavin solution of 0.25%, which is about three times more than the standard solution used in the Dres-

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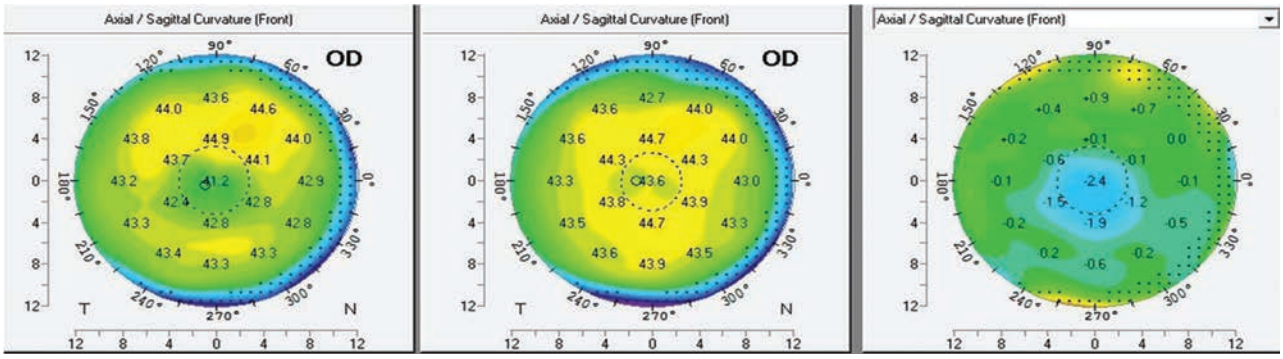


The PiXL treatment with the KXL II device treats myopia by placing the energy with a higher concentration in the central cornea and then gradually decreasing the intensity away from the center. In this myope, nine months post-PiXL treatment, the surgeon was able to achieve a little more than 2 D of flattening.

den protocol. The hyperopic profile is more of a doughnut shape 1-mm wide starting at 4 mm or 6 mm, similar in appearance to a hyperopic excimer ablation. The depth of the treatment in an endothelium-off treatment is deeper, extending to about 60 percent of corneal thickness. In epithelium-on treatments, it extends to a third or half of the corneal thickness."

PiXL's Performance

Though PiXL is proving to have an effect, some surgeons say that, like any new procedure, nomograms need to be worked out in order to increase the procedure's predictability.

The Czech Republic's Pavel Stodulka, MD, PhD, has performed PiXL on 10 patients. "I've performed it in two patient groups," he says. "I've done it in keratoconus patients and in patients with low myopic refractive surprises after IOL implantation. Both the predictability and efficacy were quite low in both groups. Our best case was a 52-year-old pseudophakic lady with a refraction of -1.25 -0.25 x 0 and uncorrected distance visual acuity of 0.1 [20/200] and best-corrected distance acuity of 1.0 [20/20]. She became [20/20] uncorrected a month after PiXL treatment. She was an outstanding case, but we didn't get any other similar result. Corneal haze wasn't really a problem and we didn't see any PiXL-specific complications."

Matthias Elling, MD, senior physician at Ruhr University Bochum in Germany, is a researcher in a study of 33 PiXL eyes with six months of follow-up. "We observed that if patients had -3 D preop, we weren't able to reach emmetropia completely," he says. "But in lower myopes we came nearer to it. The refractive outcome is stable, and the median uncorrected acuity is 0.8 [20/25] postop. So, the early results show it's possible to do a refractive treatment with cross-linking, and we're able to correct up to 2 D."

Dr. Kanellopoulos sees potential in the procedure but has run into the variability, as well. "In our patients, 80 percent were within 0.5 D of intended correction up to a year postop," he says. "We didn't see any adverse effects or complications, with the exception of one case in the epithelium-on group developing a small epithelial defect, and some epithelium-off cases having a delayed epithelialization. The only issue of relative concern was that we did encounter a few young patients who had a minimal refractive effect, even though a higher refractive effect was anticipated. For instance, one 34-year-old woman, in whom 2 D of correction was planned via a transepithelial treatment, only achieved 0.5 D. This procedure has proven its feasibility but needs further study to refine a nomogram."

