

The Best of RETINA



Subspecialty Day



2012



- The recommended dose for EYLEA is 2 mg (0.05 mL) 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.

BRIEF SUMMARY OF FULL PRESCRIBING INFORMATION

INDICATIONS AND USAGE

EYLEA® (aflibercept) Injection is indicated for the treatment of patients with Neovascular (Wet) Age-related Macular Degeneration (AMD).

DOSAGE AND ADMINISTRATION

General Dosing Information

FOR OPHTHALMIC INTRAVITREAL INJECTION ONLY. EYLEA must only be administered by a qualified physician.

Dosing

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.

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.

The glass vial is for single use only. Remove the protective plastic cap from the vial. Clean the top of the vial with an alcohol wipe. Remove the 19-gauge x 1½-inch, 5-micron, filter needle from its pouch and remove the 1 mL syringe supplied in the carton from its pouch. Attach the filter needle to the syringe by twisting it onto the Luer lock syringe tip. Push the filter needle into the center of the vial stopper until the needle touches the bottom edge of the vial. Using aseptic technique withdraw all of the EYLEA vial contents into the syringe, keeping the vial in an upright position, slightly inclined to ease complete withdrawal. Ensure that the plunger rod is drawn sufficiently back when emptying the vial in order to completely empty the filter needle. Remove the filter needle from the syringe and properly dispose of the filter needle. Note: Filter needle is not to be used for intravitreal injection. Remove the 30-gauge x ½-inch injection needle from the plastic pouch and attach the injection needle to the syringe by firmly twisting the injection needle onto the Luer lock syringe tip. When ready to administer EYLEA, remove the plastic needle shield from the needle. Holding the syringe with the needle pointing up, check the syringe for bubbles. If there are bubbles, gently tap the syringe with your finger until the bubbles rise to the top. To eliminate all of the bubbles and to expel excess drug, SLOWLY depress the plunger so that the plunger tip aligns with the line that marks 0.05 mL on the syringe.

Administration

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.

No special dosage modification is required for any of the populations that have been studied (e.g., gender, elderly).

DOSAGE FORM AND STRENGTH

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

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

WARNINGS AND PRECAUTIONS

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).

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 VEGF inhibitors. Intraocular pressure and the perfusion of the optic nerve head should be monitored and managed appropriately (see Dosage and Administration).

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 in VIEW 1 and VIEW 2 wet AMD studies during the first year was 1.8% (32 out of 1824) in the combined group of patients treated with EYLEA (see Clinical Studies).

ADVERSE REACTIONS

The following adverse reactions are discussed in detail in other sections of the labeling:

- Endophthalmitis and retinal detachments (see Warnings and Precautions)
- Increased intraocular pressure (see Warnings and Precautions)
- Thromboembolic events (see Warnings and Precautions)

The most common adverse reactions (≥5%) reported in patients receiving EYLEA were conjunctival

hemorrhage, eye pain, cataract, vitreous detachment, vitreous floaters, and increased intraocular pressure.

Injection Procedure. Serious adverse reactions related to the injection procedure have occurred in <0.1% of intravitreal injections with EYLEA including endophthalmitis, traumatic cataract, and increased intraocular pressure.

Clinical Studies 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 practice.

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 (VIEW 1 and VIEW 2) for 12 months (see Clinical Studies).

Table 1: Most Common Adverse Reactions (≥1%) in Phase 3 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%
Conjunctival hyperemia	4%	8%
Corneal erosion	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%
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 retinal detachment, retinal tear, and endophthalmitis. Hypersensitivity has also been reported in less than 1% of the patients treated with EYLEA.

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 phase 3 studies, the pre-treatment incidence of immunoreactivity to EYLEA was 1% to 3% across treatment groups. After dosing with EYLEA for 52 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.

USE IN SPECIFIC POPULATIONS

Pregnancy. Pregnancy Category C. Aflibercept produced embryo-fetal toxicity when administered during organogenesis in pregnant rabbits at intravenous doses of 3 to 60 mg/kg. A series of external, visceral, and skeletal malformations were observed in the fetuses. The maternal No Observed Adverse Effect Level (NOAEL) was 3 mg/kg, whereas the fetal NOAEL was below 3 mg/kg. At this dose, the systemic exposures based on C_{max} and AUC for free aflibercept were approximately 2900 times and 600 times higher, respectively, when compared to corresponding values 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.

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.

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

Geriatric Use. In the clinical studies, approximately 89% (1616/1817) of patients randomized to treatment with EYLEA were ≥65 years of age and approximately 63% (1139/1817) were ≥75 years of age. No significant differences in efficacy or safety were seen with increasing age in these studies.

Patients with Renal Impairment. Pharmacokinetic analysis of a subgroup of patients (n=492) in one Phase 3 study, of which 43% had renal impairment (mild n=120, moderate n=74, and severe n=16), revealed no differences with respect to plasma concentrations of free aflibercept after intravitreal administration every 4 or 8 weeks. No dose adjustment based on renal impairment status is needed.

PATIENT COUNSELING INFORMATION

Patients may experience temporary visual disturbances after an intravitreal injection with EYLEA and the associated eye examinations (see Adverse Reactions). Patients should be advised not to drive or use machinery until visual function has recovered sufficiently.

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, the patient should seek immediate care from an ophthalmologist (see Warnings and Precautions).

U.S. License Number 1760 • Issue Date November/2011

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Please see full Prescribing Information at www.EYLEA.com

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Direct all inquiries to 1-855-EYLEA-4U (1-855-395-3248)

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For U.S. Audiences

FOR THE TREATMENT OF WET AMD*



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More Information available at www.EYLEA.com

*Neovascular (wet) Age-related Macular Degeneration

IMPORTANT PRESCRIBING INFORMATION

- EYLEA® (afibercept) Injection is indicated for the treatment of patients with neovascular (Wet) Age-related Macular Degeneration (AMD).
- †The recommended dose for EYLEA is 2 mg administered by intravitreal injection every 4 weeks (monthly) for the first 12 weeks (3 months), followed by 2 mg once every 8 weeks (2 months). Although EYLEA may be dosed as frequently as 2 mg every 4 weeks (monthly), additional efficacy was not demonstrated when EYLEA was dosed every 4 weeks compared to every 8 weeks.

IMPORTANT SAFETY INFORMATION

- EYLEA 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.
- 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.
- 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 use of intravitreal VEGF inhibitors, including EYLEA, defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause). The incidence of ATEs with EYLEA in clinical trials was 1.8% during the first year.
- The most common adverse reactions (≥5%) reported in patients receiving EYLEA were conjunctival hemorrhage, eye pain, cataract, vitreous detachment, vitreous floaters, and increased intraocular pressure.
- Serious adverse reactions related to the injection procedure have occurred in <0.1% of intravitreal injections with EYLEA including endophthalmitis, traumatic cataract, and increased intraocular pressure.

Please see brief summary of full Prescribing Information as of July 31, 2012 on the following page.
Please see full Prescribing Information at www.EYLEA.com.

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EyeNet SELECTIONS

REPRINTS FOR RETINA SUBSPECIALTY DAY
CHICAGO 2012

clinical update



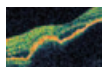
5 A New View of the Vitreous

The role of the vitreous in ocular health and disease: new research findings and their implications for practice. *Originally appeared in the January 2012 EyeNet.*



9 Retinal Prostheses: Progress and Problems

Discussion of how far prostheses have come, how they work, issues to be solved, and what the future holds. *Originally appeared in the March 2012 EyeNet.*



13 When Anti-VEGF Fails in AMD Patients

Description of complicating factors, discussion of the variety of approaches, and how Eylea fits into the picture. *Originally appeared in the May 2012 EyeNet.*

feature



16 Special-Ops Ophthalmology

With the rapid increase of superbugs, the obsolescence of many once-reliable drugs is a concern for all ophthalmologists. Strategies and tactics for fighting back. *Originally appeared in the October 2011 EyeNet.*

Letter From the Editor

Dear Retina Subspecialty Day Attendee,

There have been significant developments in this field over the last year, including progress with retinal prostheses, a new look at the function of the vitreous, and helpful strategies for dealing with the increasingly problematic superbugs.

"The Winds of Change," as this Retina Subspecialty Day meeting in

Chicago is named, is an appropriate designation—both for the sweeping advancements in the field, as well as for tipping our hat to the "windy city" that is our host for this meeting.

Richard P. Mills, MD, MPH
Chief Medical Editor
EyeNet Magazine/EyeNet Selections

COVER: Carla J. Siegfried, MD, measures oxygen partial pressure in the anterior chamber as part of a study conducted among patients undergoing cataract, glaucoma, or retinal surgery. She and her colleagues were exploring oxygen distribution within the eye and its effects on the development of glaucoma after vitreous surgery. *Courtesy of Carla J. Siegfried, MD.*

FIVE DAYS IN CHICAGO



Pick up each of *EyeNet's* meeting publications for a quick heads-up on key meeting-related information, news and events.

EyeNet Magazine, November: includes the final installment of Destination Chicago.

EyeNet's Academy News: a two-issue convention hall tabloid available November 9 and 11.

EyeNet's Guide to Academy Exhibitors: comprehensive exhibitor listings, map and contact information.

EyeNet's Academy Live: a series of four daily e-newsletters reported on site that provide clinical highlights from the meeting.

