REVIEW® of Ophthalmology

October 2016

reviewofophthalmology.com

Is Bigger Always Better?

Waves of practice mergers are sweeping across the world of medicine. What's in it for you? ***P. 32***

ALSO INSIDE:

WHEN TREATING INFLAMMATION AND PAIN
IN YOUR CATARACT SURGERY PATIENTS

#1 Prescribed Branded Ophthalmic NSAID[1]

POTENCY, PRECISELY WHERE YOU NEED IT

ILEVRO® Suspension offers **proven efficacy**, **once-daily postoperative dosing**, and **affordable access** for your patients[2-4]

INFLAMMATION COMPLETELY CLEARED IN **2 OUT OF 3** PATIENTS AT **DAY 14**[2,3*†]

OCULAR PAIN COMPLETELY RESOLVED IN **>80%** OF PATIENTS AT **DAY 14**[3†‡]

1x DAILY POSTOPERATIVE DOSING REGIMEN[3]

- ILEVRO® Suspension should be applied to the affected eye one-time-daily beginning 1 day prior to cataract surgery, continued on the day of surgery and through the first 2 weeks of the postoperative period. An additional drop should be administered 30 to 120 minutes prior to surgery[3]
- Use of ILEVRO® Suspension more than 1 day prior to surgery or use beyond 14 days post-surgery may increase patient risk and severity of corneal adverse events[3]

BROAD COVERAGE[4]

ELIGIBLE COMMERCIAL PATIENTS MAY PAY AS LITTLE AS **$35** OUT OF POCKET[§]

To learn more about treating postoperative inflammation and pain with ILEVRO® Suspension, visit **myalcon.com/ilevro**

INDICATIONS AND USAGE

ILEVRO® (nepafenac ophthalmic suspension) 0.3% is a nonsteroidal, anti-inflammatory prodrug indicated for the treatment of pain and inflammation associated with cataract surgery.

Dosage and Administration

One drop of ILEVRO® Suspension should be applied to the affected eye one-time-daily beginning 1 day prior to cataract surgery, continued on the day of surgery and through the first 2 weeks of the postoperative period. An additional drop should be administered 30 to 120 minutes prior to surgery.

IMPORTANT SAFETY INFORMATION

Contraindications

ILEVRO® Suspension is contraindicated in patients with previously demonstrated hypersensitivity to any of the ingredients in the formula or to other NSAIDs.

Warnings and Precautions

- *Increased Bleeding Time* – With some nonsteroidal anti-inflammatory drugs including ILEVRO® Suspension there exists the potential for increased bleeding time. Ocularly applied nonsteroidal anti-inflammatory drugs may cause increased bleeding of ocular tissues (including hyphema) in conjunction with ocular surgery.
- *Delayed Healing* – Topical nonsteroidal anti-inflammatory drugs (NSAIDs) including ILEVRO® Suspension may slow or delay healing. Concomitant use of topical NSAIDs and topical steroids may increase the potential for healing problems.
- *Corneal Effects* – Use of topical NSAIDs may result in keratitis. In some 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.

  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.

  Use more than 1 day prior to surgery or use beyond 14 days post-surgery may increase patient risk and severity of corneal adverse events.
- *Contact Lens Wear* – ILEVRO® Suspension should not be administered while using contact lenses.

Adverse Reactions

The most frequently reported ocular adverse reactions following cataract surgery occurring in approximately 5 to 10% of patients were capsular opacity, decreased visual acuity, foreign body sensation, increased intraocular pressure, and sticky sensation.

For additional information about ILEVRO® Suspension, please refer to the brief summary of prescribing information on adjacent page.

*With ILEVRO® Suspension versus 24% to 32% with vehicle; $P<0.05$.[3]

†Results from 2 randomized, multicenter, controlled, double-masked trials of adult patients undergoing cataract extraction. In Study 1, patients were randomized to receive either ILEVRO® Suspension (n=851), NEVANAC® Suspension (n=845), ILEVRO® Suspension vehicle (n=211), or NEVANAC® Suspension vehicle (n=213). In Study 2, patients were randomized to receive either ILEVRO® Suspension (n=540) or ILEVRO® Suspension vehicle (n=268).[2,3]

‡84% to 86% with ILEVRO® Suspension versus 38% to 46% with vehicle; $P<0.05$.[3]

§This offer is not valid for patients who are enrolled in Medicare Part D, Medicaid, Medigap, VA, DOD, Tricare, or any other government-run or government-sponsored health care program with a pharmacy benefit. Additional eligibility terms apply. See copay savings material for specific details.

References: 1. IMS Health Xponent, January 2015-December 2015. Accessed December 2015. **2.** Data on file. **3.** Ilevro [package insert]. Fort Worth, TX: Alcon Laboratories, Inc; 2014. **4.** Fingertip Formulary, October 2015 (estimate derived from information used under license from Fingertip Formulary, LLC, which expressly reserves all rights, including rights of copying, distribution and republication).

ILEVRO® (nepafenac ophthalmic suspension) 0.3%

Alcon® a Novartis company

ILEVRO®

(nepafenac ophthalmic suspension) 0.3%

BRIEF SUMMARY OF PRESCRIBING INFORMATION

INDICATIONS AND USAGE
ILEVRO® (nepafenac ophthalmic suspension) 0.3% is indicated for the treatment of pain and inflammation associated with cataract surgery.

DOSAGE AND ADMINISTRATION
Recommended Dosing
One drop of ILEVRO® Suspension should be applied to the affected eye one-time-daily beginning 1 day prior to cataract surgery, continued on the day of surgery and through the first 2 weeks of the postoperative period. An additional drop should be administered 30 to 120 minutes prior to surgery.

Use with Other Topical Ophthalmic Medications
ILEVRO® Suspension may be administered in conjunction with other topical ophthalmic medications such as beta-blockers, carbonic anhydrase inhibitors, alpha-agonists, cycloplegics, and mydriatics. If more than one topical ophthalmic medication is being used, the medicines must be administered at least 5 minutes apart.

CONTRAINDICATIONS
ILEVRO® Suspension is contraindicated in patients with previously demonstrated hypersensitivity to any of the ingredients in the formula or to other NSAIDs.

WARNINGS AND PRECAUTIONS
Increased Bleeding Time
With some nonsteroidal anti-inflammatory drugs including ILEVRO® Suspension, there exists the potential for increased bleeding time due to interference with thrombocyte aggregation. There have been reports that ocularly applied nonsteroidal anti-inflammatory drugs may cause increased bleeding of ocular tissues (including hyphemas) in conjunction with ocular surgery. It is recommended that ILEVRO® Suspension be used with caution in patients with known bleeding tendencies or who are receiving other medications which may prolong bleeding time.

Delayed Healing
Topical nonsteroidal anti-inflammatory drugs (NSAIDs) including ILEVRO® Suspension, 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.

Corneal Effects
Use of topical NSAIDs may result in keratitis. In some susceptible patients, continued use of topical NSAIDs may result in epithelial breakdown, corneal thinning, corneal erosion, corneal ulceration or corneal perforation. These events may be sight threatening. Patients with evidence of corneal epithelial breakdown should immediately discontinue use of topical NSAIDs including ILEVRO® Suspension 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 1 day prior to surgery or use beyond 14 days post-surgery may increase patient risk and severity of corneal adverse events.

Contact Lens Wear
ILEVRO® Suspension should not be administered while using contact lenses.

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

Serious and Otherwise Important Adverse Reactions
The following adverse reactions are discussed in greater detail in other sections of labeling:
- Increased Bleeding Time (Warnings and Precautions)
- Delayed Healing (Warnings and Precautions)
- Corneal Effects (Warnings and Precautions)

Ocular Adverse Reactions
The most frequently reported ocular adverse reactions following cataract surgery were capsular opacity, decreased visual acuity, foreign body sensation, increased intraocular pressure, and sticky sensation. These reactions occurred in approximately 5 to 10% of patients.

Other ocular adverse reactions occurring at an incidence of approximately 1 to 5% included conjunctival edema, corneal edema, dry eye, lid margin crusting, ocular discomfort, ocular hyperemia, ocular pain, ocular pruritus, photophobia, tearing and vitreous detachment.

Some of these reactions may be the consequence of the cataract surgical procedure.

Non-Ocular Adverse Reactions
Non-ocular adverse reactions reported at an incidence of 1 to 4% included headache, hypertension, nausea/vomiting, and sinusitis.

USE IN SPECIFIC POPULATIONS
Pregnancy
Teratogenic Effects.
Pregnancy Category C: Reproduction studies performed with nepafenac in rabbits and rats at oral doses up to 10 mg/kg/day have revealed no evidence of teratogenicity due to nepafenac, despite the induction of maternal toxicity. At this dose, the animal plasma exposure to nepafenac and amfenac was approximately 70 and 630 times human plasma exposure at the recommended human topical ophthalmic dose for rats and 20 and 180 times human plasma exposure for rabbits, respectively. In rats, maternally toxic doses ≥10 mg/kg were associated with dystocia, increased postimplantation loss, reduced fetal weights and growth, and reduced fetal survival.

Nepafenac has been shown to cross the placental barrier in rats. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, ILEVRO® Suspension should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Non-teratogenic Effects
Because of the known effects of prostaglandin biosynthesis inhibiting drugs on the fetal cardiovascular system (closure of the ductus arteriosus), the use of ILEVRO® Suspension during late pregnancy should be avoided.

Nursing Mothers
ILEVRO® Suspension is excreted in the milk of lactating rats. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ILEVRO® Suspension is administered to a nursing woman.

Pediatric Use
The safety and effectiveness of ILEVRO® Suspension in pediatric patients below the age of 10 years have not been established.

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

NONCLINICAL TOXICOLOGY Carcinogenesis, Mutagenesis, Impairment of Fertility
Nepafenac has not been evaluated in long-term carcinogenicity studies. Increased chromosomal aberrations were observed in Chinese hamster ovary cells exposed *in vitro* to nepafenac suspension. Nepafenac was not mutagenic in the Ames assay or in the mouse lymphoma forward mutation assay. Oral doses up to 5,000 mg/kg did not result in an increase in the formation of micronucleated polychromatic erythrocytes *in vivo* in the mouse micronucleus assay in the bone marrow of mice. Nepafenac did not impair fertility when administered orally to male and female rats at 3 mg/kg.

PATIENT COUNSELING INFORMATION
Slow or Delayed Healing
Patients should be informed of the possibility that slow or delayed healing may occur while using nonsteroidal anti-inflammatory drugs (NSAIDs).

Avoiding Contamination of the Product
Patients should be instructed to avoid allowing the tip of the dispensing container to contact the eye or surrounding structures because this could cause the tip to become contaminated by common bacteria known to cause ocular infections. Serious damage to the eye and subsequent loss of vision may result from using contaminated solutions.

Use of the same bottle for both eyes is not recommended with topical eye drops that are used in association with surgery.

Contact Lens Wear
ILEVRO® Suspension should not be administered while wearing contact lens.

Intercurrent Ocular Conditions
Patients should be advised that if they develop an intercurrent ocular condition (e.g., trauma, or infection) or have ocular surgery, they should immediately seek their physician's advice concerning the continued use of the multi-dose container.

Concomitant Topical Ocular Therapy
If more than one topical ophthalmic medication is being used, the medicines must be administered at least 5 minutes apart.

Shake Well Before Use
Patients should be instructed to shake well before each use.

Released: February 2014

U.S. Patent Nos. 5,475,034; 6,403,609; and 7,169,767.

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REVIEW NEWS
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VisuMax SMILE Procedure Wins FDA Approval

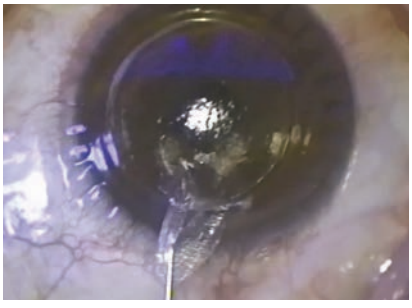
In mid-September, Carl Zeiss Meditec's VisMax SMILE (Small Incision Lenticule Extraction) vision correction procedure won market approval from the FDA, paving the way for less-invasive, single-laser vision correction.

"Commercial availability is not yet known, but should be in several months," says Jon G. Dishler, MD, of Dishler Laser Institute, Denver, Co., U.S. medical monitor for the VisuMax IDE Study. Current users of the VisuMax laser will need to upgrade their existing software. New users will need to complete SMILE training before and during their first cases.

SMILE requires the use of the Zeiss VisuMax femtosecond laser to create a disc-shaped lenticule inside the cornea, which is then extracted through a 2- to 3-mm corneal incision. Extraction of the lenticule flattens the cornea, correcting the myopia.

Unlike LASIK, SMILE doesn't entail stromal ablation or a flap. "The laser cutting portion takes less than a minute, and then the patient is repositioned slightly for a different set of optics which allows the surgeon to precisely remove the lenticule with a pair of forceps," Dr. Dishler explains.

Because SMILE leaves behind a smaller entry wound, there's less disruption to the corneal surface than with LASIK. This may mean faster recovery and less chance of postop dry eye. SMILE candidates must be at least 22 and have documented stable manifest refraction over the past year. SMILE candidates should be -1 D to -8 D with ≤ -0.50 D cylinder and MRSE -8.25 D in the affected eye(s). "Particularly well-suited candidates are ones where a corneal flap would best be avoided, such as the military or police," says Dr. Dishler.



In SMILE, removing a lenticule flattens the cornea. *Image: Jesper Hjordal, MD*

"The approved procedure doesn't correct astigmatism," he notes, "so patients who are satisfied with spherical soft contact lenses within the approved range are good potential candidates."