Dr. Hersh says the procedure's predictability is a result of a host of factors. "These are very early studies," he says. "And they've shown fairly reproducible results. Postop, on average, surgeons are getting 1.25 to 1.5 D of correction with these treatments. These are patients who start out -1 or -2 or so. Yes, some people are getting more correction than others, just as they did in the early days of PRK. I think centration of the treatment is ultimately an issue, as is proper alignment and proper registration. Clearly, since you're trying to meticulously place the treatment energy, all of these will be important components."

Singapore surgeon Jerry Tan, who has experience with cross-linking, thinks that PiXL's biggest hurdle may be current procedures. "I have used the technology and I think it will work," he says. "However, treatment times and healing times are too long. Currently, LASIK is very fast and accurate—making a LASIK flap takes 10 seconds and treating a low myope takes five to 10 seconds. How can you get any faster than that? Plus, LASIK patients see very well after a few hours with hardly any discomfort. PiXL has a tough act to follow." REVIEW

Drs. Hersh and Kanellopoulos are consultants to Avedro. Drs. Stodulka, Elling and Tan have no financial interest in the products mentioned.

A Host of New Tools for a Range of Surgical Moves

Beaver-Visitec International has introduced two new products—Bonn Forceps and Tying Forceps—that follow the capsulorhexis forceps launched in 2014, with the same design features:

- developed for micro-incision cataract surgery;
- ergonomic handle provides superior control;
- precise and consistent tip alignment; and
- safety—easily identifiable as single-use.

The Bonn Forceps offer excellent tissue grasping and grip strength; blunt teeth for minimal tissue trauma; and a precise platform alignment to grip sutures.

The Tying Forceps feature rounded platform edges to ensure sutures are not cut; fine tips for accuracy; and a precise platform alignment to grip sutures.

BVI offers a wide range of single-use instruments for ophthalmic surgery, available individually or in BVI CustomEyes kits. The benefits of single-use instruments include improved patient safety; consistent performance; time saving and greater convenience; and optimization of cost and budget control.

For information on any BVI products, call 1 (866) 906-8080 or visit visit beaver-visitec.com.

New Trio from Rhein Medical

Rhein Medical has debuted three new surgical instruments. The Tearse Meibomian Expressor Forceps, developed with James Tearse, MD, are ideal for expressing meibomian glands in all four lids and designed to be used while probing glands. Specially angled compression plates squeeze the lids to direct meibum flow out of the orifice. The physician can control compression pressure from soft to very firm. The handle is ambidextrous and allows use for both upper and lower lids, while a compression stop prevents crushing of the glands and lids. Unique compression plates are designed to express either 5 mm or 8 mm by rotating the handle. The stainless steel forceps are reusable, autoclavable and guaranteed for life.

The Younger 360 Degree Capsule Polisher, developed with Jared R. Younger, MD, features a special angulated shaft that allows quick and easy, full 360-degree polishing of both the anterior and posterior capsules with one instrument. The unique angulation eliminates the need for using two instruments, or having to exit and enter through a

This article has no commercial sponsorship.

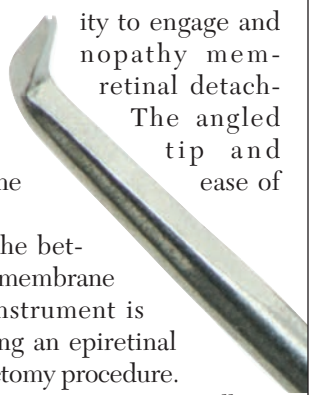
side-port incision to complete polishing.

The Folden Femto Double-Ended Dissector, 0.7 mm and 1.2 mm, developed with David Folden, MD, is a single instrument designed for smooth opening of all femtosecond laser-created corneal incisions during cataract surgery. The double-ended instrument measures 0.7 mm at one end and 1.2 mm at the other. The polished, semi-blunted leading tip allows for "scoring" of the epithelium and provides easy, glided entry into the femtosecond laser-created corneal incision. The sharp edge design cleanly separates residual tissue bridges and stromal adhesions that provide resistance to entry using standard instruments. For clear corneal incisions, the 1.2-mm end provides easy entry into standard small incisions as well as sub-2.0 mm micro-incisions. The 0.7-mm end provides adequate clearance for entry into the paracentesis. Arcuate incisions for astigmatism may be opened quickly and cleanly down to their base without risk of perforation. The polished semi-blunted leading tip glides smoothly along the base of the arcuate incision, while the sharp edge provides smooth opening of stromal tissue bridges and maintains clean epithelial edges. Fewer surface abrasions result in less foreign body sensation and improved patient comfort postoperatively.