EyeNet

MAGAZINE

RETINA

A New View of the Vitreous in Ocular Health and Disease

BY MARIANNE DORAN, CONTRIBUTING WRITER

INTERVIEWING NANCY M. HOLEKAMP, MD, CARLA J. SIEGFRIED, MD, AND MICHAEL T. TRESE, MD

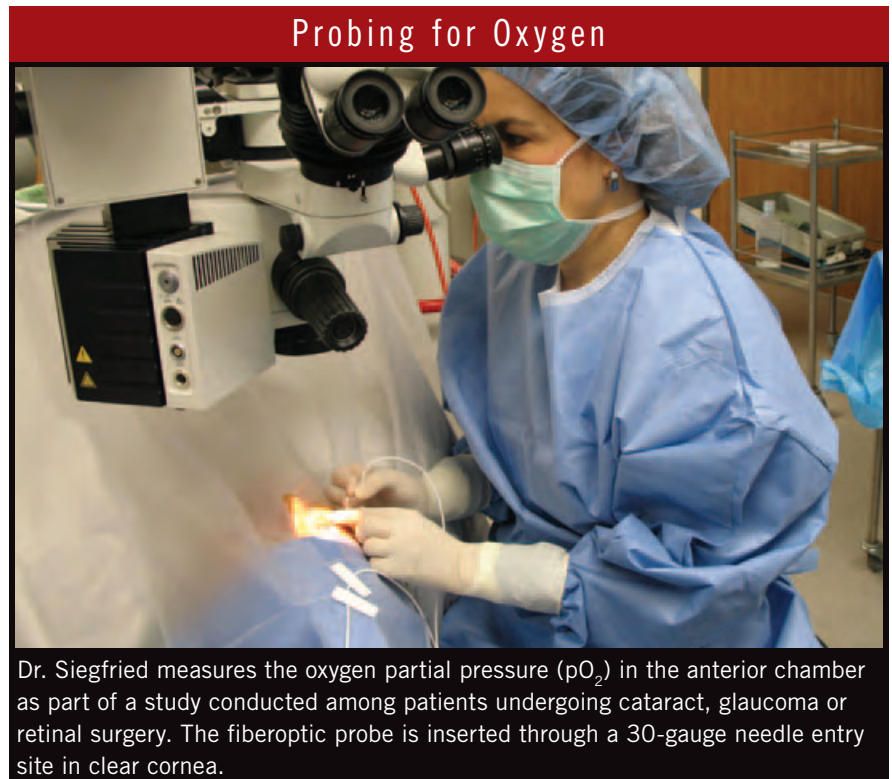
The vitreous gel doesn't get much respect. In fact, many surgeons consider it more of a nuisance than a vital component of ocular health.

But these attitudes are beginning to change, as a relatively small number of researchers work to define the vitreous gel's role in protecting against several sight-robbing conditions.

"The vitreous gel is the orphan organ of the eye," said Nancy M. Holekamp, MD, director of retina services at the Pepose Vision Institute and clinical professor of ophthalmology and visual sciences at Washington University, both in St. Louis. "If you apply for a research grant from the National Institutes of Health, you find study sections on ocular immunology, retina, glaucoma, cataract and anterior segment eye disease—but nothing on the vitreous. So it really has been understudied and overlooked."

Hard to see, easy to ignore. Michael T. Trese, MD, chief of pediatric and adult vitreoretinal surgery at Oakland University's William Beaumont School of Medicine in Royal Oak, Mich., agreed. "Physicians have commonly perceived the vitreous as an empty space and not really thought too much about it in terms of retinal disease, in part because it is very difficult to examine either clinically or with an imaging system."

This dearth of research may be sur-



prising in light of recent insights into the role the vitreous gel plays in nuclear sclerotic cataract, primary open-angle glaucoma, diabetic retinopathy, retinal vein occlusion and age-related macular degeneration.¹ Dr. Holekamp noted that the late Belgian-American surgeon Charles L. Schepens, MD, of Harvard Medical School—considered to be the father of modern retinal surgery—tried to engage his students and colleagues in discussions of potential downsides of removing the vitreous gel. "But no one wanted to talk about it," she said. "Everyone was going full

steam ahead because they now had this new surgery that had led to remarkable advances in treating retinal diseases—and until recently, no one had gone back and asked that initial question: 'What's the downside?'"

Oxygen consumption by the vitreous. The downside, it turns out, may be significant. Removing the vitreous gel inhibits the eye's ability to consume and regulate oxygen, according to experiments by Ying-Bo Shui, MD, PhD, and David C. Beebe, PhD, both researchers in the department of ophthalmology and visual sciences at

This article originally appeared in the January 2012 issue of EyeNet Magazine.

Washington University and colleagues of Dr. Holekamp's.

Based on these findings, and with informed consent and institutional review board approval in hand, Dr. Holekamp removed 0.3 cc of undiluted vitreous from a patient's eye. "We put the vitreous in a glass capillary, placed an oxygen probe inside and made it airtight; then we watched as the vitreous gel consumed oxygen," she said. "That was the first time anyone had demonstrated that vitreous gel has this biochemical property." Repeating the experiment on vitreous gel from 66 additional patients produced similar results.² "We now know that this function of the vitreous has huge implications for ocular health."

Dr. Holekamp and colleagues went on to show that oxygen was consumed by reaction with the high levels of ascorbic acid (vitamin C) in human vitreous.² In subjects with previous vitrectomy or advanced vitreous liquefaction, ascorbate levels and oxygen consumption were markedly decreased. Previous studies by Dr. Holekamp and colleagues had shown that the oxygen levels in the human vitreous are normally very low (approximately 1 percent), suggesting that these hypoxic conditions are a normal aspect of ocular physiology. Together, loss of the vitreous gel and reduced oxygen consumption exposes the posterior of the lens to increased molecular oxygen.

Among the possible implications is that the vitreous gel has a protective effect in several ocular disease processes involving oxidative damage, including nuclear sclerotic cataracts and open-angle glaucoma.

New Insight Into Cataract Formation

The concept that advancing age causes cataracts is only part of the story. A more complete explanation involves the vitreous, as well. In younger people, oxygen from the retina diffuses into the vitreous gel, where much of the oxygen is consumed. But with aging and an increasingly liquefied gel, oxygen reaches and oxidizes the lens, causing it to discolor, opacify and harden. "So the real causes of age-

related nuclear cataracts include vitreous liquefaction, as well as age," Dr. Holekamp said.

She points to evidence that as many as 95 percent of patients older than 50 years who undergo vitrectomy develop nuclear sclerotic cataracts requiring cataract surgery within two years of vitreous removal.¹ Among patients younger than 50, however, the two-year incidence of vitrectomy-related cataracts is less than 10 percent. This age-related difference may be attributable to a younger crystalline lens that is more resistant to cataract formation or to a protective effect of the younger gel structure retained behind the lens—or to a combination of both, she said.

Vitrectomy and POAG

Carla J. Siegfried, MD, professor of ophthalmology and visual sciences at Washington University, has explored the link between vitrectomy and late development of open-angle glaucoma. She traces her interest in the topic to the 2006 Jackson Memorial Lecture given by Stanley Chang, MD, professor and chairman of ophthalmology at Columbia University in New York. Dr. Chang had observed that his patients who underwent vitrectomy and subsequent cataract extraction appeared to be at higher risk of developing primary open-angle glaucoma, and he hypothesized that both cataract and glaucoma development after vitrectomy could be due to oxidative damage.

In his retrospective study, Dr. Chang followed the course of 65 patients (68 eyes) who had undergone vitrectomy (mean time since surgery, 56.9 months; range, 7 to 192 months).³ The patients were classified into three groups: suspected glaucoma, glaucoma that developed after vitrectomy, and preexisting glaucoma. Among glaucoma suspects, the mean IOP was significantly higher in the eye that had undergone vitrectomy than in the fellow eye. In patients with new-onset glaucoma, 23 of 34 eyes (67.6 percent) developed glaucoma only in the eye that had undergone vitrectomy, and the time to development of the condition was longer in phakic eyes than in non-

phakic eyes (a mean of 45.95 months versus 18.39 months, respectively). Moreover, the study participants who had preexisting glaucoma required more antiglaucoma medications to control intraocular pressure in the eye treated with vitrectomy than in the eye that did not undergo the surgery.

Koreen and colleagues conducted a subsequent case-control study to estimate the incidence of and risk factors for the development of late-onset open-angle glaucoma following vitrectomy.⁴ In their analysis of 285 eyes (274 patients), the researchers found that 11.6 percent of patients developed glaucoma after vitrectomy. In a subgroup analysis, however, the risk was 1.4 percent in phakic eyes compared with 15 percent in nonphakic eyes ($p = 0.001$), revealing that lens extraction is an important risk factor for the development of late-onset open-angle glaucoma after vitrectomy.

Oxygen distribution in the eye may be crucial. Building on Dr. Chang's work, Dr. Siegfried and her coworkers explored oxygen distribution within the eye and its effects on the development of glaucoma after vitrectomy. Dr. Chang's observations "struck a chord with us," said Dr. Siegfried.

In response, she and her colleagues recorded oxygen distribution with a fiberoptic probe in patients undergoing surgery for cataract, glaucoma or retinal disease.⁵ They measured oxygen partial pressure (pO_2) beneath the central cornea, in the mid-anterior chamber and in the anterior chamber angle. For pseudophakic patients or those who were scheduled for cataract extraction, pO_2 also was measured in the posterior chamber and near the lens.