For the study, 336 eyes underwent SMILE for nearsightedness at five investigational sites. "There was excellent and stable correction of refractive error in the clinical trial," says Dr. Dishler. Of the 328 participants evaluated at six months, 88 percent had uncorrected visual acuity of 20/20 or better, with all but one seeing 20/40 or better uncorrected. Patients also experienced rapid visual recovery with little discomfort. Intraoperative complications included difficulty removing the corneal tissue and loss of suction. Postop complications included debris at the tissue-removal site, dry eye, glare and halos.

Although no enhancements were needed in the study, Dr. Dishler states that they could be performed by PRK if needed.

A clinical trial is currently underway in myopic astigmats, but hyperopic patients will have to wait even longer to see if SMILE is an option for them. "There is an international study on treatment of hyperopia," Dr. Dishler says, "but this has not been studied yet in an FDA clinical trial, and we have no information on future plans."

Patients Unaware of Telemedicine

In August, researchers at the University of Michigan Health System examined the efficacy of diagnosing and monitoring diabetic retinopathy via telemedicine. While they found that telemedicine is indeed effective, the study also discovered that only a small portion of the participants had previously used it or even heard of it.

In the study, 97 percent of the participants hadn't heard of telemedicine, which the researchers believe to be reflective of most U.S. citizens. After being introduced to telemedicine, 32 percent of participants were still either unsure or opposed to participating in telemedicine for DR screening. University of Michigan's Maria Woodward, MD, notes that previous patient experience makes a difference: "If pa-

tients have a strong relationship with their eye doctor and have been living with diabetes for a number of years independently, they are less interested in telemedicine," she says.

Dr. Woodward also attributes skepticism of telemedicine to lack of knowledge about the process. "Certainly there's the education aspect, too, as in knowing that this is really safe and effective for patients," she says. "There has been plenty of evidence in the literature that doing diabetic screening by telemedicine is as safe as going to an eye doctor for the same exam."

Dr. Woodward notes that telemedicine also isn't very popular due to its cost. "Telemedicine programs incur a lot of cost," she explains, "so systems that can see the long-term benefits of preventative medicine have this program in place. Those systems that are set up in such a way that they see the same patients regularly see the power of long-term prevention. In other systems where patients move between systems and providers, there's a lot of infrastructure cost to set up these programs. Because of this, it really hasn't been done in the U.S. until now, when the cameras and the technology have allowed the cost of telemedicine to drop to the point that it makes sense to set up these programs for patients."

Despite its cost and patient unfamiliarity, telemedicine has been helpful in screening for diabetic retinopathy. "The benefit to the patients with diabetes is the convenience," Dr. Woodward says, "and that convenience is twofold: One, there is the convenience due to time saved; and two, the patients typically don't have to be dilated for a telemedicine exam, so it's more comfortable for them." The study also concluded that telemedicine programs should focus on individuals who have limited access to care, as these programs would allow patients to complete screenings from the comfort and convenience of their own homes. REVIEW

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The PROLENSA® Effect

POWERED FOR PENETRATION

Advanced Formulation to Facilitate Corneal Penetration[1-3]

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

INDICATIONS AND USAGE

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

IMPORTANT SAFETY INFORMATION ABOUT PROLENSA®

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

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

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

BAUSCH + LOMB

PROLENSA®
(bromfenac ophthalmic solution) 0.07%

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

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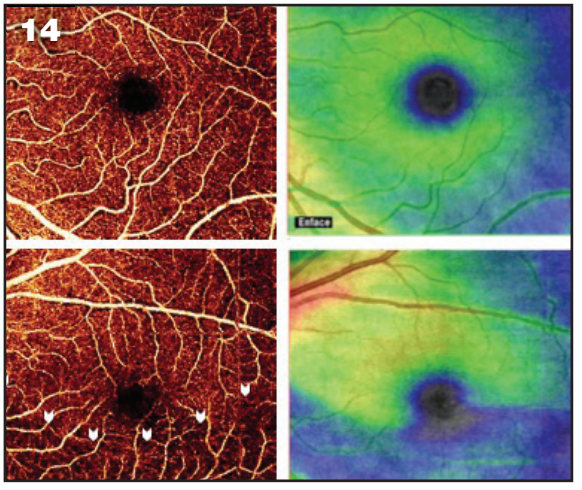
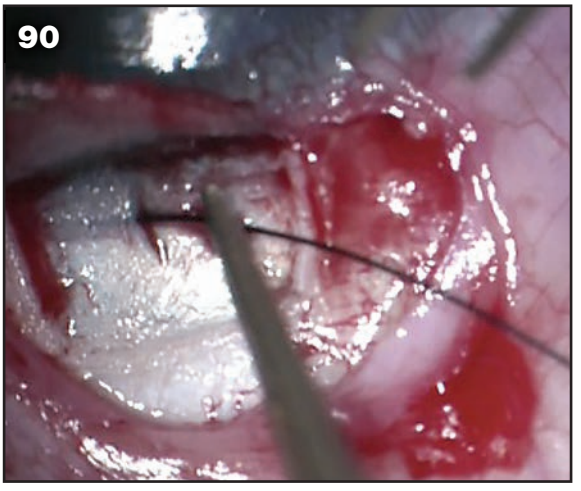
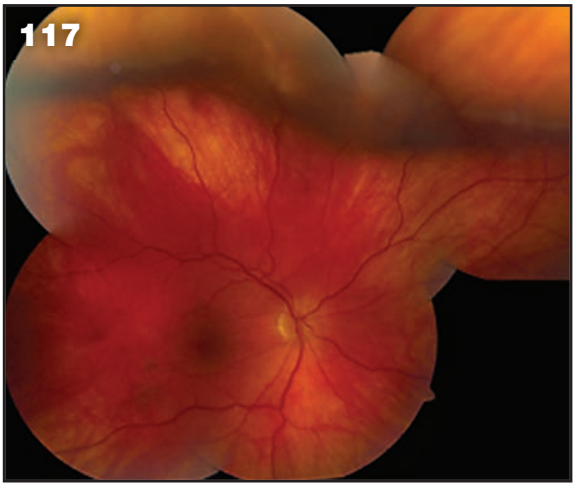
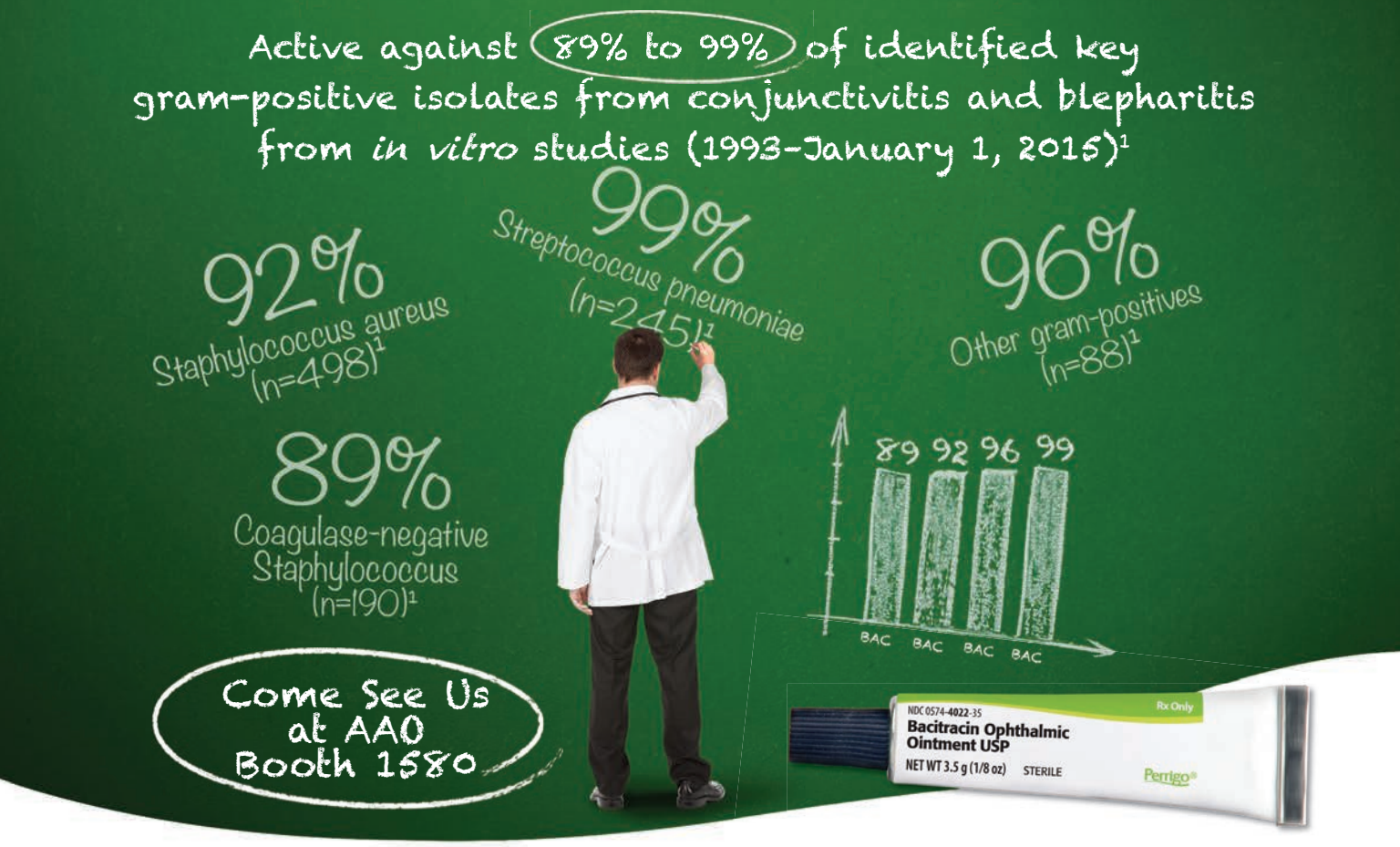






BACITRACIN OPHTHALMIC OINTMENT USP



***In Vitro* Susceptibility Data Provided Through the University of Pittsburgh Medical Center. *In Vitro* Data Should Not Be Considered Representative of Clinical Efficacy[1]**

Established therapeutic utility in blepharitis, conjunctivitis, and other superficial ocular infections caused by Bacitracin-susceptible organisms

- **Excellent safety profile**—low incidence of adverse events[2]
- Ointment provides **long-lasting ocular surface contact time** and **greater bioavailability**[3]
- **Anti-infective efficacy** in a lubricating base[2]
- **Flexible dosing**—1 to 3 times daily[2]
- **Tier 1 pharmacy benefit status**—on most insurance plans[4]

Indication

Bacitracin Ophthalmic Ointment is indicated for the treatment of superficial ocular infections involving the conjunctiva and/or cornea caused by Bacitracin susceptible organisms.

Important Safety Information

This product should not be used in patients with a history of hypersensitivity to Bacitracin.

Bacitracin Ophthalmic Ointment should not be used in deep-seated ocular infections or in those that are likely to become systemic.

There is a low incidence of allergenicity exhibited by Bacitracin. If such reactions do occur, therapy should be discontinued.

Please see adjacent page for full prescribing information.

For a closer look, visit www.perrigobacitracin.com

BACITRACIN OPHTHALMIC OINTMENT USP

Perrigo® Specialty Pharmaceuticals

Bacitracin Ophthalmic Ointment USP

STERILE **Rx Only**

DESCRIPTION: Each gram of ointment contains 500 units of Bacitracin in a low melting special base containing White Petrolatum and Mineral Oil.

CLINICAL PHARMACOLOGY: The antibiotic, Bacitracin, exerts a profound action against many gram-positive pathogens, including the common Streptococci and Staphylococci. It is also destructive for certain gram-negative organisms. It is ineffective against fungi.

INDICATIONS AND USAGE: For the treatment of superficial ocular infections involving the conjunctiva and/or cornea caused by Bacitracin susceptible organisms.

CONTRAINDICATIONS: This product should not be used in patients with a history of hypersensitivity to Bacitracin.

PRECAUTIONS: Bacitracin ophthalmic ointment should not be used in deep-seated ocular infections or in those that are likely to become systemic. The prolonged use of antibiotic containing preparations may result in overgrowth of nonsusceptible organisms particularly fungi. If new infections develop during treatment appropriate antibiotic or chemotherapy should be instituted.

ADVERSE REACTIONS: Bacitracin has such a low incidence of allergenicity that for all practical purposes side reactions are practically non-existent. However, if such reaction should occur, therapy should be discontinued.

To report SUSPECTED ADVERSE REACTIONS, contact Perrigo at 1-866-634-9120 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DOSAGE AND ADMINISTRATION: The ointment should be applied directly into the conjunctival sac 1 to 3 times daily. In blepharitis all scales and crusts should be carefully removed and the ointment then spread uniformly over the lid margins. Patients should be instructed to take appropriate measures to avoid gross contamination of the ointment when applying the ointment directly to the infected eye.

HOW SUPPLIED:

NDC 0574-**4022**-13 3 - 1 g sterile tamper evident tubes with ophthalmic tip.

NDC 0574-**4022**-35 3.5 g (1/8 oz.) sterile tamper evident tubes with ophthalmic tip.

Store at 20°-25°C (68°-77°F)
[see USP Controlled Room Temperature].

Manufactured For
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0S400 RC J1 Rev 08-13 A

References: 1. Antibiotic susceptibility: conjunctivitis and blepharitis. University of Pittsburgh Medical Center, Charles T. Campbell Eye Microbiology Lab Web site. http://eyemicrobiology.upmc.com/AntibioticSusceptibilities/Conjunctivitis.htm. Accessed March 21, 2016. **2.** Bacitracin Ophthalmic Ointment [package insert]. Minneapolis, MN: Perrigo Company; August 2013. **3.** Hecht G. Ophthalmic preparations. In: Gennaro AR, ed. *Remington: the Science and Practice of Pharmacy.* 20th ed. Baltimore, MD: Lippincott Williams & Wilkins; 2000. **4.** Data on file. Perrigo Company.