For information on any of these products, call (727) 209-2244.

B + L: New Fekrat Retinal Picks Improve Membrane Peeling

Bausch + Lomb Storz Ophthalmic Instruments has introduced the newly designed E6000 (23 ga.) and E6001 (25 ga.) Fekrat Retinal Picks. The Fekrat Retinal Pick improves the ability to engage and lift proliferative vitreoretinopathy membranes in eyes with recurrent retinal detachment and PVR membranes. The angled pick, with a pyramid-shaped tip and slightly blunt nose, improves the ease of navigation in the eye.



The tip design allows for the better initiation of the edge of a membrane while avoiding nicks. The instrument is designed for use in performing an epiretinal membrane peel during a vitrectomy procedure.

For more information, visit Storz Eye.com or call 1 (800) 338-2020.

Studies Offer Support for New Maculopathy Tracking System

Vital Art and Science released four new studies in the continuing scientific investigations of its recently

launched mVT Service, an innovative medical device that conveniently and accurately tracks the progression of maculopathies.

The device is available only by prescription and consists of an easily downloaded app that can be used on any Apple smartphone or tablet. Patient test data are automatically uploaded to a physician portal, where licensed eye-care professionals can monitor all patient test results. In the studies the device showed value in features important in a screening tool: predictive response; stability of results; ability to detect visual function improvement; and reliability.

Researchers in San Francisco and Berkeley, Calif., assessed the Service against nine other tools for predictive response, or the ability to predict which patients are at the greatest risk of progressing to advanced disease. mVT showed the most predictive promise. University of Liverpool researchers investigated the stability of mVT results. Stability prior to disease onset in at-risk eyes is essential for a reliable screening test; stability of the mVT was confirmed. The investigators also commented that unlike other tests, the mVT is convenient and users report no testing difficulties.

The National Institutes of Health supported a diabetic retinopathy study in Dallas to see if the mVT Service detects visual function improvement from anti-VEGF treatments. Results indicated that mVT clearly detects visual function improvement and, in fact, appears to be more sensitive than either visual acuity or letter contrast sensitivity in detecting changes. The fourth study, also supported by NIH, investigated the strength of the shape discrimination hyperacuity test methodology of the mVT. Results confirmed its reliability and accuracy. Researchers noted mVT should be especially valuable for longer-duration treatments because of its convenient home monitoring.

The new mVT Service is the only simple, FDA-cleared, low-cost, mobile, validated method available for these patients to test their vision at home. Patients take a simple four to six minute self-test, performed on the timetable recommended by the doctor (usually twice a week). Patient test results are automatically delivered to a HIPAA-compliant database and analyzed for prescriber review.

For information, visit myvisiontrack.com or call 1 (844) 267-8019 for information; for complete data from all four studies visit http://myvisiontrack.com/for-physicians.

Partnership Announces Halo Sterile Cornea

Stephens Instruments has partnered with Lions VisionGift to deliver the Halo Sterile Cornea Allograft. Developed at Lions VisionGift's Vision Research Lab, the Halo Sterile Cornea is a shelf-stable, e-beam sterilized graft for glaucoma tube-shunt coverage, deep anterior lamellar keratoplasty and tectonic use. Halo Sterile Cornea features patented easy-peel packaging for quick and safe introduction in the OR, no rinsing or reconstitution required. For information, visit halograft.org. REVIEW

(continued from page 46)

macular volume decreased by 0.2 mm^3 and median fluorescein leakage area within the grid decreased by 0.7 disc areas.

These researchers found that focal/grid laser in these non-center-involved eyes was associated with relatively stable visual acuity and retinal thickness measurements and decreased fluorescein leakage area at one year. The ETDRS had previously recommended considering the use of focal/grid laser in eyes with non-center-involved, clinically significant macular edema. Although this study is small, the investigators found that considering the use of focal/grid laser still seems appropriate.