The researchers found that eyes that had undergone vitrectomy had significantly increased pO_2 in the posterior chamber. Prior cataract surgery was also associated with significantly elevated pO_2 in the posterior chamber and in front of the intraocular lens. Eyes that had undergone both vitrectomy and cataract surgery showed increased pO_2 in the posterior chamber and anterior to the IOL, as expected,

and pO_2 doubled in the anterior chamber angle. These observations led them to propose that long-term exposure to increased molecular oxygen damaged the cells of the trabecular meshwork, leading to increased outflow resistance and glaucoma.

Implications for Practice

Intravitreal drug distribution. Dr.

These points out that a growing understanding of the vitreous gel raises some interesting questions about commonly performed procedures. “We inject various drugs into the vitreous cavity, and we try to judge their effects based on the results of randomized, prospective, controlled clinical trials,” he said. “But, in a way, the data set we have is a little incomplete because even though there may be a question in the examination forms about ‘Is the vitreous attached or detached?’ it may be very hard to tell clinically.

“We have some very simplistic clinical signs that we use, such as ‘Is a Weiss ring present?’” he continued. “If there is, we assume that the vitreous is separated from the retina. But that may not be the case in totality, or it may be that some of the vitreous is left along the retinal surface. The question then becomes, ‘Does that affect the drug’s ability to penetrate the retina or the subretinal space?’ And does this alter the period of time that the drug will remain in the eye, with the vitreous acting as a reservoir for drug delivery?” Dr. Trese added that ophthalmologists’ increasing reliance on intravitreal injections to treat vitreoretinal diseases makes understanding the relationship between the vitreous and the retina even more critical.

Enzymatic drugs on the horizon.

He noted that, in the not-too-distant future, some vitreoretinal diseases will likely be treated enzymatically, an approach also known as pharmacologic vitreolysis. “Then our thinking can be expanded because you avoid the risk and expense of vitrectomy. I think—and hope—that this will stimulate imaging-technology companies to find ways to image more of the vitreous and will get more people thinking about

the biochemical effects of the vitreous in the vitreous cavity—particularly at the vitreoretinal juncture.”

Dr. Siegfried added that any therapeutic approach that creates a posterior vitreous detachment may also expose the lens to higher oxygen and lead to more nuclear sclerotic cataract, indicating the need to find novel ways to protect the lens from oxygen exposure.

Possible relevance to diabetic

retinopathy treatment. Diabetic retinopathy is likely to be at the top of the list for enzymatic treatment. “This is something that clinicians have been very aware of for decades, and yet the manipulation of the vitreous in diabetes has generally been reserved for tractional retinal detachment or for bleeding into the vitreous, and not so much for earlier disease,” Dr. Trese noted. “This is despite the fact that a substantial amount of evidence indicates that changes in the retina occur after a very short period of time in diabetic retinopathy. By the time these changes become visible clinically, a long pattern of change in the retina has already occurred.

“With a disease like diabetic retinopathy, manipulating the vitreous might be a mode of management that could be preventive. A lot of work needs to be done to prove that, but it’s a really exciting new area.”

1 Holekamp NM. *Am J Ophthalmol*. 2010; 149(1):32-36.

2 Holekamp NM et al. *Am J Ophthalmol*. 2005;139(2):302-310.

3 Chang S. *Am J Ophthalmol*. 2006;141(6): 1033-1043.

4 Koren L et al. *Retina*. 2012;32(1):160-167.

5 Siegfried CJ et al. *Invest Ophthalmol Vis Sci*. 2010;51(11):5731-5738.

Drs. Holekamp and Siegfried report no related financial interests. Dr. Trese is a consultant for and has equity interest in Thrombogenics.

FURTHER READING: For more information about the anatomy and physiology of the vitreous, see the Basic and Clinical Science Course (BCSC) Section 12, *Retina and Vitreous*; and BCSC Section 2, *Fundamentals and Principles of Ophthalmology*, chapters 2 and 12.

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RETINA

Retinal Prostheses: Progress and Problems

BY MIRIAM KARMEL, CONTRIBUTING WRITER
INTERVIEWING JOSEPH F. RIZZO III, MD, STEFANIE G. SCHUMAN, MD,
AND JAMES D. WEILAND, PHD

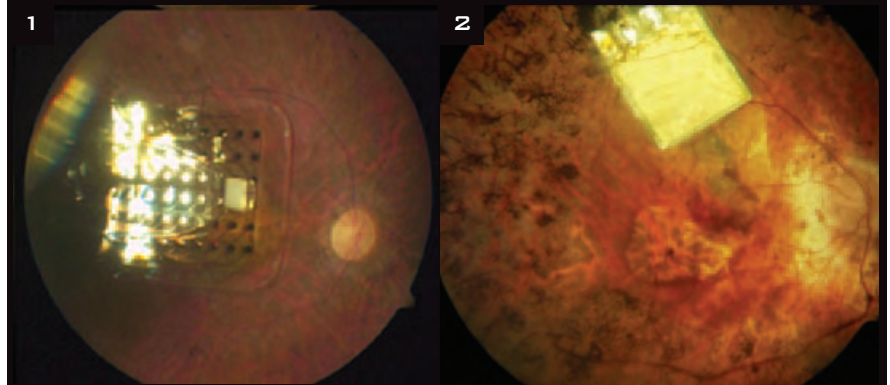
In early 2002, a team of surgeons headed by Mark S. Humayun MD, PhD, implanted an electronic device onto the surface of a blind man's retina. The patient was then able to identify the direction of an object moving in front of the device's spectacle-mounted camera. He didn't see much—but he saw.

In *USC Health Magazine*,¹ Dr. Humayun, professor of ophthalmology, biomedical engineering, and cell and neurobiology at the University of Southern California, said, “This is like the Wright Brothers. This is the first time we've been able to fly. It took a lot of work to get to this point, but this time, when we took off, we flew.”

This accomplishment represents an important milestone for a field that began in the 1980s and which now includes more than 15 companies and research groups in six countries. Those currently in or near human testing include Boston Retinal Implant Project, or BRIP (Boston), a cofounder of the field along with Second Sight (Sylmar, Calif.), Retina Implant AG (Reutlingen, Germany), Intelligent Medical Implant (Bonn, Germany) and Epi-Ret (Bonn).² (Optobionics, which had an early chip, went bankrupt in 2007 and is now under reorganization.) Of these, the two groups that appear to be farthest along in development are Second Sight, which received Europe's CE approval in 2011 to market the Argus

This article originally appeared in the March 2012 issue of EyeNet Magazine.

In the Eye



(1) The Argus II epiretinal chip. (2) The subretinal device from Retina Implant AG.

II, and Retina Implant AG. Prostheses from the former are in human clinical trials in the United States. Prostheses from the latter are in trials in Europe and, as of press time, are awaiting FDA approval for U.S. trials.

Although these devices vary in terms of where the chip is placed within the eye, the number of electrodes on the chip, and operational mechanics, they all aim to translate light into electrical stimulation of the retina to generate artificial vision. Similar to the cochlear implant, they act as sensory replacements; in the case of retinal prostheses, they replace photoreceptors damaged by degenerative disorders such as retinitis pigmentosa or AMD.

Artificial vision is no longer a sci-fi fantasy. It's here. And it's commercially available in Europe. But is it ready for prime time? The answer depends on your assessment of the progress to date as well as the problems that lie ahead.

Progress: The Blind Can See

The two retinal prostheses that are furthest advanced in clinical trials have been shown to achieve some degree of vision, but is the quality of that vision sufficient to be truly useful to blind patients?

Second Sight's Argus II. A flurry of reports at ARVO 2011 showed progress with Argus II. Dr. Humayun and colleagues presented an update from their clinical trial that is testing the device in 30 subjects with bare light perception or worse at 10 sites worldwide. According to their abstract, “Results on visual function tests with high-contrast stimuli showed a hierarchy of function, progressing from the ability to locate an object, through the ability to detect the direction of motion, and finally to the ability to distinguish the orientation of black and white gratings.”³ A presentation by other researchers showed that some subjects

were also able to read four-word sentences with letters approximately 3 to 4.5 cm high.⁴

Retina Implant AG's device. In Germany, Retina Implant AG also reported restoring visual perception in blind patients such that they could localize and recognize objects and read letters and words that were 5 to 8 cm high.⁵ In 2005, the group began its first clinical trial in humans, temporarily implanting its subretinal device in 11 subjects. In 2010, a second clinical trial began with the goal of implanting the chip in 60 patients. Pending FDA approval, the Wills Eye Institute will be the lead U.S. clinical trial site.

Retinal prostheses are in an early stage. “There have been some clear demonstrations of visual capabilities,” said Joseph F. Rizzo III, MD, professor of ophthalmology at Harvard University Medical School and director of the neuro-ophthalmology service at Massachusetts Eye and Ear. “If the goal is to be able to say that people see something after the retina is stimulated, then the goal has been met.” But Dr. Rizzo drew a distinction between the ability to identify a cup or fork in a clinical setting, after perhaps being shown such objects multiple times, and the ability to successfully navigate in a new and unstructured environment, for example, a restaurant.