REVIEW® of Ophthalmology

Thoughts on In-office Surgeries

To the Editor:

I'm writing to give another viewpoint on the topic of in-office surgery, not just for cataracts but for other procedures such as, in my case, oculofacial plastics.

I've been doing in-office plastics procedures for five years here in my Coral Gables office. I decided to write because CMS's focus has been on cataracts, but I'd like my colleagues to know that in-office can also apply to other procedures. Before opening my surgical suite, I contracted with a firm called Total Medical Consultants to guide me through the requirements, specs and structure that needed to be in place so the Florida Medical Board would accredit my facility as a certified office surgical suite. I understand that in some states there is no overseeing association/board to make sure that these in-office surgical suites are up to code. However, in my state there is, and I get inspected yearly to ensure I'm compliant.

The list of requirements doesn't fall short of those of an ASC facility, which I know about, as I'm also a minority owner of an ASC. These include proper documentation, mandatory use of RN's, appropriate physical layout of the surgical suite, backup battery power, crash cart, etc. We're also required to do quarterly risk management meetings headed up by Total Medical Consultants. My experience has been great, with no infections or complications in five years, doing hundreds of cases per year. The suite can be certified to do up to Level-III anesthesia.

In terms of the big question—reimbursement—as we know, there is no "in-office facility" code. However, third-party payers, including Medicare, will pay a bit more for procedures done in a non-facility setting, though this obviously doesn't cover the overhead costs of the procedure. There are some HMO's here in Miami that have realized the potential cost savings and have been willing to pay the physician for the use of his in-office facility, but have been unable to, as they too follow CMS guidelines. The biggest advantage at this time for me to do in-office surgery has been being more efficient with time (i.e., seeing new consults between cases, taking care of paperwork), which I wouldn't have been able to do if I were away. Also, it allows me to capture the cosmetic market because I can offer lower facility fees than hospitals and ASCs.

I use an anesthesiologist to give the sedation, as I feel it's safer and more comfortable for the patient. Also, in case of an emergency, an anesthesiologist's experience is superior to a nurse anesthetist's, and this removes the primary liability for anesthesia and airway issues from the surgeon. This is an important point: When you use a nurse anesthetist, you are 100-percent responsible for all the drugs he administers, and for any issues that may arise from anesthesia.

I hope this letter sheds some light on in-office surgery, and that CMS creates an in-office facility fee code in the near future.

Joseph Selem, MD
Coral Gables, Fla.


New Ways to Diagnose Trouble Earlier

Novel technologies may make it possible to detect signs of disease and begin treatment earlier than ever.

Christopher Kent, Senior Editor

When it comes to keeping patients from losing vision, catching a problem early is half the battle. Here, doctors and researchers talk about three new developments that might allow us to detect trouble earlier than ever in patients with keratoconus, macular degeneration and glaucoma.

Tear Markers and Keratoconus

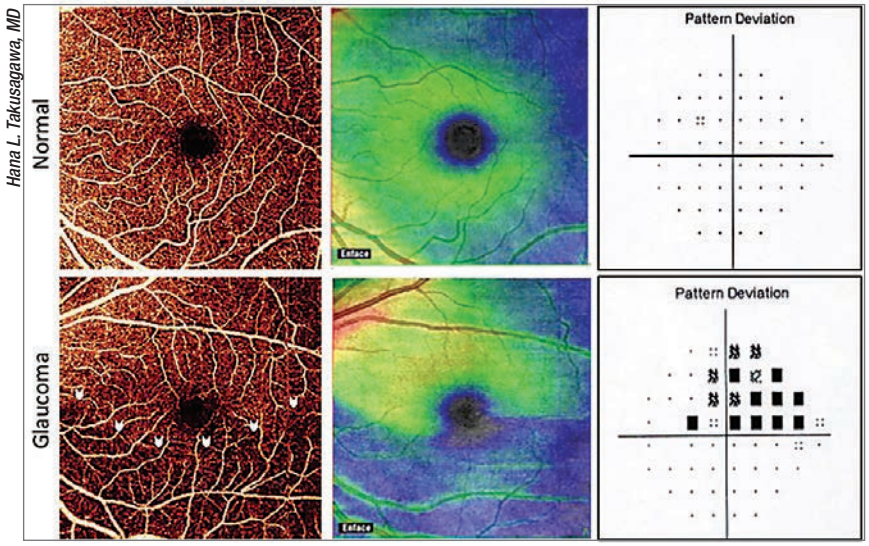
Rohit Shetty, DNB, FRCS, PhD, is a cornea and refractive surgeon and a clinical and translational scientist working at Narayana Nethralaya Rajajinagar in Bangalore, India. Although keratoconus is not generally thought of as an inflammatory disease, Dr. Shetty's work has supported the connection between inflammatory cytokines in the tear film and progressive keratoconus. His team has shown that keratoconus patients' tears contain high levels of matrix metalloproteinase 9 (MMP9) and IL6 (one of the interleukin family of cytokines), both associated with inflammation, and that these levels correlate with disease progression. In addition, one recent study conducted by Dr. Shetty and colleagues demonstrated that the elevated levels of MMP9 and inflammatory cytokines in the tears of keratoconus patients could be reduced with cyclosporine treatment, leading to a concomitant arrest of disease progression.[1]

"My interest in this idea was the result of a few papers I'd seen on the connection between inflammation and keratoconus," he explains. "Eye-rubbing, allergy and dry eye have all tentatively been linked to keratoconus, and these are often linked to inflammation. So we started our research with the question 'Is keratoconus inflammatory?' We began searching for tear biomarkers; this took time, but eventually we were able to prove that these biomarkers do exist." Dr. Shetty says that their work has also demonstrated that progressive keratoconus has a unique inflammatory signature which differs from that of nonprogressive keratoconus. "The markers associated with progressive keratoconus cause more damage to the collagen and lysyl oxidase, which is necessary for cross-linking, both natural and artificial," he says.

Dr. Shetty notes that his team's work has ramifications for current clinical settings. "Some of these factors can be measured using existing clinical products," he points out. "For example, MMP9 is one of the factors associated with progressive keratoconus, and that can be measured using the RPS InflammaDry test. We're currently developing a clinical test that will be able to measure even more keratoconus-related inflammation markers in the tear film, such as interleukin and lysyl oxidase. Eventually we'd like to have a test that can evaluate all of the relevant markers, with an algorithm to help the doctor decide whether or not treatment is needed." Dr. Shetty notes that it's even possible that measuring the biomarkers could allow clinicians to detect keratoconus before other signs or symptoms are present, although this remains to be demonstrated.

"The main message from our work is that keratoconus is an inflammatory disease," says Dr. Shetty. "Surgeons should think of keratoconus as 'white inflammation'—i.e., inflammation without cardinal signs such as redness and pain. Despite the lack of these signs, it's still creating changes in the

INDICATION FOR USE. The iStent® Trabecular Micro-Bypass Stent (Models GTS100R and GTS100L) is indicated for use in conjunction with cataract surgery for the reduction of intraocular pressure (IOP) in adult patients with mild to moderate open-angle glaucoma currently treated with ocular hypotensive medication. **CONTRAINDICATIONS.** The iStent® is contraindicated in eyes with primary or secondary angle closure glaucoma, including neovascular glaucoma, as well as in patients with retrobulbar tumor, thyroid eye disease, Sturge-Weber Syndrome or any other type of condition that may cause elevated episcleral venous pressure. **WARNINGS.** Gonioscopy should be performed prior to surgery to exclude PAS, rubeosis, and other angle abnormalities or conditions that would prohibit adequate visualization of the angle that could lead to improper placement of the stent and pose a hazard. The iStent® is MR-Conditional meaning that the device is safe for use in a specified MR environment under specified conditions, please see label for details. **PRECAUTIONS.** The surgeon should monitor the patient postoperatively for proper maintenance of intraocular pressure. The safety and effectiveness of the iStent® has not been established as an alternative to the primary treatment of glaucoma with medications, in children, in eyes with significant prior trauma, chronic inflammation, or an abnormal anterior segment, in pseudophakic patients with glaucoma, in patients with pseudoexfoliative glaucoma, pigmentary, and uveitic glaucoma, in patients with unmedicated IOP less than 22 mmHg or greater than 36 mmHg after "washout" of medications, or in patients with prior glaucoma surgery of any type including argon laser trabeculoplasty, for implantation of more than a single stent, after complications during cataract surgery, and when implantation has been without concomitant cataract surgery with IOL implantation for visually significant cataract. **ADVERSE EVENTS.** The most common post-operative adverse events reported in the randomized pivotal trial included early post-operative corneal edema (8%), BCVA loss of ≥ 1 line at or after the 3 month visit (7%), posterior capsular opacification (6%), stent obstruction (4%) early post-operative anterior chamber cells (3%), and early post-operative corneal abrasion (3%). Please refer to Directions for Use for additional adverse event information. **CAUTION:** Federal law restricts this device to sale by, or on the order of, a physician. Please reference the Directions for Use labeling for a complete list of contraindications, warnings, precautions, and adverse events.



Perfusion alterations in the superficial vascular complex of the macula—detectable using OCT angiography—show high sensitivity for differentiating glaucomatous eyes from normals, and correlate well with visual fields. Above: *En face* OCT angiograms, ganglion cell complex thickness maps and visual fields for a normal and a glaucomatous eye. In the glaucomatous eye, the angiogram and thickness map reveal an inferior arcuate defect (arrows); the visual field shows a superior defect at the same location.

nerves and collagen. For that reason, it makes sense to treat any inflammation that's present before doing any surgery or cross-linking. This is especially important in children. It's also worth testing the levels of MMP9 before you perform cross-linking, to ensure that levels are normal. Then, after surgery or cross-linking, it's important to continue to treat any inflammation with a drug such as cyclosporine for at least six months.

"It's especially important for American surgeons to understand this, now that cross-linking has been approved in the United States," he adds.

Dark Adaptation and AMD

It's been known for some time that abnormal dark adaptation is an early sign of retinal trouble. The problem has been testing it; in the past, a patient had to sit in the dark for a half hour or more prior to lengthy testing, making it clinically impractical. Now a device called the AdaptDx (MacuLogix, Middletown, Pa.) can reliably test a patient's dark adaptation function in six and a half minutes or less, making it a practical in-office test with multiple uses—in particular, detecting early evidence of age-related macular degeneration. (The test is Medicare reimbursable.)

Gregory R. Jackson, PhD, chief scientific officer at MacuLogix, says the device is easy to use and operator- and patient-friendly. "The device is also easy to interpret," he notes. "The machine gives the doctor a printout showing a parameter we call the rod intercept, which is the amount of time it takes for you to have nearly complete recovery of rod function. If the rod intercept is less than six and a half minutes, it's likely your macula is normal; if it's over six and a half minutes, it's likely your macula is abnormal."

Dr. Jackson says that a number of studies have demonstrated that dark adaptation is highly sensitive and specific for age-related macular degeneration.[2,3] "In a multisite clinical evaluation study, we found that dark adaptation was 90 percent accurate in classifying patients as having AMD or normal retinal health," he says.[2] "When patients were followed over a period of years, those with impaired dark adaptation in early testing were very likely to develop age-related macular degeneration.

"In 2016, Cynthia Owsley, PhD, at the University of Alabama Birmingham published the ALSTAR study," he continues. "In this study, they enrolled 325 normal adults age 60 or older whose retinal health was verified by AREDs grading of fundus photographs. At baseline, 24 percent of those patients had clinically impaired dark adaptation, the first symptom of age-related macular degeneration. Three years later, they redid the imaging and graded the fundus photographs in a masked fashion using the AREDs criteria, and found that if you had impaired dark adaptation at baseline, you were about twice as likely to have clinically evident macular degeneration at three years of follow-up. Furthermore, patients with impaired dark adaptation at baseline were eight times as likely to progress from normal retinal health to intermediate macular degeneration."[4] (Dr. Owsley is the patent holder for the AdaptDx technology.)

Dr. Jackson says the reason for this is now well understood. "Work by Christine Curcio, PhD, at the University of Alabama Birmingham—among others—has shown that before you have visible drusen in a macular degeneration patient, deposits of cholesterol coat the back of the macula, impeding the transport of nutrients into the eye, including vitamin A.[5] The resulting localized deficiency of vitamin A in their eyes slows the regeneration of rhodopsin, and thus dark adaptation. By the time you see one large druse in the back of the eye of an early macular degeneration patient, the whole back of the macula is coated with these cholesterol deposits, gumming up the works, denying the retina nutrition and keeping oxygen from the choroidal vasculature,

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IMPORTANT SAFETY INFORMATION

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

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

Systemic exposure of phenylephrine may cause elevations in blood pressure.

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

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

Use of OMIDRIA in children has not been established.

INDICATIONS AND USAGE

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

Reference: 1. OMIDRIA [package insert]. Seattle, WA: Omeros Corporation; 2015.

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

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impairing dark adaptation."

Dr. Jackson says that doctors using the AdaptDx are excited to have functional information about these patients. "Not only does the AdaptDx help doctors identify patients with early disease, it also allows them to baseline their existing macular degeneration patients so they can tell whether the patient is doing better or worse," he says. "We know from the Lucentis clinical crossover studies that if you're seeing a patient every six months and the patient develops choroidal neovascularization shortly after a visit, the patient can lose five lines of visual acuity before the next visit. If you see impaired dark adaptation, you can be more proactive and tighten up the observation period."