"In patients who have few symptoms, decent vision and a cluster of leakage outside the center, many ophthalmologists are still recommending laser, because immediate results are not needed and because laser may have a longer-term benefit," Dr. Stone says. "In fact, the Diabetic Retinopathy Clinical Research Network is evaluating what to do with these patients, and they have randomized patients who have center-involved diabetic macular edema but good vision to anti-VEGF agents, laser or observation." REVIEW

Dr. Stone's practice has ongoing research projects with Genentech and Regeneron, and Dr. Boyer is a consultant to Regeneron and Genentech.

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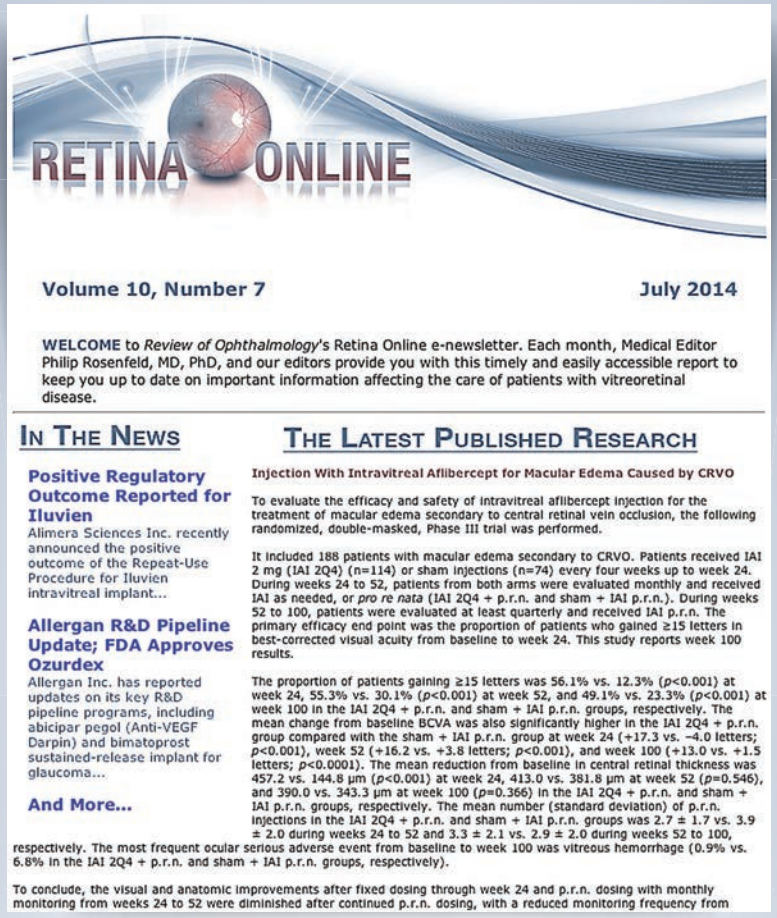

RETINA ONLINE

Volume 10, Number 7 July 2014

WELCOME to *Review of Ophthalmology*'s Retina Online e-newsletter. Each month, Medical Editor Philip Rosenfeld, MD, PhD, and our editors provide you with this timely and easily accessible report to keep you up to date on important information affecting the care of patients with vitreoretinal disease.

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THE LATEST PUBLISHED RESEARCH

Injection With Intravitreal Aflibercept for Macular Edema Caused by CRVO

To evaluate the efficacy and safety of intravitreal aflibercept injection for the treatment of macular edema secondary to central retinal vein occlusion, the following randomized, double-masked, Phase III trial was performed.

It included 188 patients with macular edema secondary to CRVO. Patients received IAI 2 mg (IAI 2Q4) (n=114) or sham injections (n=74) every four weeks up to week 24. During weeks 24 to 52, patients from both arms were evaluated monthly and received IAI as needed, or *pro re nata* (IAI 2Q4 + p.r.n. and sham + IAI p.r.n.). During weeks 52 to 100, patients were evaluated at least quarterly and received IAI p.r.n. The primary efficacy end point was the proportion of patients who gained ≥15 letters in best-corrected visual acuity from baseline to week 24. This study reports week 100 results.