Dr. Rizzo, a BRIP cofounder, continued: “We’re trying to provide enough vision to allow patients to do activities that are beyond what they could otherwise accomplish with their severely limited vision. Just demonstrating improvement isn’t sufficient. You have to justify the risk the patient takes [with surgery and long-term safety] to have an implant.”

Stefanie G. Schuman, MD, assistant professor of ophthalmology in medical retina at Duke University, agreed. Although she tells all of her patients whose vision is 20/200 or worse about clinical trials, none of them have pursued the option. Like her, they’re waiting for a device that provides the quality and type of vision that can improve their function day to day. “They want a little more of a guarantee that

it will make them see better,” she said. “With the type of visual results the devices are getting, a lot of these patients would rather not go through surgery and the cost of travel.”

How They Work

A retinal prosthesis first has to capture a visual image, either with an external camera or a sensor inside the eye. Ultimately, those images provide electrical input to the visual pathway; thus, patients must have healthy optic nerves.

The Argus device uses a camera and transmitter mounted on eyeglasses, an implanted receiver, and an array of electrodes secured to interface epiretinally with retinal ganglion cells. A battery pack worn on the patient’s belt powers the system.

The camera captures images as the subject’s head moves to view objects and track movement. These images are processed by the transmitter and receiver and turned into electrical impulses on the epiretinal array. These impulses are intended to stimulate the retina’s remaining cells and generate corresponding perception of patterns of light in the brain, which patients interpret as meaningful images.

The Retina Implant AG prosthesis doesn’t have an external camera. Rather, it uses a light-sensitive microchip that is surgically implanted under the retina, in the macular region where photoreceptor cells are located. The implant moves with the eye, which provides for “more natural processing of the image.”⁵ Aside from the subretinal microphotodiodes, the only other equipment is a power module implanted behind the ear.

Problems to Overcome

Although the prosthetic technology has come a long way since 2002, researchers have many challenges ahead if visual quality is to improve.

Placement of chip affects electrodes. Whether to place the device on or under the retina is an engineering decision, and each decision has trade-offs, said James D. Weiland, PhD, associate professor of ophthalmology and biomedical engineering at the

University of Southern California. The subretinal device requires more surgical skill than the epiretinal implant, which goes through the pars plana. The subretinal Retina Implant AG prosthesis has 1,500 pixel-generating electrodes; the epiretinal Argus II has only 60. Experts agree that a minimum number of electrodes is required in order to achieve useful vision, but it’s not known for sure what that number is.

Dr. Weiland said he believes it takes somewhere between 300 and 1,000 pixels to create a usable image. But, he noted, “You can have an array with a million pixels. But if a single electrode doesn’t have enough energy to activate the retina, then really you don’t have a million-pixel array. It’s the functional pixels that matter.” He drew an analogy: You have a high-definition TV, but you’ve lost your glasses. “If you don’t have your glasses, it doesn’t matter how high the resolution of the TV is.”

Dr. Weiland continued, “We still need to understand how to get better resolution.”

Hermetics. Dr. Rizzo said that hermetics is also a great challenge. For example, the BRIP’s stimulating chip, which is inside a titanium case, has wires running to the outside, which connect to other parts of the prosthesis. BRIP is trying to develop a connecting mechanism that allows egress from the case while keeping water vapor and sodium ions from entering and damaging the electronics.

The Argus II has a hermetic package for its 60 electrodes that has allowed it to remain in place—at least in one patient—for more than four years so far.⁶

To date, the subretinal Retina Implant device has remained in subjects’ eyes for up to three months before explantation,⁶ so it hasn’t been determined how long it can last in vivo.

Next Steps: Mimicking Normal Vision

In normal vision, light enters the eye and is focused on the retina. “Some parts of the retina are activated, and some are not,” Dr. Weiland said. “We’re trying to do the same thing with electricity. We’re trying to ac-

tivate a small part of the retina. But we don't know how to stimulate that precisely. We need to understand the biological side of the interface."

Functional MRI may provide some answers. "There are many points along the way where the signal is being processed by the brain," said Dr. Weiland. "We'd like to activate the device and then scan the brain as it is working." He added that basic animal studies may also "give us access to the signals from the retina. Then we can stimulate a retina and see how it responds to electric stimulation."

State of the art. "We have a longer way to go before we can deliver to people the vision that will change their lives," Dr. Rizzo said. The current generation of devices yields images that Dr. Rizzo compares to an impressionist painting, something beautiful but "blobby." His goal is something closer to the effect of pointillist paintings, composed of thousands of individual pixel-like points.

In the meantime, Dr. Rizzo said the quality of the devices is getting better and better, and they are generally well tolerated. "Now we have to show that there's real benefit."

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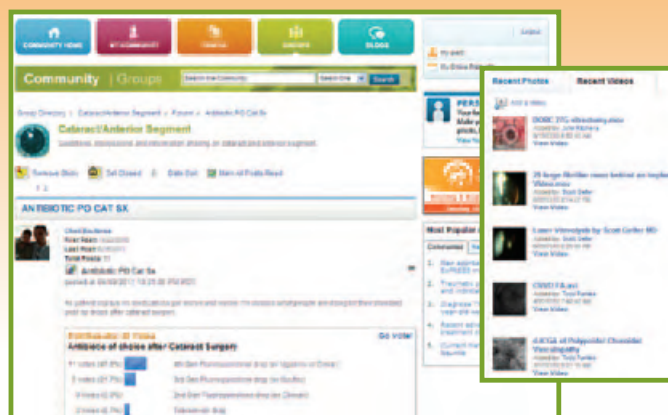
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Dr. Rizzo is cofounder of the Boston Retinal Implant Project. Dr. Schuman reports no related financial interests. Dr. Weiland receives research funding from Second Sight. He has no equity in the company.

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– **Todd J. Purkiss, MD, PhD,**
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RETINA

When Anti-VEGF Fails in AMD Patients: 3 Treatment Approaches

BY GABRIELLE WEINER, CONTRIBUTING WRITER

INTERVIEWING SUSAN B. BRESSLER, MD, SANDER R. DUBOVY, MD, AND AMANI A. FAWZI, MD

The advent of anti-VEGF therapy has revolutionized the treatment of patients with neovascular age-related macular degeneration (AMD), but it has also led to a range of therapeutic approaches among retina specialists, with limited consensus on best practices. This is true even for patients who have a robust response to either ranibizumab (Lucentis) or bevacizumab (Avastin).¹ So when it comes to patients who don't respond—or have lost responsiveness—the absence of evidence-based guidelines makes treatment decisions more challenging.

"It's not like there are hard-and-fast rules," said Susan B. Bressler, MD, professor of ophthalmology at Wilmer Eye Institute at Johns Hopkins University in Baltimore. "Every patient is different, and every doctor is shooting from the hip right now when treating refractory patients."

Apart from treating these patients, even just defining "nonresponders" varies among clinicians, said Amani A. Fawzi, MD, associate professor of ophthalmology at Northwestern University in Chicago. Among the complicating factors are the unknown causes of nonresponsiveness, as well as financial and treatment burdens.

Fortunately, anti-VEGF drugs work well for most neovascular AMD patients. It is only a minority of patients in whom loss of reactivity is a problem.²

Complicating Factors

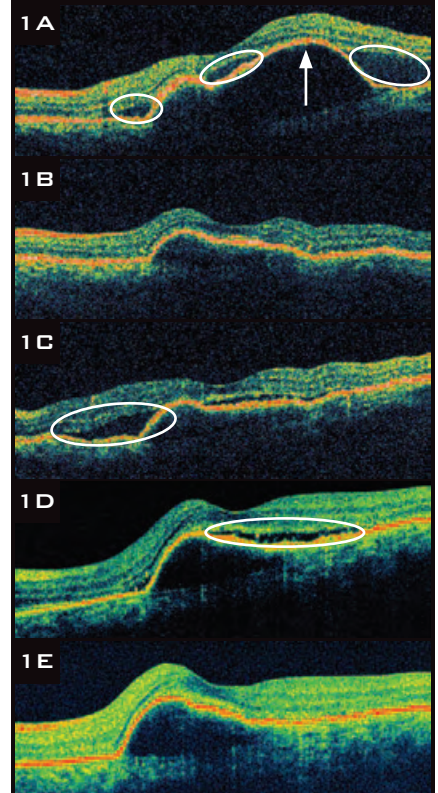
Terminology confusion. There is no universally accepted nomenclature for describing different types of non-responsiveness. "This is the very first problem with delving into this topic. It's difficult to compare outcomes when we're defining things differently from one another, let alone figure out what we can do to improve outcomes," said Dr. Bressler.

The terms tachyphylaxis and tolerance are both used to describe a decreasing therapeutic response to a pharmacologic agent. Some authors use the words synonymously, while others make distinctions based on the mechanism and time course—with tachyphylaxis denoting rapid onset over a short period and tolerance developing more slowly.³ But there are also patients who don't respond from the start (true nonresponders) and people who take a drug holiday after successful treatment but cease to respond when re-treated.

"At the end of the day, the important thing is that there is a group of people who are not responding well to the drug, albeit a small group. Whether it's tolerance or tachyphylaxis or something else, what we care about is finding something they do respond to," said Sander R. Dubovy, MD, associate professor of ophthalmology and pathology at the Bascom Palmer Eye Institute.