Dr. Jackson says he wants to be clear that dark adaptation can't predict the onset—or severity—of choroidal neovascularization or geographic atrophy. "It gives you a more complete picture of the retinal health of the patient," he says. "If you have a number of patients with intermediate macular degeneration, some will have much worse dark adaptation than others. Up until today, we've been using visual acuity as the canary in the coal mine; we don't get concerned until visual acuity drops substantially. As a result, we do a really bad job of saving visual acuity in the first eye. Having this new information lets us use night vision as the canary in the coal mine."

Dr. Jackson points out another recurring problem: patients referred to a cataract surgeon because of diminished vision that was actually caused by macular degeneration. "Many of our doctors are using the AdaptDx to help make a differential diagnosis," he says. "Dark adaptation as measured by the AdaptDx is not affected by cataract, so if you test a patient's dark adaptation and it's normal, you're probably looking at an optical cause for their acuity detriment or night vision problem. However, if the dark adaptation is impaired, you have to consider that you may be looking at a retinal problem."

"Having this new information lets us use night vision as the canary in the coal mine."
–Gregory Jackson, PhD

Dr. Jackson says the AdaptDx might also help a surgeon decide if someone is a good candidate for a multifocal IOL. "Multifocal IOLs reduce the amount of light reaching the retina," he notes. "So if a patient has impaired night vision, many doctors think it's not a good idea to put this type of lens into that eye."

Dr. Jackson says the AdaptDx costs $39,900, and is most useful for a primary care ophthalmologist. "Ophthalmologists can use dark adaptation to test their older and at-risk patients to find out whether they have subclinical macular degeneration or macular disease that they might otherwise have missed," he says.

Glaucoma and Macular Perfusion

Hana L. Takusagawa, MD, a glaucoma specialist and assistant professor at Oregon Health & Science University, has been working with David Huang, MD, PhD, and his team at the Center for Ophthalmic Optics and Lasers at the Casey Eye Institute, evaluating the potential for using OCT angiography to detect early glaucomatous damage in the upper layers of the macula.

"Glaucoma specialists who are interested in perfusion tend to study the optic nerve because that's where obvious clinical signs of glaucoma such as cupping happen," she says. "This new technology, OCT angiography, allows us to look at blood vessels in a quick, noninvasive way, without having to inject any dyes into the blood. Using the AngioVue OCT angiography system [Optovue, Fremont, Calif.], we've been comparing the perfusion in patients with glaucoma and those with healthy eyes. [Note: OCT angiography can also be done using the Zeiss Angioplex (Carl Zeiss Meditec, Dublin, Calif.)] Early on, we found that there's significantly decreased perfusion in the optic nerve. Then, in a later paper we looked at the area around the optic nerve, the peripapillary retina, which shows decreased perfusion in glaucoma as well.

"Most recently, we've looked at the macula," she continues. "We found that perfusion at the macula is also significantly decreased in people with glaucoma. About 30 percent of the retinal ganglion cells live in the macula, and those are the cells that are damaged in glaucoma; that may turn out to be the area in which we'll see the earliest changes from glaucoma."

Dr. Takusagawa explains that their most recent work has found that the superficial layer of the macula—the superficial vascular complex—shows much more blood vessel alteration in glaucoma patients than the deeper levels of the macula. "We've shown that there are four major plexuses of blood vessels in the retina," she notes. "It's the uppermost blood vessel complexes that are affected in glaucoma."

One advance that has helped them detect this difference is an algorithm created by Dr. Huang's team that removes flow projection artifacts from the scans. "OCT angiography detects motion based on changes in the OCT signal over time," Dr. Takusagawa explains. "It detects flow signals in blood vessels, but also shows flickering shadows projected on deeper structures. This makes it hard to get clean mea-

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surements of blood flow in different levels of the retina. So, we've done our studies using an algorithm that removes those projections. At the moment, the algorithm is not part of any commercial device, but I'm sure it will become available at some point in the future.

"At the same time, we also looked at the all-layer macular blood flow, which the OCTA instruments can determine without using these algorithms," she continues. "We found that all-layer retinal blood flow was decreased in the macula in glaucomatous eyes as well, so that measurement might also be clinically useful. However, just looking at the superficial layer of the macula was better at differentiating normal from glaucomatous eyes." (In their study of 30 glaucoma patients and 30 age-matched normal participants, reported at the 2016 annual meeting of the American Glaucoma Society, when specificity was fixed at 95 percent, the sensitivity of superficial vascular complex vessel density for differentiating glaucomatous eyes from normal eyes was 90 percent; in contrast, the sensitivity was 80 percent using all-layer retinal vessel density, and 77 percent when using GCC thickness.)

"The other exciting thing about OCT angiography is that our findings correlate really well with the patient's visual fields," she says. "I can envision that OCTA might someday become a quantitative stand-in for the visual field test, which most patients dislike. Also, a lot of damage happens before a deficit is detectable on visual field testing; it's possible that quantifying the vessel density in the upper layers of the macula might allow us to pick up damage earlier. Of course, it could turn out that OCT angiography measurements of the upper macula layers will be most effective when combined with other OCT measures like structural information about the ganglion cell complex."

In terms of the future, Dr. Takusagawa says the team has been conducting a longitudinal trial using OCT angiography on both glaucoma suspects and those with confirmed glaucoma to determine the effectiveness of this technology for following progression. "Hopefully we'll be coming out with some data about that in the next year or two," she says. REVIEW

Dr. Shetty has research grants from Allergan and Zeiss.

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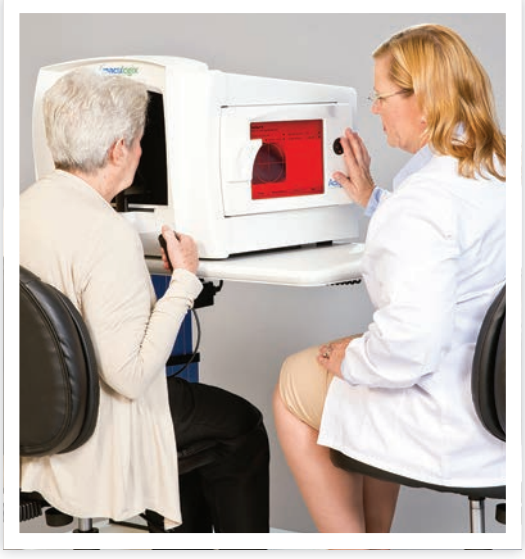

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ICD-10 Updates

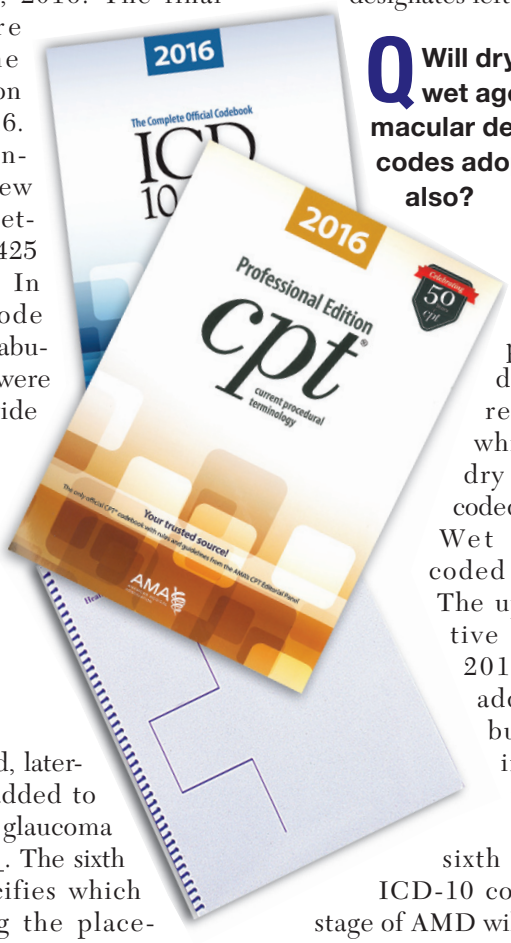
An overview of the recent updates for ICD-10, covering coding for wet and dry AMD and glaucoma.

Q Will changes or updates be made to ICD-10 coding and, if so, when?

A Yes. In March 2016, the Centers for Disease Control released proposed ICD-10 changes for October 1, 2016. The final changes were posted on the CDC website on August 22, 2016. The changes include 1,974 new codes, 311 deleted codes and 425 revised codes. In addition to code changes, some tabular instructions were revised to provide clarity.

Q What type of changes can we expect when coding for glaucoma?

A As expected, laterality was added to the open-angle glaucoma code, H40.11x _. The sixth digit now specifies which eye—replacing the placeholder "x." The seventh digit remains the stage of glaucoma. For example: Prior to October 1, 2016, a patient with primary open angle-glaucoma, moderate stage, left eye, was coded as H40.11x2. After October 1, 2016, it will be coded as H40.1122. The "2" in the sixth place designates left eye.



Q Will dry and wet age-related macular degeneration codes adopt laterality also?

A Yes. When originally published, dry AMD—regardless of which eye had dry AMD—was coded as H35.31. Wet AMD was coded as H35.32. The update effective October 1, 2016 not only adds laterality but also staging. The eye will be indicated by the sixth digit in the ICD-10 code, and the stage of AMD will be the seventh digit.

Q How are the stage codes described for dry AMD?

A There are five stages, including "unspecified," listed for dry AMD. They are:

- 0 - stage unspecified
- 1 - early dry stage
- 2 - intermediate dry stage
- 3 - advanced atrophic, without subfoveal involvement, advanced dry stage
- 4 - advanced atrophic, with subfoveal involvement.

The seventh character, the stage, of the ICD-10 code for dry AMD will be coded 0 to 4.

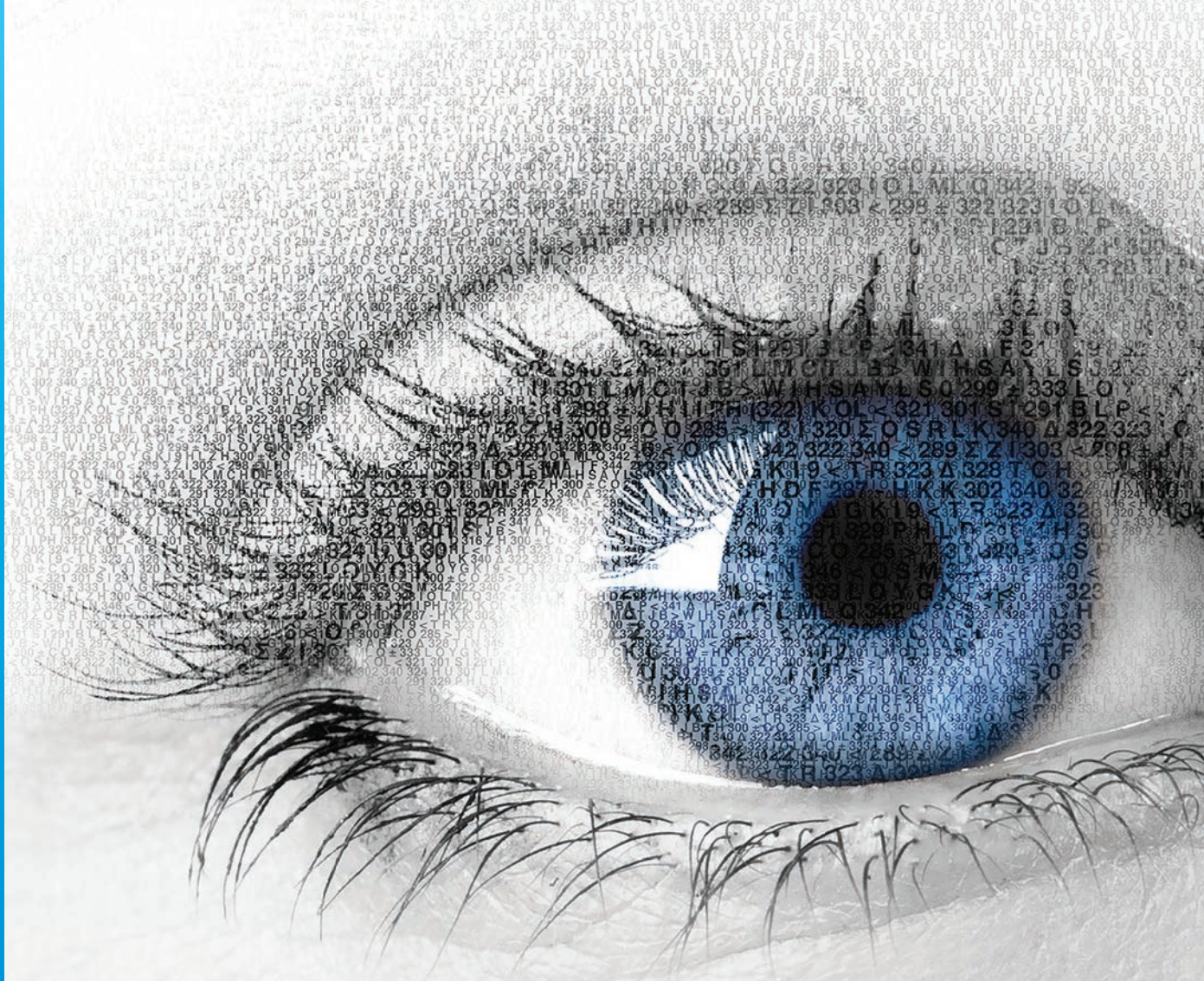
For example: H35.3112 describes a patient with nonexudative AMD in the right eye, intermediate stage. The sixth digit "1" indicates the right eye, and the seventh digit "2" represents intermediate stage.