The proportion of patients gaining ≥15 letters was 56.1% vs. 12.3% (p<0.001) at week 24, 55.3% vs. 30.1% (p<0.001) at week 52, and 49.1% vs. 23.3% (p<0.001) at week 100 in the IAI 2Q4 + p.r.n. and sham + IAI p.r.n. groups, respectively. The mean change from baseline BCVA was also significantly higher in the IAI 2Q4 + p.r.n. group compared with the sham + IAI p.r.n. group at week 24 (+17.3 vs. −4.0 letters; p<0.001), week 52 (+16.2 vs. +3.8 letters; p<0.001), and week 100 (+13.0 vs. +1.5 letters; p<0.0001). The mean reduction from baseline in central retinal thickness was 457.2 vs. 144.8 µm (p<0.001) at week 24, 413.0 vs. 381.8 µm at week 52 (p=0.546), and 390.0 vs. 343.3 µm at week 100 (p=0.366) in the IAI 2Q4 + p.r.n. and sham + IAI p.r.n. groups, respectively. The mean number (standard deviation) of p.r.n. injections in the IAI 2Q4 + p.r.n. and sham + IAI p.r.n. groups was 2.7 ± 1.7 vs. 3.9 ± 2.0 during weeks 24 to 52 and 3.3 ± 2.1 vs. 2.9 ± 2.0 during weeks 52 to 100, respectively. The most frequent ocular serious adverse event from baseline to week 100 was vitreous hemorrhage (0.9% vs. 6.8% in the IAI 2Q4 + p.r.n. and sham + IAI p.r.n. groups, respectively).

To conclude, the visual and anatomic improvements after fixed dosing through week 24 and p.r.n. dosing with monthly monitoring from weeks 24 to 52 were diminished after continued p.r.n. dosing, with a reduced monitoring frequency from

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After noticing a black spot in his central vision two weeks earlier, an HIV-postive man seeks treatment at Wills.

Nathan Cutler, MD, and Ehsan Rahimy, MD

Presentation

A 67-year-old male presented with a two-week history of seeing a central black spot in his left eye. The scotoma was fixed and had not changed in appearance since its onset. He denied any associated diplopia, pain, redness, photophobia, scalp tenderness or jaw pain. On review of systems, he denied any recent trauma, fever, rash, cough, weight loss or recent illness.

Medical History

The patient was HIV-positive, first diagnosed in 2009. He was compliant on HAART therapy with an unknown CD4 count, but stated that his viral load was most recently undetectable. Other medical history included hypertension, hyperlipidemia and chronic kidney disease. His medications included abacavir/lamivudine 600 mg/300 mg daily, raltegravir 400 mg daily, lisinopril 2.5 mg daily and fenofibrate 54 mg daily. The family history was unremarkable. He denied any tobacco or other illicit drug use. He did report a history of unprotected sex with other men, though he denied any history of other opportunistic infections or sexually transmitted diseases. He had no known drug allergies.

Examination

The patient was afebrile with stable vital signs. His visual acuity was 20/25 in the right eye and count fingers in the left eye at presentation without any improvement on pinhole. A positive relative afferent pupillary defect was present in the left eye. Extraocular motility was full bilaterally and intraocular pressure was normal in both eyes. Color plates were full in the right and 0/8 in the left.

External examination was unremarkable. Anterior slit-lamp examination revealed occasional cell in the left anterior chamber. Fundus examination of the left eye revealed occasional vitreous cell and a subtle annular subretinal lesion that was lighter centrally and extended beyond the superior arcade *(See Figure 1)*. Fundus examination of the right eye was unremarkable.