Financial costs and treatment burden. In clinical practice, few retina specialists adhere to the strict sched-

Switching Treatments



RANIBIZUMAB TACHYPHYLAXIS. (1A) A 65-year-old with neovascular AMD presented with subretinal fluid (SRF, circled) and a large serous pigment epithelial detachment (PED, arrow). **(1B)** After three ranibizumab injections, SRF resolved completely, and PED size decreased. **(1C)** SRF re-occurred. **(1D)** Despite six more ranibizumab injections, SRF and PED persisted. **(1E)** The patient was switched to bevacizumab. After six injections, SRF resolved, but the PED remained.

This article originally appeared in the May 2012 issue of EyeNet Magazine.

ule of regular monthly intravitreal anti-VEGF injections for two years, as established by the two major trials of ranibizumab. Variable regimens have become the de facto practice because of the financial costs of the drug and procedure, patient preferences, and practice workload.¹

“Discussing anti-VEGF drugs without mentioning their financial burden is like ignoring the elephant in the room,” said Dr. Bressler. “It would be naive to think that the financial burden and practice burden of anti-VEGF agents don’t influence drug choices and treatment schedules.” These same issues affect how clinicians treat refractory patients.

The average drug cost per injection is about \$50 for Avastin, \$2,000 for Lucentis, and \$1,850 for the recently approved Eyelea (Regeneron). Overall treatment costs will vary depending on the dosing regimen and possible manufacturers’ reimbursement programs.

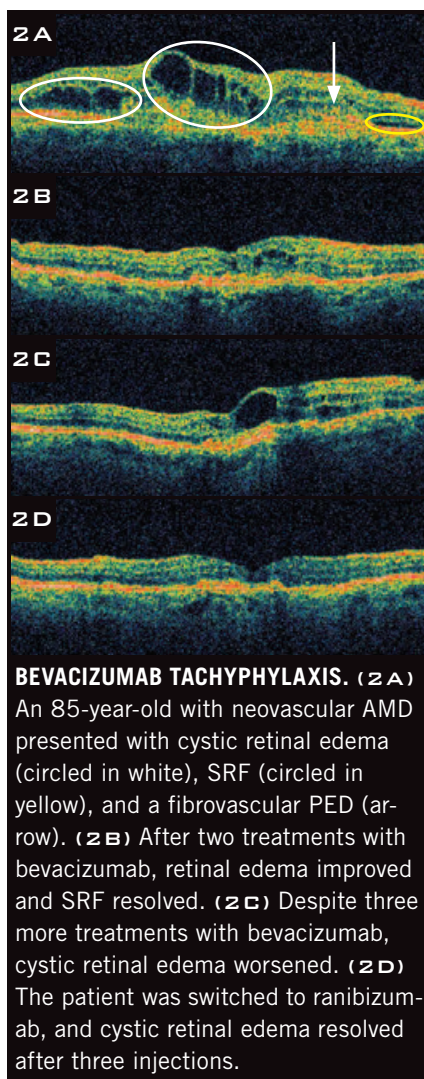
Unknown factors in nonresponsive-ness. “Until we know what’s actually happening to cause a lack or loss of efficacy, it’s difficult to determine the best way to counter the problem,” said Dr. Dubovy. “It may be that there are structural differences or changes in the retina that lead to differences in response, such as increased fibrosis that acts as a barrier to fluid resorption.”

“Our therapies may be blocking the VEGF pathway to the point that a parallel angiogenic mechanism is up-regulated in the membrane, enabling continued growth despite anti-VEGF therapy,” said Dr. Fawzi. “This is the whole premise behind doing combination therapy and studying new drugs with different mechanisms of action.”

Spectrum of Approaches

Clinicians currently have several options for managing a poor response to anti-VEGF injections. These include reducing treatment intervals, giving the patient a drug holiday, combining therapies with different modes of action, or switching to a different drug.³

In light of a recent study analyzing the outcome of switching anti-VEGF drugs, the last option is currently at



the forefront of discussion. Researchers reported that, among patients who were treated primarily with either ranibizumab or bevacizumab and who showed an attenuated response, switching to the other drug was successful in continuing to reduce fluid in 81 percent of cases.⁴ These findings are surprising given that ranibizumab and bevacizumab are similar molecules that act at the same location.³ However, this promising news is tempered by some limitations noted in the study, including retrospective design and relatively small patient population.

Each of the three AMD experts interviewed for this article takes a different therapeutic approach to the problem of nonresponsiveness.

Dr. Fawzi switches anti-VEGF drugs; may add PDT. Dr. Fawzi, co-author of the study mentioned above,

treats her refractory patients according to the study protocol. She said:

“We treat our neovascular AMD patients until they are completely dry; we don’t tolerate any fluid in the sub-retinal space. When patients are dry, we take a drug holiday but continue to follow them on the same schedule. If fluid returns or vision drops, we resume treatment with the same drug that worked before. If a patient doesn’t respond to the drug when it’s resumed, then we consider him or her a nonresponder (these patients were not included in our study).

“Patients on anti-VEGF therapy who improve initially and are on their way to becoming dry but then start accumulating fluid again are considered to have tachyphylaxis (these patients were included in our study). We might give another couple of injections of the same drug to convince ourselves that what’s really going on is tachyphylaxis, and if the loss of responsiveness continues, at that point we switch to the other anti-VEGF agent. In our study, we saw that 50 percent of patients got better with the first injection just by switching from ranibizumab to bevacizumab or vice versa.

“For the subset of patients with polypoidal lesions, the Asian literature suggests that photodynamic therapy (PDT) is superior to anti-VEGF therapy. We have found that this group responds much better to either a combination of PDT and anti-VEGF (closing the polyps with PDT helps the anti-VEGF effect) or full-dose PDT alone. My approach is to use half-dose PDT every three months in combination with anti-VEGF on its standard schedule.”

Dr. Dubovy considers different schedules, alternating drugs. Dr. Dubovy’s approach focuses on the dosing schedule. This is not surprising given that he was coauthor of the PRONTO study,⁵ which had a strong influence on the widespread adoption of alternative variable-dosing regimens. Dr. Dubovy said:

“If patients are not responding, a reasonable thing to do is to bring them back in a week or two rather than a

month to assess whether they're dry at that interval. If they are, then you know they have responded to the drug and perhaps need more frequent injections. If fluid is present in that short interval, then you know they are true nonresponders.

"For patients with attenuated response, some have advocated more frequent dosing. This often solves the problem. In some cases, alternate dosing between ranibizumab and bevacizumab every two weeks has anecdotally been successful. When dry, the patients are returned to a four-week schedule on the original drug they responded to. Once back on a monthly schedule, some patients revert, but some don't. An every-two-week dosing schedule deviates significantly from the standard schedule, so some clinicians are uneasy about it.

"Switching back and forth between ranibizumab and bevacizumab has not been a major concern because the drugs are very similar. If you look at the data, Lucentis probably dries the retina a little bit better so that patients need slightly fewer injections, but essentially they work about the same."

Dr. Bressler sticks with ranibizumab. Dr. Bressler treats her patients almost exclusively with ranibizumab and doesn't necessarily consider residual fluid a reason to make a change. She said:

"I'm a ranibizumab-first person, unless there's a financial barrier from the patient's perspective, but most of my patients have secondary insurance. I see no rationale in switching from ranibizumab to bevacizumab when the CATT study shows no suggestion that bevacizumab is superior to ranibizumab in terms of vision; and, anatomically, it appears it may be inferior to ranibizumab.⁶

"In what I consider to be refractory cases—those in which the vision, angiogram, and OCT are essentially unchanged after about nine to 12 consecutive monthly injections—the first thing I do is check whether the patient has been coming in religiously within the three- to five-week window established as the treatment interval

in phase 3 studies of ranibizumab. If the drug hasn't been administered consistently within that window, then it hasn't been used in the fashion in which it was demonstrated to work. If the schedule is off, I correct it. If it's fine, then I might hedge the treatment interval closer to the three-week mark for an additional consecutive series of injections.

"Does it distress me that some patients have fluid after 12 consecutive injections? Sure. But it would be pretty hard to argue that I should jump ship if, over the course of that 12 months, their vision had improved. Maybe they're not 20/20, but they've gained a couple of lines of acuity, they have far less fluid at month 12 than when they started, and they show no leakage on their angiogram.

"By contrast, in cases where I've given consecutive monthly injections of reasonably long duration, but it looks as if I've been doing absolutely nothing other than maintaining the status quo, I'm more apt to ask myself what to do next. After confirming that treatments have been administered at three- to five-week intervals, in the past I have considered adding PDT to continued ranibizumab therapy. Although I was more excited about this particular combination therapy when I had a few successes, the more I've tried it, the less enthusiastic I've become. Controlled trials have not shown that combination PDT plus ranibizumab provides advantages when compared to ranibizumab monotherapy."

How Eylea Fits Into the Picture

Eylea, formerly known as VEGF Trap-Eye (aflibercept), is a protein that acts as a decoy receptor for VEGF. The recommended dosing is once every four weeks for the first three injections, followed by once every eight weeks thereafter. This reduced frequency of injections is considered by many to provide a clear advantage.

The FDA approved Eylea in November 2011. Dr. Dubovy has switched over some of his patients. "Reimbursement is currently only approved for patients who've been on Lucentis and

have residual fluid. So I've started with that subset, and the group appears to be doing very well." (Since this article was published, reimbursement codes have changed, and payers may have different coverage policies.)