Q Does the same approach apply to wet AMD?

A Yes, but with some variation. The sixth digit will be for laterality but for wet AMD only four stages, including "unspecified," exist. They are:

- 0 - stage unspecified
- 1 - with active choroidal neovascularization
- 2 - with inactive choroidal neovascularization with involuted or regressed neovascularization
- 3 - with inactive scar.

This article has no commercial sponsorship.



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The seventh character, the stage, of the ICD-10 code for wet AMD will be coded 0 to 3.

For example: H35.3221 describes a patient with exudative AMD, with active CNV in the left eye. The sixth digit "2" indicates the left eye, and the seventh digit "1" indicates active CNV stage.

Q Is there a definition of the various stages of AMD?

A Yes. There are several classifications of AMD in various publications. The American Academy of Ophthalmology uses the Age Related Eye Disease Study to classify AMD. They published it in their Preferred Practice Patterns document on AMD.

Q Were changes made to the diabetic combination codes?

A Approximately 260 new diabetic combination codes become effective on October 1, 2016. Some examples include:

- Diabetic retinopathy codes have added laterality, changing them from six to seven digits. For example, E11.3293 (Type II DM, mild NPDR, no DME, bilateral).
- There are new diabetic codes, including other retinal disease and resolved disease, including: E11.3531 (Type 2 diabetes mellitus with proliferative diabetic retinopathy with traction retinal detachment not involving the macula, right eye); E11.3552 (Type 2 diabetes mellitus with stable proliferative diabetic retinopathy, left eye); and E10.37x3 (Type 1 diabetes mellitus with diabetic macular edema, resolved following treatment, bilateral).

Q Are there additional changes to the retinal disease section of ICD-10?

A Yes. A seventh character further describing the patient's disease was added to the retinal vascular occlusion codes. The sixth digit continues to indicate each eye. For example:

H34.81 Central retinal vein occlusion:

One of the following seventh characters is to be assigned to codes in subcategory H34.81 to designate the severity of the occlusion:

- 0 - with macular edema
- 1 - with retinal neovascularization
- 2 - stable

H34.83 Tributary (branch) retinal vein occlusion:

One of the following 7th characters is to be assigned to codes in subcategory H34.83 to designate the severity of the occlusion:

- 0 - with macular edema
- 1 - with retinal neovascularization
- 2 - stable

Q What types of changes were made to the instructions to provide more clarity?

A After the introduction of ICD-10, considerable confusion surrounded the instructions for applying "Excludes 1" and "Excludes 2." Many complained that some conditions with an "Excludes 1" notation could also have a second condition, but the "Excludes 1" note did not permit using both codes. In the updated manual, some "Excludes 1" notes were changed to "Excludes 2" notes, allowing for conditions excluded by the "Excludes 1" note to now be coded together.

For example, ICD-10 code H42 *Glaucoma in diseases classified elsewhere previously contained an "Excludes 1" notation of diabetes mellitus (E08.39, E09.39, E10.39, E11.39, E13.39)*. This indicated that you could code one or the other, but not both. The update deletes the "Excludes 1" and adds *Excludes 2: glaucoma (in) diabetes mellitus (E08.39, E09.39, E10.39, E11.39, E13.39).*

Q Will we continue to see coding leniency from CMS as long as we are in the right "family" of codes?

A Very unlikely. CMS stated in July 2015 that it would not deny or audit claims just for specificity for one year after implementation of ICD-10, as long as the ICD-10 code was from the appropriate "family of codes." Most Medicare contractors accepted and paid claims with unspecified codes as long as the code was from the appropriate family of codes. However, the "honeymoon period" ends as of October 1, 2016.

Q What other possible issues are of concern for us with the implementation of these ICD-10 changes?

A There are several things to monitor:

- updating your EHR and practice management system;
- training regarding the new codes;
- monitoring coverage guidelines and Local Coverage Determinations by payers; and
- being prepared to contact payers if new codes are not added to coverage policies. REVIEW

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

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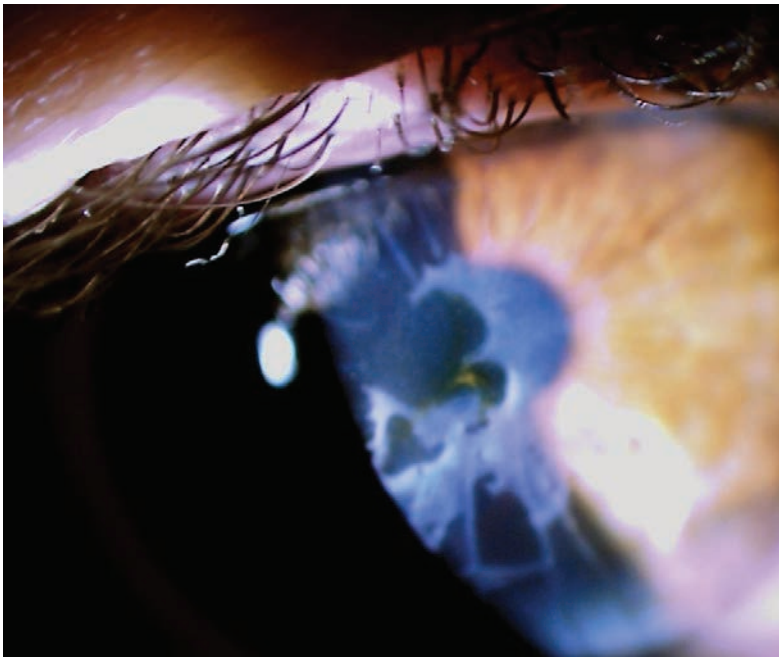
BioDOptix AMNIOTIC MEMBRANE IMPROVES POSTOPERATIVE VISUAL OUTCOMES

BY:
MIHIR J. PARIKH, MD

Obtaining accurate visual outcomes with cataract extraction and intraocular lens implant surgery requires optimizing the corneal surface. The lens implant selection is highly dependent on creating a pristine corneal surface for preoperative measurements, and then maintaining that surface throughout the postoperative recovery. However, a patient oftentimes desires lofty visual outcomes, but has a compromised cornea. The surgeon needs to either deploy effective management protocols prior to the cataract surgery or implement additional treatment methods after the procedure to achieve the results. Fortunately, with improved amniotic membrane delivery models, like BioDOptix®, surgeons can now offer effective, in-office techniques to efficiently optimize these corneas.



Patient presented with a corneal scar during cataract surgery work-up. We removed the scar, and placed a BioDOptix® amniotic membrane in the eye.

One of the most common challenges in achieving desired visual outcome goals is accurately measuring corneal curvature in the presence of corneal pathology. Pre-existing conditions, such as central corneal haze or a peripheral corneal scar, can induce irregular astigmatism, generating inaccurate measurements and subsequently yielding off-target results following lens implant surgery. It is paramount for anterior segment surgeons to remove these scars to optimize surgical outcomes.

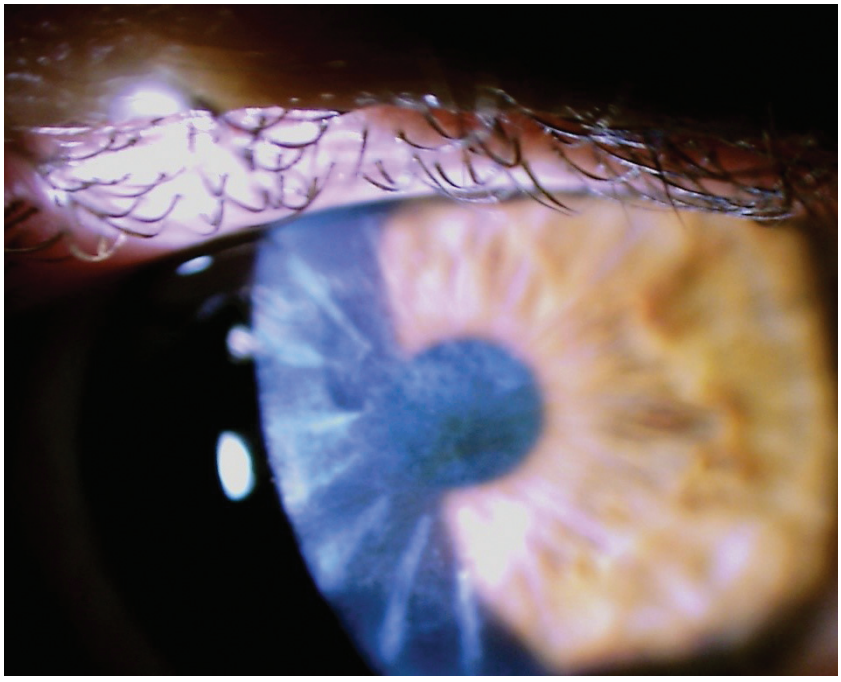
The amniotic membrane is a known product that can assist in the process of healing after corneal scar excision. If a scar is simply excised, the recovery may be unnecessarily long and painful with a high chance of recurrence.

However, amniotic membrane application serves as a biological contact lens for the cornea after the scar is removed. Its presence acts as a basement membrane—a scaffold for the progenitor epithelial cells to grow across—as well as an attractant for the patient's own

CASE REPORT: CORNEAL SCAR REMOVAL PRIOR TO CATARACT SURGERY

It is a challenge to obtain regular central corneal curvature measurements for lens formula calculations for patients with multiple-cut radial keratotomies (RK), with or without crossed arcuate (AK). However, this task becomes even more complex when the patient also has undergone a photorefractive keratectomy (PRK) "enhancement" after the initial RK/AK operations, and now presents with a dense corneal scar. In this case, following diluted alcohol instillation to remove the native central epithelial layer, our patient's scar was excised with the use of a spatula to remove the gelatinous but tenaciously adherent central corneal scar. A cellulose corneal sponge soaked in mitomycin C (MMC) was then applied for two minutes. After flushing away the MMC with balanced salt solution, a BioDOptix® amniotic membrane was placed on the cornea and then a bandage contact lens overtop it. Five days later, the amniotic membrane had self-dissolved and the bandage contact lens was removed. Within one month, the central corneal scar was almost completely absent. The patient's cornea is now better prepared for the task of selecting a lens implant for the cataract surgery.

limbal stem cells to collect within. It also serves as an anti-inflammatory agent by modulating cytokine release, which controls the inflammatory cascade. Equally importantly, it suppresses the release of transforming growth factor beta (TGF-B), which in turn inhibits myofibroblast differentiation— the cell type responsible for the scar formation. The microenvironment with the amniotic membrane improves nerve growth regeneration and overall patient comfort. These properties cumulatively make amniotic membrane an attractive biologic contact lens that a simple plastic contact cannot provide.



Less than one month after BioDOptix® placement, the patient's cornea was well healed and ready for IOL selection.

Historically, the rate-limiting step to using amniotic membranes in the office setting was accessing a low-temperature storage or keeping fresh tissue in a cost-efficient manner. Fortunately, however, sufficient cold freezer storage or the limited shelf life of fresh grafts may not pose quite the challenges they once did.

BioDOptix® is a dry amniotic membrane that can be stored on a shelf for five years at ambient temperature, and is easily made available when needed. In this instance, the membrane is reconstituted simply by adding moisture. BioDOptix® is secured on the cornea by placing a bandage contact lens over it. Within one week or less, the amniotic membrane will dissolve and the bandage contact lens can be removed. A large-diameter plastic ring to hold the amniotic membrane is not required, and thus the comfort level is dramatically improved.

BioD LLC is a vertically integrated company that processes BioDOptix®. BioD recovers the amnion from pre-screened, healthy, live donors during cesarean childbirth. These tissues are processed into their dehydrated state and terminally sterilized for final distribution to the physician's office. The acquisition cost of BioDOptix® is affordable for doctors and is a highly effective, in-office solution to optimize corneas and achieve superior visual results.

Get to Know Your New Surgical Options

Experts familiar with the new Symfony IOL and the Raindrop corneal inlay share their tips for optimizing outcomes.

Walter Bethke, Editor in Chief

In recent months, U.S. ophthalmologists gained acces to two new options designed to possibly give patients better depth of focus: the Tecnis Symfony intraocular lens (Abbott) and the Raindrop corneal implant (ReVision Optics). Though the devices are new to most U.S. ophthalmologists, surgeons who took part in their U.S. trials or have worked with them overseas already have a bank of experience new surgeons can draw from as they begin their first cases. Here are tips and techniques from these experienced physicians.

The Symfony

This IOL, a toric version of which was also approved, is the first in a new category of implants dubbed extended depth of focus lenses. Here's how to get the most from it:

• ***Best candidates.*** Sioux City, Iowa, surgeon Jason Jones, who participated in the Symfony's FDA trial, says the best candidate "is someone who desires reduced spectacle dependence but is also willing to pay for that privilege," he says. "He also wants to enjoy a high quality of vision and, lastly, he has to accept the use of glasses for occasional needs, specifically for reading, or for reading for long periods of time, for fine print, et cetera." In the FDA study, 85 percent of the Symfony patients reported wearing correction a "little or none of the time" vs. 60 percent of monofocal IOL controls.

"Outside the United States," Dr. Jones continues, "some surgeons have reported that patients with shorter stature/shorter arms, who have kind of a close near point due to their stature, can find it challenging to achieve spectacle independence without some extra modifications to their treatment. The alphabet they use can affect this, as well. Specifically, some Asian fonts are quite intricate, with the required reading distance being very close, and there's quite a lot of detail that needs to be absorbed to read appropriately. It's important to have a preop discussion with these types of patients, to let them know that they have options: either use reading glasses more in these circumstances; let us choose a myopic refractive target for their non-dominant eye; or have us perhaps pair the Symfony with a multifocal IOL that would provide that near performance as well as maintain distance performance."