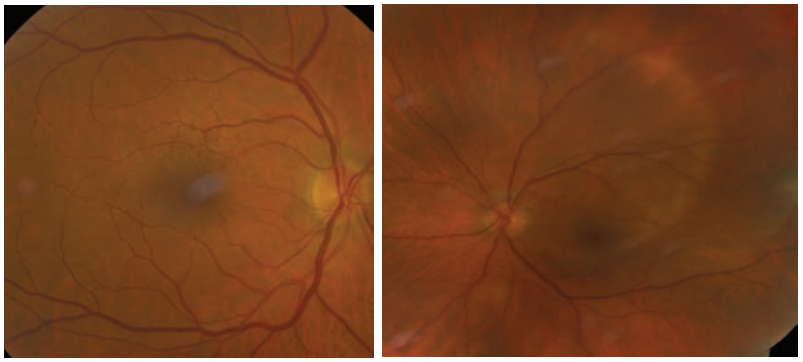

Figure 1. Color fundus photographs of the right and left eye respectively. In the left eye, a subtle subretinal annular lesion is present.

What is your differential diagnosis? What further workup would you pursue? Please turn to p. 80

Diagnosis, Workup and Treatment

Given the patient's acute onset of a unilateral isolated macular lesion, inflammatory and infectious etiologies were high on the differential. These included acute posterior multifocal placoid pigment epitheliopathy (APMPPE); serpiginous choroidopathy; persistant placoid maculopathy; acute syphilitic posterior placoid chorioretinitis; and viral retinitis. Less likely were neoplastic etiologies, including lymphoma or metastatic disease.

Fluorescein angiography demonstrated early patchy hyperfluorescence of the lesion with progressive staining of the outer rim. There was also a mild amount of disc leakage *(See Figure 2)*. FA of the right eye was unremarkable. Indocyanine green angiography demonstrated hypofluorescence of the large placoid lesion *(See Figure 3)*. Spectral domain optical coherence tomography demonstrated choroidal thickening and loss of the photoreceptor inner/outer segment band in the macular region of the left eye *(See Figure 4)*.

Given the clinical presentation and findings on imaging studies, a diagnosis of acute syphilitic posterior placoid chorioretinitis (APPC) was made. This diagnosis was confirmed with serologic testing, which showed a positive rapid plasma reagin (RPR) with a high titer of 1:256 and a positive fluorescent treponemal antibody absorption (FTA-ABS) test.

The patient denied ever being treated for syphilis. He was promptly admitted to the hospital for neurosyphilis treatment with IV penicillin G. He received a two-week course of IV PCN at a dose of 3 million units every four hours and had significant improvement to 20/60 vision in his left eye. At one-year follow-up the lesion had completely resolved on examination and his vision had returned to 20/30.

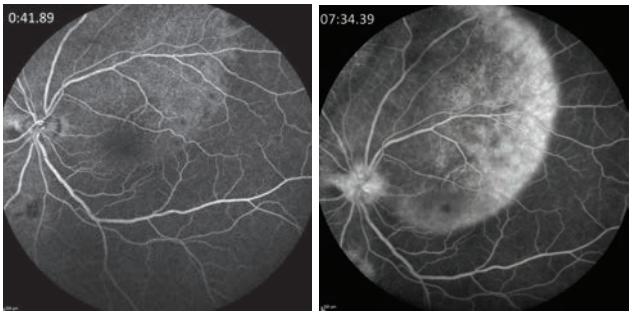

Figure 2. Fluorescein angiography of the left eye. Note the progressive hyperfluorescence of the macular lesion.

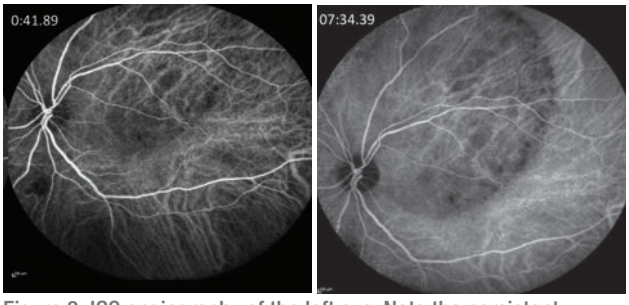

Figure 3. ICG angiography of the left eye. Note the persistent hypofluorescence of the macular lesion.