Most experts agree that the first patients for whom the drug will be recommended are most likely to be those with inadequate response to other anti-VEGF therapy. It remains to be seen how Eylea will behave in such patients. Compared with the population that participated in the phase 3 trials assessing Eylea, refractory patients may be different genetically or may have a highly mature membrane that does not respond to anti-VEGF drugs, said Dr. Fawzi. Because her study found that 50 percent of patients with tachyphylaxis got better with the first injection after switching between ranibizumab and bevacizumab, if she doesn't see a benefit after the first post-switch injection, she plans to move to Eylea right away.

Dr. Bressler also plans to incorporate Eylea in her clinical practice by switching over her more refractory patients. "As I gain this experience, I'll initiate therapy in some treatment-naïve patients, assuming there are no financial barriers."

Drs. Dubovy and Fawzi cautioned that, eventually, cases of attenuated response to Eylea will probably emerge, so therapies with different modes of action are still very much needed.

Dr. Bressler reports that Johns Hopkins University School of Medicine receives research grants from Genentech, the manufacturer of Lucentis and Avastin. Drs. Dubovy and Fawzi report no related financial interests.

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Special-Ops Opht

A detailed illustration of three rod-shaped bacteria against a dark, textured background. Each bacterium has numerous thin, red flagella extending from its surface. Inside the bacteria, there are colorful, tangled structures representing DNA or RNA. One bacterium at the top left has a blue and yellow structure. The one at the top right has a green and blue structure. The one at the bottom has a green and yellow structure. The title 'Special-Ops' is in large, orange-outlined letters, and 'Opht' is in large, blue-outlined letters.

With the continuing rise of resistant bacteria, once-reliable drugs are rapidly becoming obsolete.

Here are strategies and tactics for fighting back.

This article originally appeared in the October 2011 issue of EyeNet Magazine.

ALFRED T. KAMAUJIAN
ADAPTED FROM AN ILLUSTRATION BY BJÖRN NORBERG

ophthalmology

in the Age of Antibiotic Resistance

BY ANNIE STUART, CONTRIBUTING WRITER

"WE'RE SEEING MOTHER NATURE AT HER BEST," said John D. Sheppard, MD, clinical director of the Lee Center for Ocular Pharmacology at Eastern Virginia Medical School in Norfolk, Va. "Quintillions of organisms adapting en masse to environmental stress, which is antibiotics."

Among these organisms, staphylococci are, perhaps, the source of greatest concern. According to Dr. Sheppard, methicillin-resistant *Staphylococcus aureus* (MRSA) and methicillin-resistant *S. epidermidis* (MRSE) are increasingly common causes of infectious conjunctivitis, keratitis, endophthalmitis, and preseptal and orbital cellulitis. Both the community-acquired and the more virulent hospital-acquired strains of methicillin-resistant organisms are on the rise.

"Within the next decade, we may find that 100 percent of the staph we culture in ophthalmic practice is methicillin resistant," he said. "And that phenomenon may be eerily similar to what we saw in the 1960s, when virtually all staph became penicillin resistant, and in the '70s, when pneumococci grew increasingly resistant to a wide variety of antibiotics."

Have we learned anything from that earlier experience to avoid repeating history? The first step is to size up the enemy and determine exactly what kinds of challenges ophthalmologists are now facing—and, just as important, what ophthalmologists can contribute to the fight against growing resistance.

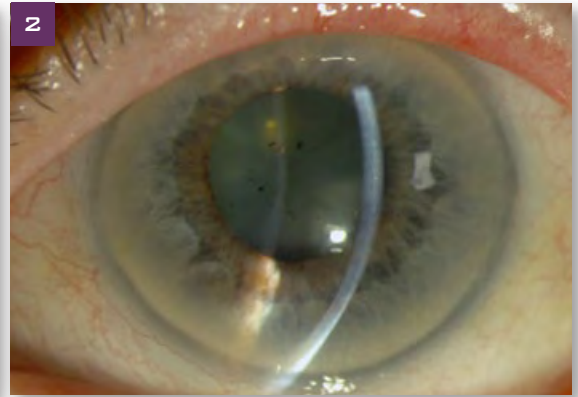
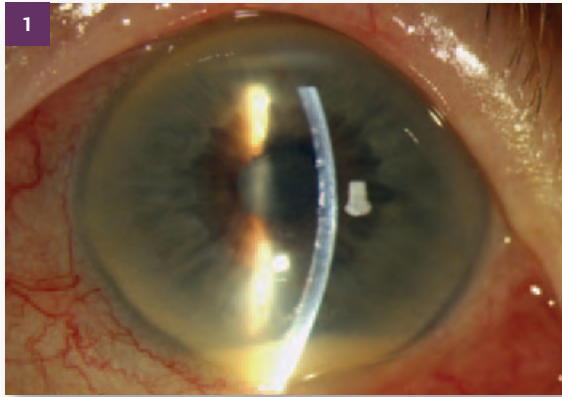
RESISTANCE—A MOVING TARGET

Once confined to hospitals, MRSA is advancing into the community and into ophthalmology clinics.

Not just a hospital problem. At 10 U.S. sites last year, cataract surgeons isolated methicillin-resistant staph from the eyelids and conjunctiva of about 40 percent of their patients, 90 percent of whom had no prior exposure to hospital environments,¹ demonstrating the growing prevalence of community-acquired resistance. And even though this type of resistance is generally less virulent than that acquired in hospital settings, said Dr. Sheppard, any resulting postoperative endophthalmitis is still devastating for patient and surgeon alike.

In the same study, higher levels of resistant staph were found in areas of the country with large poultry industries. This is likely not a coincidence, said lead author Randall J. Olson, MD, director of the Moran Eye Center at the University of Utah in Salt Lake City. Along with livestock industries, he said, poultry producers are one of the biggest offenders in the development of community-acquired resistance due to their continual use of newer and stronger antibiotics in animal feed.

"Until the poultry and livestock industry practices change," said Dr. Olson, "what we do is like spitting in the ocean. Physicians have a role to play, but it pales by comparison."



Ophthalmologists must battle against bugs.

Ophthalmologists account for only a sliver of overall antimicrobial use. But they still need to be careful; mass quantities of systemic antibiotics aren't required to prompt resistance, said David G. Hwang, MD, professor of ophthalmology and codirector of the cornea service and director of the refractive surgery service at the University of California, San Francisco. Suboptimal topical ophthalmic prescribing patterns can lead to increased development of local, yet clinically relevant, antibiotic-resistant infections. Prior topical ophthalmic fluoroquinolone use has been identified as a risk factor for subsequent development of fluoroquinolone-resistant ocular infections.²

Unfortunately, with increasing resistance, fewer options remain for treating these superbugs, said Dr. Olson. Moreover, overall production of antibiotics is reduced due to financial disincentives for pharmaceutical companies.

"There's a growing awareness that the solution is not just the next drug in the pipeline," said Dr. Hwang. This is true not only because the pipeline has meager offerings but also because simply reaching for the latest and greatest antimicrobial relentlessly leads to resistance—and more quickly than many might expect. Resistance has emerged against even the newest fluoroquinolones, which can't be relied upon to effectively treat MRSE and MRSA.³

Fluoroquinolones: part of the problem. Ocular TRUST (Tracking Resistance in U.S. Today), an annual report on in vitro antimicrobial susceptibility, shows consistent patterns of resistance against second- to fourth-generation fluoroquinolones, with about one-third of MRSE resistant to all four commonly prescribed fluoroquinolones, said Dr. Sheppard. "Alarming, more than 80 percent of MRSA were also resistant across the board at the same percentages," he said. "With increasing resistance, the strategy needs to be *prevention* of these infections."

Fluoroquinolones may be particularly likely to

MRSE ENDOPHTHALMITIS.

(1) Despite receiving prophylactic moxifloxacin topical drops immediately after an intravitreal injection, this 82-year-old patient presented four days later with pain, blurred vision and redness in the left eye. Her anterior chamber showed diffuse fibrin and a hypopyon, and VA was light perception. (2) One month later, after being treated with vitreous aspiration and intravitreal vancomycin, ceftazadime and dexamethasone, the infection was resolved, but VA was 20/400.

promote the development of antimicrobial resistance in real-world clinical usage, said Dr. Hwang. When dosed ideally, fluoroquinolones disrupt the fidelity of DNA replication, exerting a bactericidal effect. But when used inadequately, because of either inappropriate prescribing or patient noncompliance, their mechanism of action may actually rev up resistance because the surviving bacteria show a greatly increased random mutation rate.

"By not killing off the enemy and supplying them with small arms," Dr. Hwang said, "you allow them to overcome your defenses more easily." The longer you treat with a sublethal dose, the greater the cumulative acquisition of mutations, which confers a survival advantage. "The mutated organisms multiply rapidly from just a few to a large proportion of the bacterial flora, and this can happen in a matter of weeks," he said.

Tactic: target the mutants. A key principle, said Dr. Hwang, is to hit hard and get out fast. Ideally, you should aim for a target called the *mutant prevention concentration (MPC)*, which for fluoroquinolones is typically three to four times higher than the minimum inhibitory concentration (MIC). At the MPC, the likelihood of development of mutational resistance in any given exposed bacterium is less than one in 10.⁴

When given early and in sufficient concentrations, the newer fluoroquinolones, including gatifloxacin, moxifloxacin and besifloxacin, are better than the older ones at achieving the MPC because of their increased potency (i.e., lower MICs)

against gram-positive cocci in particular. “So even if patients don’t dose as frequently, peak antibiotic tissue levels can be well in excess of the MIC and can approach the MPC,” Dr. Hwang said. Unfortunately, this benefit applies largely to methicillin-susceptible staphylococci, and even these newest fluoroquinolones cannot be relied upon to clear established MRSA infections.