Surgeons say the preop discussion with Symfony candidates is also a good time to manage their expectations in terms of qualitative vision issues. "The other thing patients should be made aware of is that there will be some halo formation and perhaps some glare symptoms," Dr. Jones says. "It's a very low rate, much lower than what has been reported in FDA trials for multifocal lenses, but it's still present. And, if your patient has such an experience and wasn't prepared for it preop, sometimes he'll find that his experience isn't very acceptable. It's one of those things that, if you make them aware of it but they don't have it, all is good. But if they do, it's often manageable with encouragement. My patients from the study, some of whom I have more than a year of follow-up on, actually report to me that they rarely notice glare and halo issues anymore."

Dean Corbett, BSc, MBChB, FRANZCO, who has extensive experience with the Symfony, says the halos and starbursts are there, but "the amount of trouble people have with them is vastly less." He says he equates them to more of a "soft" dysphotop-

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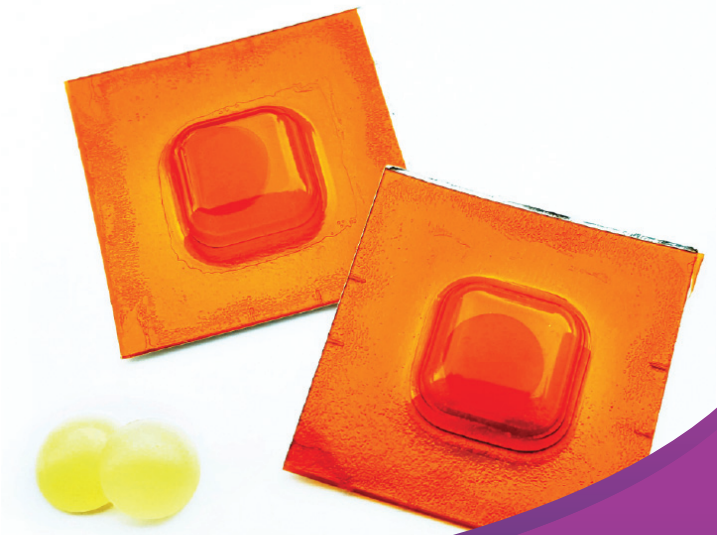

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sia, as opposed to a "hard" one, meaning they're better tolerated as a group. "In my experience," he says, "between 30 and 50 percent of patients have no more symptoms than they'd have with a monofocal, but the remaining group will see night-vision disturbances. However, it's much less common to get a patient who is bothered by them."

• ***Choose a refractive target.*** Adjusting the eye's final refractive target can help the lens work with patients' needs, surgeons say. "That's the fun thing about the use of this lens," says Dr. Corbett. "It opens up a new approach for a surgeon trying to deliver a visual outcome to patients. One decides with the patient what the emphasis of visual performance is going to be. For instance, if the patient hunts, shoots or is a golfer and is passionate about having distance focus and isn't overly discerning about his near vision, I would put a Symfony lens in and target the 'first or second plus' on the IOLMaster or Lenstar [referring to the first and second IOL options in the hyperopic range when these devices are programmed to target emmetropia]. Then, on the basis of the refractive outcome of the first eye, we determine what he wants for the second eye. In another patient, say an office worker who doesn't undertake any leisure activities that require distance acuity, we'd be inclined to choose the 'first minus' [on a biometry device]—or even the 'second minus' if it's a low myope, because low myopes have traditionally been in glasses that have often undercorrected their distance vision. The patient's two lenses will overlap at 90 percent of the range of vision, but we can just give one eye some extra power over the other, at either end of the spectrum. When we see the patients after a week, one in five will say, 'It's perfect,' and I'll put the same refractive-targeted lens in the other eye. But, more often than not, I'll be choosing a lens either on the plus side or the minus side, depending on what the patient wants." Investigators say this targeting is possible because vision doesn't drop off as fast with defocus as a monofocal IOL does.

Suggested Symfony Exclusion Criteria

- Ocular diseases other than cataract
- Lifestyle and job criteria:
  - -unrealistic visual expectations
  - -patients demanding visual precision (e.g., pilots, professional drivers, architects)
  - -patients satisfied with reading glasses
  - -people over age 70 (there may be difficulties with neuroadaptation to new optical conditions)
- Personality:
  - -psychiatric disease of any type
  - -patients unsatisfied with progressive glasses
  - -a history of brain stroke or dyslexia
  - -type-A personality (perfectionists)

Presented at the 2016 ESCRS meeting by Ante Barišic, MD, after 614 cases

Dr. Jones says that, in addition to the technique of targeting the non-dominant Symfony eye for some minus in patients with strong reading needs—he says the general consensus is that -0.5 is the most surgeons will target in this way—some Symfony surgeons are also doing a "mix-and-match" approach to get certain patients the near point they want. "Some surgeons have tried to boost the reading range of this lens by pairing it with a multifocal lens, specifically the Tecnis ZLB00, though I've heard of the ZKB00 being used, as well," he says. "Those lenses deliver a definitive near focusing point, as multifocal lenses do. In my experience, however, even using the low-add multifocals from Abbott, there are some halo issues. However, from the reports I've heard, the halos are different than the Symfony's; multifocal lenses have a more distinct ring structure, and the Symfony's tends to be softer, less intrusive. With appropriate counseling, a mix between the two technologies is reasonable."

In terms of refraction, one thing surgeons say to be aware of with the Symfony is that, after implantation, auto-refractors will give unusual results. "The auto-refractor will always come up with minus," Dr. Corbett notes. "You can either ask the patient what his vision's like or, if you're more scientific, you can do a refraction and push the plus."

The Raindrop

The Raindrop corneal inlay has no refractive power of its own, but when placed beneath a flap in a patient's non-dominant eye, it changes the cornea's refractive power to boost near vision. Here are surgeons' tips for using it:

• ***Preop considerations.*** Jeffrey Whitman, MD, a Dallas surgeon who participated in the FDA trial of the inlay, says the contraindications are similar to those for LASIK. "The topography should be good, the tear film acceptable—dry eye is a problem for this just as it's a problem for LASIK," he says. "Unrealistic expectations are a contraindication, too. In terms of baseline refractive error, within the FDA parameters we're looking for patients who are +1 to -0.5 D spherical equivalent, with 0.75 D or less of cylinder. This is because the procedure treats a little hyperopia. In Europe, though, where they usually do LASIK on these patients as well, they usually shoot for an endpoint of +0.25 to +0.5 D before they put the inlay in." Also, there should be 300 µm of stroma remaining below the flap, notes Dr. Whitman.

• ***The surgery.*** Dr. Whitman says the flap for the Raindrop is made at 30 percent corneal depth. Flaps are usually thicker than those used in LASIK, about 150 µm on average. "Disregarding this and going for a thin flap will result in failure and removal of the inlay due to a high rate of inflammatory response," he says. *Review*'s Refractive Surgery editor, Arturo Chayet, MD, of Tijuana, Mexico, errs on the side of thicker flaps. "I recommend using at least 150-µm flaps," he says. "You don't

want to be close to the surface because you may get corneal haze."

Dr. Chayet implants the Raindrop under the Allegretto excimer laser's microscope. "I activate the HeNe beam, which allows the pupil to dilate a little more and provides retro-illumination to center the lens better," he says.

Once the flap is made, the surgeon reflects it back and loads the inlay onto its delivery instrument. "It has to be just wet enough—not too wet," notes Dr. Whitman. "You then lay the tip of the delivery instrument just beyond the center of the light-constricted pupil. There are a number of instruments you can use to manipulate the Raindrop, but I use the elbow of a Sinskey hook. I push down on the inlay as I pull away the delivery device. The trick is doing this so you leave it as close to the center of the pupil as possible. While the inlay is still wet, you can use your instrument to slightly tap it in one direction or another and get it centered."

Hydration now becomes crucial, says Dr. Whitman. "At this point, when you've placed the inlay, wait a minute to a minute-and-a-half to allow the Raindrop to dry," he explains. "The endothelial pump pulls fluid through the cornea and the inlay—and you'll see the Raindrop start to dimple like the skin of an orange as it dries. You know that it's stuck down properly when it's fairly dimpled. While that's occurring, since we are leaving the flap open longer than we typically do for LASIK, it's important to keep the stromal side of the flap and the area around the inlay moist. This is for striae avoidance. I rewet the stromal side of the flap every 20 seconds or so, and I also gently rewet the cut stromal side but take care not to rewet the inlay itself. If you rewet the inlay, it can float, requiring you to restart the drying period."

Dr. Whitman says that once you've achieved dimpling of the inlay, you replace the flap. "Again, unlike LASIK, you can't go back under the flap and irrigate back and forth because you'll perhaps irrigate off the inlay," he warns. "Once it's laid back, just irrigate and smooth the epithelial surface of the flap, then wait a minute or two for it to dry. Once the area's dry, let the patient sit for 10 to 15 minutes, and then look at the eye at the slit lamp to ensure the inlay looks well-centered. Fortunately, the inlay can tolerate about 0.7 mm of decentration and still function fine."

• ***Postop notes.*** The postop period is focused on catching any immune response. "We place the patient on a Durezol tapering dose for a month," says Dr. Whitman. "Then, once that month has passed, we put him on Lotemax for a two-month taper. We've found that cutting the steroid dose short can lead to an inflammatory response, fibrosis and possible removal of the inlay down the line. That full three months of steroids postop is very important. We also put him on an antibiotic drop for a week."

The patients are seen at a day, a week, a month and then every three months for the first year, looking for signs of inflammation or fibrosis. "Inflammation will often cause a decrease in distance vision, an increase in near vision and a steepening of the cornea," Dr. Whitman explains. "If we see either inflammation or fibrosis, we immediately start a one-month course of tapering Durezol, and we may do a taper of Lotemax after that. This got rid of it in a majority of cases in the study. We were allowed to do this regimen three times in the study before having to remove the inlay, which we'll probably do in commercial practice, too. As part of the preop discussion, we tell patients that if removal is indicated, their vision will go back to close to where it was preop—we never say the term 'reversible.'" REVIEW

Drs. Jones and Corbett have received compensation/speaker's fees from AMO. Drs. Whitman and Chayet are clinical investigators for ReVision Optics.

Coming Together: Is a Bigger Practice Better?

Christopher Kent, Senior Editor

Consolidation has become a trend in ophthalmology. Should you be riding the wave?

It's often said that there is strength in numbers. Today, that sentiment helps explain one of the clearest trends in the field of ophthalmology: practice consolidation. In a world of increasingly complex government regulation, expensive instrumentation that's becoming the standard of care, giant corporate entities looking to buy up practices and patients expecting ease of access and acceptance of their insurance, the solo practitioner may be on the endangered species list.

Here, a practice management expert and three doctors in different types of practice situations share their experiences and insights regarding the reasons for this trend, the pros and cons of consolidation, and advice for anyone thinking of becoming part of a group practice or health-care organization.

Coming Together

"The world of medicine is changing," notes Robert J. Noecker, MD, MBA, in private practice at Ophthalmic Consultants of Connecticut in Fairfield, Conn., and an assistant clinical professor at Yale University School of Medicine, whose practice has acquired a number of other small practices in the past few years. "Thirty years ago, most ophthalmologists were solo practitioners. If you wanted to practice medicine somewhere, you set up your office and started doing it. These days, that's rare. I don't think any residents start out with their own practice anymore, and practice consolidation is occurring at a number of levels.

"There are multiple reasons for this trend," he continues. "Part of it is purely demographic; the doctors who are part of the baby boomer generation are getting to retirement age. But another part of it is the logistics and economy of scale you need to create today because of all the administrative requirements and greater overhead. In a couple of practices we've acquired, ophthalmologists nearing retirement age hadn't converted to EHR. They didn't want to deal with PQRS and all of the new quality measures that require adding more staff to manage. Integrating ICD-10 was hard for everybody, but it was really hard for the smaller guys without a lot of infrastructure.

"In the old days you could just practice as long as you wanted to, because nothing changed for decades," he adds. "But now every year the ante is being upped, in terms of reporting metrics and compliance with programs to avoid having your reimbursements cut, et cetera. All of these

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changes are largely handled administratively, and when you're getting toward the end of your career, you may not want to take on all of that additional cost by yourself. So these doctors think about selling or joining a bigger group. At the same time, health systems are also starting to move in and acquire practices."

"The biggest reason for consolidation at this time is declining reimbursement coupled with the increasing cost of practicing medicine," says Kenneth J. Rosenthal, MD, FACS, surgeon director at Rosenthal Eye and Facial Plastic Surgery in New York, attending physician at New York Eye and Ear Infirmary of Mt. Sinai and associate professor of ophthalmology at the University of Utah School of Medicine. (Dr. Rosenthal has been in solo practice for many years, but is now considering joining with other practices in his area.) "A larger practice allows doctors to achieve efficiencies of scale, makes it easier to comply with regulatory burdens and divides up some of the costs. The reality is, a large percentage of the costs involved in medical practice are per-practice fixed costs, not per-doctor costs.

"Part of that is the increasing cost of medical equipment, especially in the field of ophthalmology," he continues. "If I want to buy a new OCT as a solo doctor, I have to spend $80,000. If you're part of an eight-man group, then your cost is $10,000, so you're definitely not taking as much financial risk. You can afford to purchase the sophisticated and increasingly necessary equipment needed to maintain a state-of-the-art practice. Meanwhile, your reimbursement for each procedure will be exactly the same."