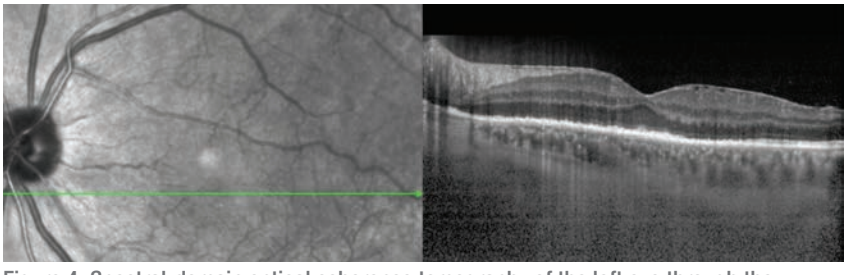
Figure 4. Spectral-domain optical coherence tomography of the left eye through the macula demonstrating loss of the IS/OS band.

Discussion

While the incidence of syphilis in the United States hit a low in 2000 at 2.1 per 100,000 people, it has since been on the rise with increased incidence even as recently as 2012-2013.[1] A particularly vulnerable group is men who have sex with men, who account for 75 percent of new syphilis cases in the United States today.

Acquired syphilis can be divided into four stages. Primary syphilis is characterized by a painless chancre that lasts for two to six weeks. Secondary syphilis has nonspecific systemic symptoms (e.g., malaise, fever and arthralgia) and a maculopapular rash, which can last for four to 10 weeks. Latent syphilis occurs between secondary and tertiary stages, is clinically silent and can last for years to decades. Tertiary syphilis includes cardiovascular and neurological manifestations and occurs months to years after initial infection.

Ocular syphilis can occur at any stage, but is most common during secondary and latent stages.[3] Syphilis can infect nearly every ocular

structure ranging from the conjunctiva and sclera, to the uvea and lens, to every section of the posterior segment including the retina, choroid and vasculature.[4] Most of these manifestations are nonspecific, and there is no pathognomonic feature of the disease. Uveitis is the most frequent manifestation of ocular syphilis. It has been shown that 8 percent of all uveitis cases can be attributed to syphilis.[2]

APPC is a rare manifestation of ocular syphilis. The clinical findings of APPC show a large, placoid, yellowish lesion with central fading at the level of the retinal pigment epithelium in the macular and peripapillary areas.[5] Fluorescein angiography demonstrates a characteristic early hypofluorescense or faint hyperfluorescence, often with scattered hypofluorescent spots, a pattern referred to as leopard spotting.[5] Later-phase FA shows progressive staining, especially at the rim of the lesion. The lesion shows hypofluroescence on ICG angiography and hyperautofluorescence. The SD-OCT findings described in APPC include disruption of the IS/OS band; nodular thickening of the RPE; loss of the external limiting membrane; accumulation of subretinal fluid; and punctate hyperreflectivity in the choroid.[6]

Other associated findings on examination can include variable amounts of vitreous inflammation (present in up to 90 percent of patients); retinal hemorrhages; retinal vasculitis; disc edema; and subretinal fluid.[3] APPC presents bilaterally in roughly half of patients.

Diagnosis of syphilis involves the use of serum nontreponemal tests, venereal disease research laboratory (VDRL) and RPR, and serum treponemal specific tests, fluorescent treponemal antibody absorption (FTA-ABS), treponema pallidum particle agglutination assay (TPPA), and syphilis enzyme immunoassay (EIA). The treponemal tests usually remain reactive for life, regardless of treatment. RPR or VDRL titers are used to measure response to treatment. Recently, EIA tests, which detect specific IgM and IgG antibodies to *Treponema pallidum*, have become more common as the initial test of choice due to ease of laboratory automation.[7]

Testing algorithms now generally start with EIA or another treponemal test followed by a nontreponemal titer for confirmation (RPR ≥32 indicates increased risk of reactive CSF-VDRL).[8] Patients positive for syphilis should be tested for HIV given the high rate of co-infection, and all positive patients should be reported to the local health authority so that sexual partners can be notified.

Patients with ocular syphilis should be managed as having neurosyphilis. This includes obtaining a lumbar puncture with cerebrospinal fluid examination. Ocular syphilis is treated as neurosyphilis, regardless of CSF findings. Treatment consists of penicillin G3 to 4 million units IV every four hours or 24 million units continuous IV infusion for 10 to 14 days. Alternatively, penicillin G procaine 2.4 million units IM daily, in addition to probenecid 500 mg four times daily orally for 10 to 14 days can be used. Patients who have an allergy to penicillin should be desensitized before undergoing treatment with penicillin.[9]

Monitoring of therapy should be done with RPR or VDRL titers at six, 12 and 24 months following treatment. Repeat lumbar punctures should be performed at six-month intervals until the CSF white blood cell count is normal and CSF-VDRL is nonreactive. Non-falling titers or positive CSF findings are an indication for repeat treatment with antibiotics.