ROUTES AND RATES OF INFECTION

Among common ophthalmic procedures, including intravitreal injections of anti-VEGF agents and refractive or cataract surgery, rates of infection remain relatively low. However, each type of procedure poses specific challenges.

Intravitreal injections. According to a large meta-analysis,⁵ the most common organisms encountered with intravitreal injections are the coagulase-negative staphylococci and streptococci, said Harry W. Flynn Jr., MD, professor of ophthalmology at Bascom Palmer Eye Institute in Miami.

“*Staphylococcus* is the most common bacterial isolate cultured in postinjection endophthalmitis. *Streptococcus* is right behind, in second place, and occurs more frequently in injection-related than in post-cataract surgery endophthalmitis,” he said. One theory is that aerosolized moisture droplets from talking, coughing, sneezing or breathing over the patient during injection may contaminate the needle or the field around the eye.⁵

Although the rate of infection with intravitreal injections is still low—between one in 2,000 and one in 5,000 injections, said Dr. Flynn, the number of injections has markedly increased in

recent years. Certain practices may not readily show a difference on a per-injection basis, said Dr. Hwang, but the magnitude increases with multiple injections given over a multiyear treatment regimen and may make a clinically and statistically meaningful difference in the cumulative risk of endophthalmitis.

Refractive surgery. Because refractive procedures are generally performed in an office setting with high patient traffic, there is a potential for breaks in sterile processing or introduction of adventitious bacteria into the surgical field, said Dr. Hwang. Atypical mycobacteria, an important cause of post-LASIK infection, can be found in ultrasound water baths used for instrument processing or in tap water or moisture that gains entry into the surgical field, he said. “Fortunately, the risk of infection is relatively low, well under one in 1,000,” he said.

“But if we see an infection in that setting, we want to think about MRSA strains, as well as atypical organisms such as *Mycobacterium chelonae* and *M. abscessus*.” Both of these species of mycobacteria have poor response to typical fluoroquinolone monotherapy.

Cataract surgery. Mark Speaker’s landmark study published in 1991⁶ shed light on the central role of surface flora in intraocular infections, said Dr. Sheppard. “We learned that ocular surface contamination of the aqueous humor through the surgical wound was the main route for the development of endophthalmitis.”

BEST PRACTICES AGAINST BAD BUGS

Despite a dearth of data, some simple practices may help keep infections at bay in ocular procedures.

Start with the surface. Dr. Sheppard recommends being fastidious about alleviating a patient’s dry eye or blepharitis preoperatively. Both can predispose the patient to postoperative infection.

Copy Mr. Clean. Meticulous operating room technique and careful prep are fundamental for avoiding infections, said Dr. Flynn. Application of povidone-iodine (PI) for antisepsis provides broad, fast antimicrobial activity before ocular surgery or intravitreal injections: topical 5 percent PI for the conjunctiva and 10 percent PI for lids and lashes. It’s also widely available at low cost.

Dilute effectively. Careful irrigation and aspiration to remove all residual debris and viscoelastic effectively dilutes any bacteria introduced into the anterior



chamber during surgery, noted Dr. Sheppard.

Frequent irrigation of the ocular surface also dilutes and removes potential pathogens.

Don’t dabble. “Use antibiotics for a defined period at an effective dosage, then stop cold turkey,” said Dr. Olson. “It’s the slow dribbling of antibiotics over time that essentially guarantees that all you’ll have left are very bad, very resistant organisms.”

Reserve the big guns. “You don’t always need to reach for the \$100 bottle of antimicrobial,” said Dr. Hwang. The CDC recommends reserving drugs like vancomycin for an established infection that’s sight- or life-threatening. Dr. Olson added that, although still episodic, vancomycin-resistant staph are becoming less rare.

In the era of unsutured clear corneal incisions, said Dr. Sheppard, certain studies showed a two- to fivefold higher rate of postoperative endophthalmitis compared with current practice. Today, rates stand at between one in 1,000 and one in 5,000. “With a trend toward smaller incisions, we hope to see a continuous improvement in the infection rate,” he said. Interestingly, he added, infection rates are lower for busier cataract surgeons and cataract centers. This could be related to perfected techniques, less risky practices, quicker surgeries, experienced operating room personnel, healthier patients and lower rates of capsular rupture.

IDENTIFYING THE RISKS

Given the overall low infection rates in ophthalmic procedures, it makes sense to focus on high-risk patients, taking extra precautions and performing cultures as needed to more carefully target the antimicrobial attack. But how do we identify where to focus our efforts?

Careful patient evaluation. A thorough risk assessment and exam can help guide the clinician’s approach. For example, said Dr. Flynn, if a patient has conjunctivitis or a periocular infection, it’s best to postpone the procedure until the condition has resolved.

Patients with diabetes or suppressed immunity, who have had previous ocular surgery, or who already have an exposed vitreous cavity through capsular disruption, as well as patients receiving an anterior chamber lens, are at increased risk of developing endophthalmitis, said Dr. Sheppard.

When to culture. In addition, Dr. Hwang recommended performing culture and susceptibility testing *prior* to initiating empiric therapy in patients with presumed infectious keratitis who have risk factors or clinical features that predict a potentially severe or recalcitrant infection, such as:

- Poor response to or noncompliance with previous antibiotic therapy
- Hospitalization or residence in a chronic care facility during the prior three months
- Risk factors for colonization with health care-associated MRSA (e.g., health care workers) or community-acquired MRSA (e.g., prisoners)
- Use of topical or systemic fluoroquinolones within the previous three months
- Previous documented or suspected ocular infection with MRSA or other antibiotic-resistant pathogens
- Compromised ocular surface or host immune function
- Previous corneal surgery or LASIK
- A corneal infiltrate that threatens or involves the central visual axis, exceeds 3 mm in diameter,

is associated with hypopyon or threatens perforation.

In vitro vs. clinical susceptibility. The Clinical and Laboratory Standards Institute has formulated methods for testing the activity of antimicrobial agents against various bacteria and fungi, said Dr. Flynn. Its findings are valuable because they alert the clinician to the likelihood of in vitro and often-associated in vivo resistance. But are the laboratory findings borne out in clinical practice?

Although the correlation between in vitro and in vivo activity is quite good, said Dr. Olson, the route of administration plays a role in a drug’s efficacy. For example, it’s important to remember that you can achieve higher antibiotic levels on the surface of the eye. Thus, in practical terms, the organism may not appear to be resistant when treated on the surface, but “that same strain of bacteria inside the eye may indeed be very resistant,” he said.

Dr. Hwang added that low laboratory resistance rates don’t take into account the real-world effects of patient noncompliance—such as missing doses or using the medication longer than needed—which can *increase* the rates of resistance. It’s also critical to remember that drug susceptibility profiles can differ from region to region and between patient subgroups.

Dr. Sheppard said that he routinely observes local microbiology lab reports, which confirm excellent staphylococcal sensitivity to aminoglycosides, such as gentamicin and tobramycin, polymyxin B, sulfamethoxazole and vancomycin. These sensitivities are generally conserved even when staphylococci become resistant to methicillin or oxacillin.

PROPHYLAXIS PROTOCOLS

Ophthalmologists employ a variety of overlapping but not identical preventive measures, making it difficult to design studies and draw conclusions about efficacy, said Dr. Hwang.

Intravitreal injections. At a 2004 meeting, experts on infectious disease and intravitreal injection reviewed protocols and developed guidelines to minimize complications for intravitreal injections, said Dr. Flynn. There was general agreement on:

- 1) use of a lid speculum,
- 2) application of povidone-iodine (PI) to the ocular surface, eyelids and eyelashes,
- 3) avoidance of contact between the needle and eyelid margin or lashes and
- 4) avoidance of excessive eyelid manipulation.⁷

However, there was less agreement about the use of topical antibiotics before, during or after intravitreal injections, in part because of the poor penetration of topicals into the vitreous. Moreover,

given the increasing frequency of intravitreal injections, said Dr. Flynn, repeated exposure of ocular and nasopharyngeal flora to broad-spectrum topical antibiotics such as azithromycin and third- and fourth-generation fluoroquinolones may allow more virulent resistant bacterial strains to emerge.⁸

Topical fourth-generation fluoroquinolones before the day of injection have not been shown to reduce the rate of postinjection endophthalmitis, said Dr. Flynn, and demonstrate no added benefit in reducing conjunctival bacterial colonization beyond the effect of 5 percent PI alone.

A recently published editorial coauthored by Dr. Flynn identified several advantages of antiseptics with PI over the use of prophylactic antibiotics for intravitreal injections: PI is substantially less expensive, provides broad-spectrum coverage and has a faster bactericidal rate. Perhaps most important, PI does not contribute to the worsening problem of antibiotic resistance.⁹

Dr. Hwang said that, if used, prophylaxis should be brief; a three-day perioperative regimen should be sufficient, and more than five days should never be necessary. “The major risk of infection is from

microorganisms introduced during the injection, not after,” he said. “The overlying conjunctiva heals rapidly and provides a substantial physical barrier to the further entry of organisms.”¹⁰

Refractive surgery. “To my knowledge, we don’t have any data that prophylactic antibiotics reduce the risk of infection after LASIK or that certain ones reduce risk more than others,” said Dr. Hwang. “Yet, despite low rates of infection, we continue to use them due to concerns about rare but potentially sight-compromising infections.”