Dr. Rosenthal notes that a group practice has other advantages, including combining different skill sets under one roof. "For example," he says, "if one physician in a group does complex surgical case management, other members of the group will be able to keep those cases in the practice instead of referring them out. Consolidation is also a defensive move in the face of acquisition of smaller practices by big hospitals and HMOs. In the event that a group is purchased, it's in a much stronger position. A larger practice also brings with it a better retirement plan, a greater degree of security and better health insurance. For example, some practices are now dropping standard disability insurance in favor of self-insuring; if someone gets sick, they keep paying the individual a preset amount of money. If a group is large enough to afford that, it saves them the cost of an insurance plan that may never yield any return on investment. With a group practice you also have a built-in retirement strategy because your patient load can be assumed by other members of the practice."

Dr. Rosenthal notes that size also makes a difference when it comes to negotiating rates. "I've never had a managed care plan seriously sit down with me and negotiate a fee structure," he says. "They just don't care. That's one of the impetuses that's made me consider joining with other practices."

Dr. Rosenthal acknowledges, however, that there are downsides to becoming part of a group. "You lose some independence in terms of deciding practice style, the hours and days you work, when you take vacations and choice of technology," he notes. "In a big group, if you want to buy that OCT but nobody else wants to, you can't buy it, or you'll have to pay for it yourself. In a solo practice, you can do whatever you want."

Historical Perspective

"Consolidation of any kind, whether it's a merger or an acquisition, and whether it involves joining a private equity company or a larger practice or aligning with a hospital, is ultimately driven by two principal emotions,"

says John Pinto, president of J. Pinto & Associates, an ophthalmic practice management consulting firm. "It's either driven by fear: 'If we don't merge, something bad is going to happen'; or by a kind of greed: the belief that something better could happen for me if I go in with you.

"Waves of consolidation occur whenever our industry is under stress, as it is now," he continues. "The last major wave of consolidation occurred in the mid-1990s when Hillary Clinton was pushing for health-care reform. Everyone was concerned that reform might sweep us away. After the 1990s, those concerns and the merger-consolidation activity waned dramatically. Everybody sort of dusted themselves off and said, 'Well, that wasn't such a great idea.'

"Today, we have the same sort of tensions arising as we did in the 1990s," he notes. "We're seeing the same kind of opportunistic corporate activities taking place, both in terms of large practices acquiring smaller ones, and in terms of providers joining private equity companies. The numbers are even greater today because we have a larger cohort of ophthalmologists in their last few years of practice who are looking for an exit strategy. If they're not already in a group practice, where the succession is automatically to the younger doctors, they're coming up out of the trenches and looking for other practices or private equity companies that might be interested in buying them."

Mr. Pinto likes to think of these periods as two epochs of consolidation. "Epoch I was in the 1990s," he says. "Now we're in epoch II, where it's occurring again. Of course the big difference between these two epochs is that in the 1990s the general economy turned around very nicely and consolidation dampened sharply as the economy improved. This time we may see an ongoing trend toward consolidation. Also, health-care costs as a percentage of GDP are much higher than they were in the '90s, partly because the baby boomer wave is beginning to gobble up Medicare resources. And, the government also prefers larger practices that can be more efficiently regulated from above."

Choosing an Option

So, if you're in a small practice and want to become part of something bigger, which option makes the most sense? "A lot depends on how many years you want to practice, post-transaction, and how much control or lack of control you can tolerate," says Mr. Pinto. "For example, in a typical transaction in which a practice is being bought up by a hospital, multispecialty clinic, private equity company or large, private regional eye-care provider, I tell clients not to go through with the transaction unless: 1) they're nearing retirement and the proceeds they receive will put them over their retirement finish line; and 2) they're no longer emotionally connected to their practice, so that whatever the new owner does with it won't throw them for a loop.

"For doctors who are midcareer, who want to take their toolbox and put it in a four-stall garage, the motivation is different," he continues. "They want to know what kind of income they're

From Solo Act to Team Player

One key aspect of moving from having an independent practice to being part of a larger organization is the psychological impact of the change. Giving up autonomy can be tough, even when you gain other benefits in exchange.

"When we bring doctors into our group who've been in solo practice, it's a big adjustment," notes Tommy Korn, MD, FACS, a member of the Sharp Rees-Stealy Medical Group in San Diego. "It's like taking a tennis player who always plays singles and asking him to play doubles; it requires some adjustment and getting used to communicating with your teammate. Solo practitioners are accustomed to having their way. But you'll find that there are advantages to being part of a group that offset the loss of total control. When our daughter was born, she got used to having everything her way. Then when her baby brother arrived in the world, all of a sudden she had to share things and compromise. But over time she realized that by working with her brother as a team they had more power to convince Mom and Dad to order pizza or take them to the park. That's the power of a group."

"Often," notes John Pinto, president of J. Pinto & Associates, an ophthalmic practice management consulting firm, "when doctors join large groups, whether it's an august group like the Cleveland Clinic or Mayo Clinic or a large academic department, they're not trying to optimize control or maximize their personal incomes, they're just people who are very affable, who enjoy being part of a group. They like being able to kibitz with a colleague in a different specialty down the hall. Of course, most ophthalmologists don't fit that description; they're not social animals so much as eagles and lone wolves, which is why they sometimes find it challenging even to be part of a group of ophthalmologists."

Dr. Korn notes that some studies have suggested that physicians who do well in medical groups are those who played team sports when they were in high school or college.[1] "I didn't play team sports," he says. "I was a solo tennis player. So even though I'd never been a solo practitioner, when I went into my group I had to make some changes in the way I did things. But now that I've been here for 15 years, I'm very glad I did it. I'm now a part of a great team."

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going to make over the longer term compared to their baseline before the transaction, and what kind of control and voice in governance they're going to have. In that situation it's just a matter of vetting each deal, one at a time."

Here are some considerations that accompany the different options doctors may be considering:

• ***Joining an existing multidoctor practice.*** Dr. Noecker points out that the scope of the group you join can make a difference in how happy you are in the new situation. "If you become part of a multispecialty group, interests start to diverge very rapidly," he says. "That can be true even within ophthalmology, because each subspecialty has its own concerns. I think that's why you tend to see, for example, retina-specific groups. Retina specialists have a lot of retina-related issues that have to be watched very closely, such as managing their medications inventory; that's really important in terms of earning revenue and not losing money. An anterior segment surgeon might not be as tuned in to that. Glaucoma specialists have different concerns about what needs to be billed, patient throughput, patient experience, what diagnostic tests are done, and so forth, than LASIK surgeons. The more subspecialties that are subsumed within a group, the more likely it is that you'll encounter inertia and find it harder to move the needle.

"At the same time, of course, a larger organization has more purchasing power; you can get better deals when it comes to equipment and more favorable rates with payers," he notes. "You can also afford to have a full-time administrator and billing specialist, because you can spread out the cost of that administrator over a number of doctors. So deciding what type of organization to join is always a balancing act."

• ***Consolidating with other small practices.*** Mr. Pinto notes that one potential pitfall when combining two or more practices is failing to consider the issue of leadership. "There's a tendency to have two practices that are not particularly well-led decide to come together for some kind of strength-in-numbers benefit," he says. "They don't gain any strength from coming together because they still don't have the leadership or business skills to run a practice, and now the practice is larger, with even greater need for coherent leadership. I often advise a couple of doctors thinking about a merger to consider whether they really will be more successful together than separate. Sometimes it's just not the case."

Mr. Pinto also points out that the size of a practice impacts the individual profitability of the practice. "The most efficient practices—in terms of net profit delivered to the doctor/owner per hour of time worked—are three-to-seven-doctor practices," he notes. "Optimal profits seldom occur in the largest practices, or in the small one-

or-two-doctor practices. There's a kind of 'sweet spot' there, with the possible exception of situations in which there are difficulties with access to contracts or difficulties responding to regulatory reform.

"Small practices don't do as well financially, because a few doctors have to carry large, fixed costs, whether that's computer systems or sophisticated administrative oversight or regulatory response," he continues. "On the other hand, once a practice has eight to 12 doctors, there are some pretty well-recognized issues that occur. The enterprise becomes more complex; there are more people in the boardroom, more locations, slower decisions, and more conflict and controversy, generally speaking. An eight-doctor practice is four times more complex to run than a four-doctor practice, so a larger group puts a real burden on doctor leadership and lay administrative leadership, both of which are increasingly difficult to find in today's world. I get many calls from practices that have doubled in size saying that things were going great when they had three, four or five doctors. The boardroom was intimate, they made decisions fluidly and everybody had their eye on the ball. Then they doubled or tripled in size, and now nobody knows what's going on. They don't have enough business leadership to be able to run an organization at this scale, and they're kind of folding in on themselves."

Mr. Pinto notes that this reality isn't combining well with current trends. "If someone wanted to make ambulatory health care as efficient and effective as possible, they'd be putting together regulations that encouraged practices to have three to five doctors, because those are economically the most efficient, in my experience," he says. "What's happening, however, is that payment reform and all the regulations and all the demands for IT are pushing practices into much larger groups with all the aforementioned problems, and into hostile settings where the cost of delivering care is higher. And of course, the individual provider has less control in this setting."

"When doctors first join a large group, they tend to notice the things that seem negative, such as no longer having total control over the practice, and probably less income. But if you've chosen your group wisely, the benefits soon become apparent."
—Tommy Korn, MD

• ***Assembling a new group.*** Dr. Rosenthal notes one advantage of starting a group from scratch: the ability to set it up following any model you choose. "A group practice may be in a good position to own its own surgical center or other type of health-care facility," he says. "You can engage both ophthalmologists and optometrists, so that optometry referrals of surgical cases flow to the ophthalmologists in the group.

"Some groups offer potential members different options," he continues. "For example, they can become an affiliate practice, in which the larger group manages their practice, taking care of billing, appointment scheduling, even providing technicians. The doctor shows up for work; the organization bills the patients for him—in his name, not the group's—and provides support services. The group takes a percentage of the practice's income for providing the services; the doctor, meanwhile, pays his own rent and does his own marketing. The doctor can leave the core group any time he wants to.

"In the end, when the doctor is ready to retire, his practice would become part of the larger group, by default," he adds. "This arrangement could work for someone who still likes practicing by himself but is tired of hiring people and managing the paperwork."

• ***The private equity model.*** "Private equity firms are looking to cobble together practices to wring out some efficiencies of scale, run them well for a while and improve their prospects, and then flip them back into the public markets," explains Mr. Pinto. "The private equity model is relatively new. It's been going on for a few years now, quietly, under cover of night. Nevertheless, there are easily 20 or 30 of these companies that are in that space or about to be in that space. I get a call every two or three weeks from one of the new, emerging companies trying to find out what's happening in eye care, so it's a pretty hot area right now. However, I believe it will become increasingly difficult for private equity companies to get much of a foothold in the current environment. Ophthalmology is a lot more difficult to centralize because ophthalmologists are rare, and it's difficult and expensive to create new ones."

Mr. Pinto points out that very little of the consolidation activity in ophthalmology consists of hostile takeovers. "That was true in the 1990s as well," he says. "Ophthalmologists are seen as a very small part of the premium dollar; maybe three percent of the total. It's just not enough for hostiles to be all that interested."

Joining a Large Organization

Some ophthalmologists have chosen to become part of much larger health-care entities, although others find this option worrisome. "In those situations, you basically become an employee," notes Dr. Rosenthal. "Very few doctors in those circumstances maintain any sense of either ownership or control, including hiring and firing. If you join a hospital, for example, there's no guarantee that they won't come to you five years down the line and say, 'You're too old, you're too inefficient, your outcomes are too poor,' or 'We just don't want you.' I've actually seen that happen, more than once. In a group of doctors you can maintain partial ownership. There, you're more likely to get a guarantee that you can stay as long as you want."

Nevertheless, many ophthalmologists who have joined large organizations are quite happy with their choice. Tommy Korn, MD, FACS, chose to join Sharp Rees-Stealy Medical Group in San Diego after finishing his fellowship rather than enter private practice. "At the time, others thought it was not a good move," he says. "But looking back 15 years later, it was the best decision I ever made. I'm a firm believer in the team concept. You accomplish more as a team. When doctors first join a large group, they tend to notice the things that seem negative, such as no longer having total control over the practice, and probably less income. But if you've chosen your group wisely, the benefits soon become apparent." Dr. Korn notes several of those benefits:

- ***Getting regular feedback from peers and coworkers.*** "Getting feedback bothers some doctors at first, but in my experience, that feedback helps doctors to innovate and adapt the practice to challenging environments," he says. "Without it, you're more likely to stagnate and fall behind. Getting good feedback makes a big difference."
- ***Being better prepared to deal with regulatory challenges.*** "We have great providers and great support staff, so we've been able to face whatever regulatory challenges come up," he says. "When changes like health-care reform happen, we've often already implemented many of the 'best practices' they require. And, we have lots of support. If I have a billing problem, we have an entire department to take care of that. If there's a problem getting authorization for a medication, I don't have to worry about it. We have a department that handles that."
- ***Less likelihood of burnout.*** "I have people to help me out when I have a problem," he says. "Burnout is a big problem among physicians, and doctors in solo practice may not have someone to talk to. They may not have the sense that other people are facing the same problems. In a group practice you always have camaraderie and a dialogue among the doctors. You know you have support."

Benefits for the Practice Buyer

Robert J. Noecker, MD, MBA, in private practice at Ophthalmic Consultants of Connecticut in Fairfield, Conn., says there are multiple benefits for a practice that buys out a retiring doctor's practice. "Towards the end of their careers, many surgeons slow down a bit," he says. "Often, everyone in a family has been seeing the doctor for years. That's a lot of time to accumulate pathology, and with the doctor slowing down, some of that backlogs. So when we acquire a practice, we usually get a bump in the number of surgical patients needing treatment. Sometimes we also gain access to a pool of patients in an area in which we didn't work before."