Acute syphilitic posterior placoid chorioretinitis is a rare disease entity that can be the presenting sign of syphilis. While much more common in HIV-positive patients, APPC has been described in immunocompetent individuals as well.[10] Patients with APPC and other forms of ocular syphilis should be treated as having neurosyphilis, with 10 to 14 days of intravenous penicillin. With prompt antibiotic treatment, patients have a good visual prognosis. Ophthalmologists can play an important role in the early detection and treatment of this disease. REVIEW

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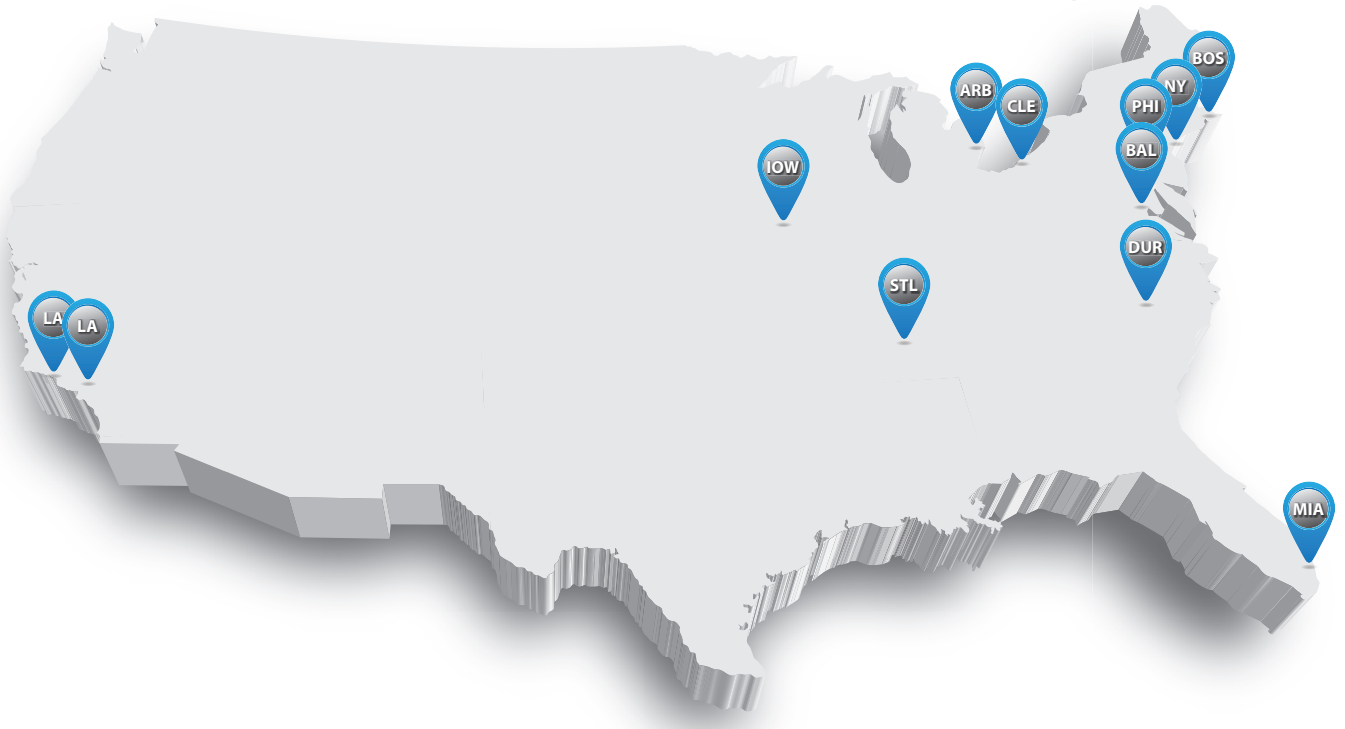

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