Although the optimal prophylaxis regimen for LASIK is unknown, he said, its duration after surgery can be as short as three or four days. That’s because the flap goes down immediately and is completely sealed within 24 hours, unlike procedures with larger incisions, where the potential for disruption of the epithelium poses a greater risk of postprocedure contamination.

Cataract surgery. “Until recently, there were no level 1 data in any prospective randomized analysis that a certain practice has an absolute effect upon the rate of endophthalmitis,” said

ROUGH ROAD FOR INTRACAMERAL THERAPY

The challenges of using intracameral antibiotics are clearly reflected in the Academy’s 2011 survey of comprehensive ophthalmologists. Nearly eight in 10 do not use an intracameral antibiotic during cataract surgery. The rest put an antibiotic in the irrigating bottle or inject it into the anterior chamber at the end of surgery.

The latter is the preferred practice of Douglas D. Koch, MD, cataract surgeon and professor of ophthalmology at Baylor College of Medicine in Houston. He injects 1 mg of vancomycin in 0.1 cc of balanced salt solution at the end of every cataract procedure. He also uses topical preoperative and postoperative treatment with a fourth-generation fluoroquinolone.

“I think many more physicians would inject at the end of surgery if appropriate drugs were readily available,” said Dr. Koch, “but we don’t have unit dose syringes or preparations, so these antibiotics have to be mixed and drawn up, which requires a fair amount of effort. And if you get the concentration wrong by a power of 10, which can happen fairly easily, you turn a potential rare case of endophthalmitis into a whole day’s worth of disastrous surgery,” he said.

To reduce the risks of in-

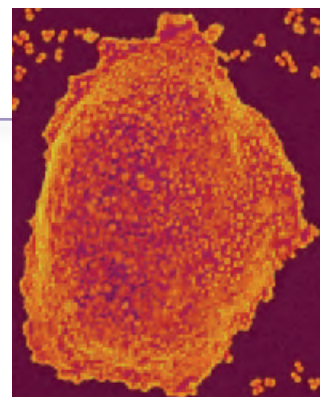
correct mixing, Dr. Koch follows a strict protocol that was developed by Howard V. Gimbel, MD, MPH. In addition to a two-step dilutional technique, his ambulatory surgery center has one nurse do the mixing and a second verify that it was done correctly.

A simpler approach is to inject preservative-free moxifloxacin into the eye, although this will be less effective against methicillin-resistant staph organisms. Alternatively, some surgeons put the antibiotic into the irrigating bottle, he said, but the data are not convincing, and there are questions about its efficacy because of dilution.

Although unit dose availability of these antibiotics may not be imminent due to cost-prohibitive FDA hurdles, Dr. Koch said that he sees more physicians turning to compounding or formulating pharmacies for this purpose. The downside? “This increases the cost of surgery,” he said.

Dr. Koch is a consultant for Alcon.

CLINICAL INSIGHT. To better understand current practices on a number of topics, the Academy surveyed comprehensive ophthalmologists about how they would handle various clinical situations. Here *EyeNet* features one question—on use of antibiotics for cataract surgery—and asks an expert to provide perspective on the response.



Dr. Sheppard, “although level 2 data supported the effectiveness of preoperative PI with cataract surgeries.¹¹ Now, despite some controversy, the large European Society of Cataract and Refractive Surgeons (ESCRS) endophthalmitis study¹² provides level 1 data supporting postoperative intracameral cefuroxime.” Regardless of antibiotic use, he said, the best advice is to control ocular surface inflammation and to carefully monitor patients who are potentially at higher risk.

Dr. Olson recommends applying PI before lidocaine jelly, which can block its effect, and then reapplying the PI before starting surgery. His prophylactic regimen includes 0.5 percent gatifloxacin eyedrops, four times daily, starting two days before surgery, with multiple drops applied just before surgery.

“I assume that everything on the surface of the eye is contaminated, particularly the conjunctiva,” he said, explaining his extreme caution at every step of the procedure. “When I finish the case, if the incision doesn’t seal easily and there is even a thought in my head that it may be less than a perfect wound, I’ll put a suture in. I don’t hesitate for a nanosecond.”

Right after surgery, he applies a series of fourth-generation fluoroquinolones before the patient leaves; the drops are used every two hours for the rest of that day and then four times a day for a week. “That gets you good, high antibiotic levels,” he said.

However, the effectiveness of postoperative topical prophylaxis remains debatable. “Once the epithelium has sealed the incisions,” said Dr. Hwang, “the risk of subsequent postoperative microbial contamination into the anterior chamber is extremely remote.”

Intracameral controversies. Despite the results

of the large ESCRS trial showing the efficacy of intracameral cefuroxime in reducing the incidence of endophthalmitis, there is no standard in the United States regarding this approach, according to Dr. Sheppard. Whether—and how—this method is used varies widely between different countries and regions. (See “Rough Road for Intracameral Therapy,” on the previous page, for results of an Academy survey of current clinical practices among comprehensive ophthalmologists.)

Dr. Hwang said that the choice of antibiotic is not clear, with most authors advocating for cefuroxime, some promoting vancomycin because of concerns about MRSA/MRSE, and others investigating the use of nonpreserved fluoroquinolones such as moxifloxacin. Dr. Flynn added that MRSA, *Enterococcus* and *Pseudomonas* have reduced susceptibility to cefuroxime.

“What we’re lacking is a good single-dose intracameral antibiotic,” said Dr. Olson. Some surgeons use nonpreserved topical drops as an intracameral injection, but topical formulations haven’t undergone testing to ensure safety for that use. Dr. Olson predicted a move toward a belt-and-suspenders approach with staph-specific drugs: topicals to minimize surface contamination and an intracameral to ensure a supralethal dose in the anterior chamber.

Dr. Flynn is opposed to such an approach. He says that, in addition to concerns about increased resistance, the use of intracameral antibiotics carries the risk of contamination during mixing, toxicity from incorrect dosage and cystoid macular edema with certain antibiotics.

Irrigating solutions. To bypass the challenges of intracameral preparation and delivery, some surgeons simply add vancomycin to irrigating solutions, said Dr. Hwang. But this raises concerns

MEET THE EXPERTS

HARRY W. FLYNN JR., MD Professor of ophthalmology at the Bascom Palmer Eye Institute in Miami. *Financial disclosure: Consults for Alcon and Allergan.*

DAVID G. HWANG, MD Professor of ophthalmology and codirector of the cornea service and director of the refractive surgery service at the University of California, San Francisco. *Financial disclosure: Consults for Inspire Pharmaceuticals.*

RANDALL J. OLSON, MD Director of the Moran Eye Center at the University of Utah School of Medicine in Salt Lake City. *Financial disclosure: None.*



JOHN D. SHEPPARD, MD Professor of ophthalmology, microbiology and molecular biology, and clinical director at the Lee Center for Ocular Pharmacology at Eastern Virginia Medical School, and president, Virginia Eye Consultants in Norfolk, Va. *Financial disclosure: Is a consultant, speaker and advisory board member for Alcon, Allergan, Bausch + Lomb, Inspire, Ista and Vistakon.*

about widespread exposure of periocular flora to a last-line agent against MRSA and MRSE.

"Furthermore, the relatively low concentration of vancomycin used in irrigating solutions, combined with the pharmacodynamics of vancomycin, renders this mode of delivery unfavorable for surgical prophylaxis," he said. "Vancomycin has a relatively short half-life in the anterior chamber [approximately two hours], yet killing occurs in a time-dependent fashion." Therefore, it makes more sense to use it in bolus form as an intracameral injection at the end of surgery. To achieve widespread adoption, he said, this approach would require a commercially available option, as well as studies supporting its safety and efficacy.

"An intriguing option for prophylaxis," said Dr. Flynn, "is the use of dilute povidone-iodine for constant surface irrigation during the surgical procedure." He pointed out a recent study that showed a significant reduction in anterior chamber bacterial contamination with use of a 0.25 percent PI irrigating solution.¹³

Other options. Dr. Hwang noted that some older drugs, such as trimethoprim-polymyxin B, may be excellent choices for perioperative ocular surface prophylaxis against MRSA and MRSE. Even today, he said, more than 90 percent of MRSA remain susceptible to the trimethoprim component of the combination.

"It doesn't penetrate well, so you can't rely upon it to achieve therapeutic levels in the aqueous against MRSA that have already entered the eye, but it can be helpful in intercepting MRSA on the ocular surface before it enters the eye."

Dr. Hwang has also used collagen shield delivery of high-dose cephalosporin into the eye for two decades. "You can get a level of delivery that is comparable to or better than subconjunctival injection, which can approximate the effect of an intracameral cephalosporin injection."

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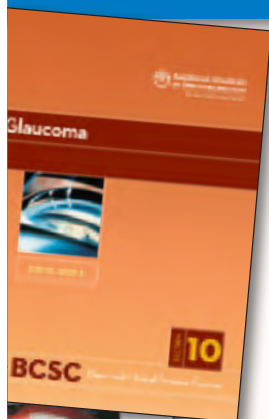
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