Dr. Noecker says his group has acquired three or four practices in recent years. "In some respects, it's a safe way to grow your practice, because you're taking on an established patient base," he says. "The key is making a smooth transition and making sure the patients are comfortable. When doctors retire, patients can feel abandoned, especially if they've seen the doctor for 30 years. So I think the best model is the one where the retiring doctor continues to work for a few more years, perhaps cutting back on surgery. That also gives him a nice transition out of practice. He becomes an employee, which eliminates the headaches of the administrative issues. Also, from our perspective, older practices usually have a better Medicare and commercial payer mix, and in our experience, that's a good thing."

Another powerful motivation to consolidate practices has to do with negotiating power. "The lesson is, become bigger or die," says Dr. Noecker. "The bigger you are, the harder it is to be cut out. We've seen this in our market and a number of others. A few years ago United Health Care cut out a lot of the smaller players; they wanted to reduce the number of doctors they were contracted with. But the bigger you are, and the more patients you have, the harder it is for them to cut you out of the loop. If you're big and they cut you out, they're adversely affecting a much larger number of patients. You want to be a big enough player to have a lot of negotiating power."

Dr. Noecker also notes that a larger practice that covers more geographic area is a plus for potential new patients. "The more geography you cover, the easier it is for patients to choose you when they're looking over a list of doctors," he says. "People like it when you're in the next town over, as opposed to being 30 miles away. That's a big deal."

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• ***Many minds working on the big problems.*** "In a large organization you have a collective, 'hive mind' that's able to address multiple problems and bring the best ideas or solutions to the top, because they been vetted by many people coming from many directions," says Dr. Korn.

• ***Having more time for yourself, your patients and your family.*** Dr. Korn says this is the single most important benefit that comes with being in a large group. "It's not uncommon to make more money as a solo practitioner, and some doctors focus entirely on that when considering joining a group," he says. "But I don't believe you should make life choices based on numbers alone. You should look at the entire situation. Being in a group practice allows me to spend more time with patients. It allows me to have more time to do productive things like research projects. I can take vacations without worrying about someone covering for me, or worrying about the practice losing income while I'm away. Most important, it allows me to have more time with my family. You can have all the money in the world, but if you have no time, you won't end up happy. To me, it's a no-brainer. I'd rather be with a good team than by myself."

Dr. Korn acknowledges that if you're planning to join a group, it's important that the group recognizes the value of every member. "When you're part of a group that's in sync and not afraid to have disagreements, things can really take off," he says. "People assume that joining a group means you have to conform to some set of ideas. In our group, different opinions are always welcome. Even with more than 500 doctors in our medical group, I always feel that my voice is heard.

"Of course, being part of a group means that sometimes the majority won't agree with you, and you have to be brave enough to accept being voted down," he admits. "But in a good group, your voice will be heard, and you may be able to sway the group to agree with you if your argument is sound. Mainly, you want to know that your opinion has been heard and treated with respect."

Will Solo Practices Disappear?

Given the mounting pressures faced by solo practitioners, many believe this way of practicing may become a thing of the past.

"I think the solo practitioner will go the way of the dinosaurs," says Dr. Noecker. "Consolidation is a societal trend—you see it everywhere. Furthermore, the government wants it to happen because it's inefficient for the government to contract with so many individual doctors. They'd rather just negotiate with one group in a region, give them the money and let them disperse it downstream.

"In general, it's much harder to be a solo ophthalmologist," he continues.

"Startup costs are a problem because ophthalmologists use a lot of special equipment. Being on call is another issue. If you're part of a group, you can spread out the on-call requirements among a number of doctors. A solo doctor may be game to deal with that at the outset, but over time it wears thin. Meanwhile, the billing side of practice today is so complex, and the pitfalls are so large, that you need to have extra staff just dedicated to dealing with all the HIPAA paperwork. Many of these rules and requirements didn't exist five years ago, and every year more of them come out. In some ways, taking care of the patient is the easiest thing we do.

"So I think solo practices are going away," he concludes. "I don't see any new ones are being created, and it's just a matter of time before the existing ones retire or consolidate. In my market, I know of one oculoplastics person who recently started a solo practice after leaving a larger group, but that's it. I haven't seen any other new ones."

Dr. Rosenthal believes the future of solo practice will depend on the environment. "For example, there are still a lot of doctors in New York City that don't accept insurance," he points out. "If your clientele is able to pay you cash for an office visit, you can keep on doing your thing. But younger doctors are just not doing that. And in rural areas with few doctors and few patients there will still be small practices. But even there, the small practices may become a branch or satellite office of a larger corporate entity. Even if solo and small practices continue to exist, I don't think they'll make as much money or have as much security as the larger practices, so I think it will become increasingly rare for people to go out on their own.

"When I started in practice I really never thought about anything except starting my own practice," he adds. "It was what doctors did. Back then, the largest practice in this area had three doctors in it."

Mr. Pinto believes the solo practice still has a future, despite all the pressure to consolidate. "It's true that it will be increasingly challenging to be a soloist, just because the regulatory obligations are rising and it's harder for a soloist to play strength-to-strength with all of that," he says. "But in secondary and tertiary markets, small markets in which there are more people than doctors, I think the solo practice will be preserved as an enterprise model. In fact, I think markets all over the country will continue to see private, independent, small group practices do just fine. Today there are roughly 7,000 ophthalmology practices, and the vast majority of them consist of one, two or three doctors. A generation from now we might see that number shrink to 5,000 discrete, individual entities, and the average entity may be somewhat larger—perhaps five, six or seven doctors. But health-care reform in the past failed to sweep our worlds away, so I doubt that the current trends

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are going to change the profession as much as many fear. I think there will still be a place at the table for the private, independent, smaller practice, even 25 years from now."

Making Your Way Forward

So, if you're still in a solo or very small practice, should you be thinking about growing? And if so, which way forward makes the most sense?

Dr. Rosenthal clearly has some mixed feelings about moving from solo to group practice—feelings that are probably shared by many ophthalmologists. "I like being my own boss," he says. "I really would prefer not to do any consolidating. But *en balance*, a properly structured group practice can still hold the promise of retaining much independence and has many advantages."

"This is a tough decision that involves careful consideration," says Dr. Korn. "Of course, you have to talk to family, friends and advisers, but in the end, I think an ophthalmologist has to trust intuition. When I made my decision to join a large medical group, I asked myself what would make me happy. What was my purpose in life? To generate maximum income? Help other people? Feel good about myself? In the end, I went with my gut. I wanted to be in a position to focus on being the best physician I could be, without the financial pressures of running a medical practice. Looking back now, joining a large multispecialty medical group was one of the best decisions I ever made."

And what of ophthalmology as a whole? "Where this trend toward consolidation will lead remains to be seen," notes Mr. Pinto. "Back in the 1990s, ophthalmologists thought that within 25 years we'd all be working for one of three American eye-care companies. That obviously didn't come to pass; we still have more than 7,000 private practices and thousands of different health-care systems. Likewise, I don't think the current wave of consolidation is going to follow a linear course to the endpoint of one megalithic health care delivery system in this country. But consolidation is an appropriate trend for many doctors and practices to be following right now. It isn't a good or bad thing; it just rises and falls with the mood of the industry. Whether it makes sense for a given doctor or practice depends on the individuals and situation in question."

As to the demise of solo practice, Mr. Pinto says he doesn't see that happening any time soon. "The field of ophthalmology is like a battleship," he observes. "It turns slowly. I don't think we're going to see 'lights out' for a long, long time." REVIEW

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The Latest Medicare Payment Initiatives

Michelle Stephenson, Contributing Editor

Earlier this year, CMS took its first step to implement legislation modernizing how Medicare pays physicians for quality.

In April of this year, the U.S. Department of Health and Human Services issued a proposal to tie Medicare payments to the cost and quality of patient care for hundreds of thousands of doctors and other clinicians. This is the first step in implementing the Medicare Access and CHIP Reauthorization Act of 2015 (MACRA), which makes three important changes to the way Medicare pays physicians who provide care to Medicare beneficiaries. These changes create a Quality Payment Program that will: end the Sustainable Growth Rate formula for determining Medicare payments for physicians' services; create a new framework for rewarding health-care providers for giving better care rather than just more care; and combine the existing quality reporting programs into one new system.[1]

The goal of the MACRA QPP is to pay for value and better care via two pathways: the Merit-based Incentive Payment System and Alternative Payment Models. The MIPS program combines parts of the Physician Quality Reporting System, the Value Modifier, and the Electronic Health Record incentive programs into one program. MIPS and APMs will go into effect over the next few years, impacting physician payments in 2019.

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MIPS

According to a U.S. Department of Health and Human Services press release, most Medicare physicians will initially participate in the QPP through MIPS.[2] Consistent with the goals of the new law, the proposed rule would improve the relevancy and depth of Medicare's quality-based payments and increase physician flexibility by allowing doctors to choose measures and activities appropriate to the type of care they provide. MIPS allows Medicare physicians to be paid for providing high-value care

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through success in four performance categories: Quality; Advancing Care Information; Clinical Practice Improvement Activities; and Cost.

• ***Quality will make up 50 percent of a physician's total score in year one.*** Ophthalmologists would choose to report six measures from among a range of options that accommodate differences among specialties and practices.

• ***Advancing Care Information will contribute 25 percent of a physician's total score in the first year.*** Ophthalmologists would choose to report customizable measures that reflect how they use technology in their day-to-day practice, with a particular emphasis on interoperability and information exchange. Unlike the existing reporting program, this category wouldn't require all-or-nothing EHR measurement or redundant quality reporting.

• ***Clinical Practice Improvement Activities would be 15 percent of the total score in year one.*** This category would reward clinical practice improvements, such as activities focused on care coordination, beneficiary engagement and patient safety. Ophthalmologists would be able to select activities that match their practices' goals from a list of more than 90 options.

• ***Cost would account for 10 percent of a physician's total score in year one.*** This score would be based on Medicare claims, which means no reporting requirements for health-care providers. This category would use 40 episode-specific measures to account for differences among specialties.

The purpose of the proposal is to streamline and reduce reporting burden across all four categories, while adding flexibility for practices. CMS would begin measuring performance for physicians and other health-care providers through MIPS in 2017, with payments based on those measures beginning in 2019.

"The first phase of implementation is in 2017, which is when CMS is going to begin to accumulate data on performance so that they can give us a report card," says Michael Repka, MD, the American Academy of Ophthalmology's Medical Director for Government Affairs. "On the basis of that report card, they will adjust our fees up or down in 2019. The reality is that it is extraordinarily complex to do all of the grading steps in the MIPS program, and that's the program that most ophthalmologists will end up in. MACRA will ultimately replace pay-for-performance, but it includes things that are really reminiscent of pay-for-performance. If you provide quality care, you're going to get a boost in payment. There were two main reasons for ophthalmology to support MACRA. One was getting rid of the Sustainable Growth Rate formula, and the second was to delay elimination of surgical global periods and study the postoperative period to determine how to pay correctly for postoperative visits. The assertion from people in nonsurgical fields has been that postoperative care is not as intense nor are there as many visits as the current payments reflect."

He notes that physician scoring will begin in a few months. "That's what people are not really up to speed on," he says. "Ophthalmologists like to be good students, so I think there is going to be frustration with the scoring. Fees can be adjusted ±4 percent in the first year, and that escalates to ±9 percent in the fifth year. It's designed so that you will have some losers and some winners. There will be some very big winners, and I'm concerned about that."

According to Donna McCune, CCS-P, COE, CPMA, vice-president of the Corcoran Consulting Group, MACRA was initially good for physicians because it eliminated the Sustainable Growth Rate formula calculation. "This was always flawed and created year-after-year anxiety and angst over what physicians were going to be paid," she says. "The law itself contains fee-schedule updates, so we know that that is part of the MACRA regulation. The biggest issue is the initiation of MIPS, which is supposed to be implemented as of January 1, 2017. The various components of MIPS and the success or failure of a particular physician or practice will affect their reimbursement rates two years from then, in 2019. All of these programs that are part of MIPS and all of the quality programs that we have been participating in for the past several years always have a two-year look-back. Anything you do in a particular year affects your reimbursement two years later. That has been an issue for some physicians because they don't realize that what they do this year is going to affect their reimbursement in 2018, or what they did last year will affect their reimbursement in 2017."

She notes that there is concern about the time frame. There will not be a final ruling on this latest proposal until mid-November, and the implementation date is January 1. "It will be very difficult for practices to be able to pull off a January 1 implementation date with probably only six weeks of notice," she notes. "Implementation will most likely involve updating and reprogramming EHRs. I personally have concerns about EHR companies being able to update their software programs fast enough to accommodate a January 1 implementation date."

Additionally, when MACRA eliminated the Sustainable Growth Rate formula approach, it provided for an annual update of 0.5 percent through 2019. "Physicians are realizing that the reimbursement rates are going to pretty much be flat from the Medicare perspective for the next several years, and then go to a 0-percent

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1 Chapter 4. Section: The Glaucoma Suspect. 2015-2016 edition of the *AAO Basic and Clinical Science Course on Glaucoma.*
2 Banitt et al. Progressive Loss of Retinal Ganglion Cell Function Precedes Structural Loss by Several Years in Glaucoma Suspects. *Invest Ophthalmol Vis Sci.* 2013 Mar 28;54(3):2346-52.
3 Ventura et al. Progressive loss of retinal ganglion cell function is hindered with IOP-lowering treatment in early glaucoma. *Invest Ophthalmol Vis Sci.* 2012 Feb 13;53(2):659-63.
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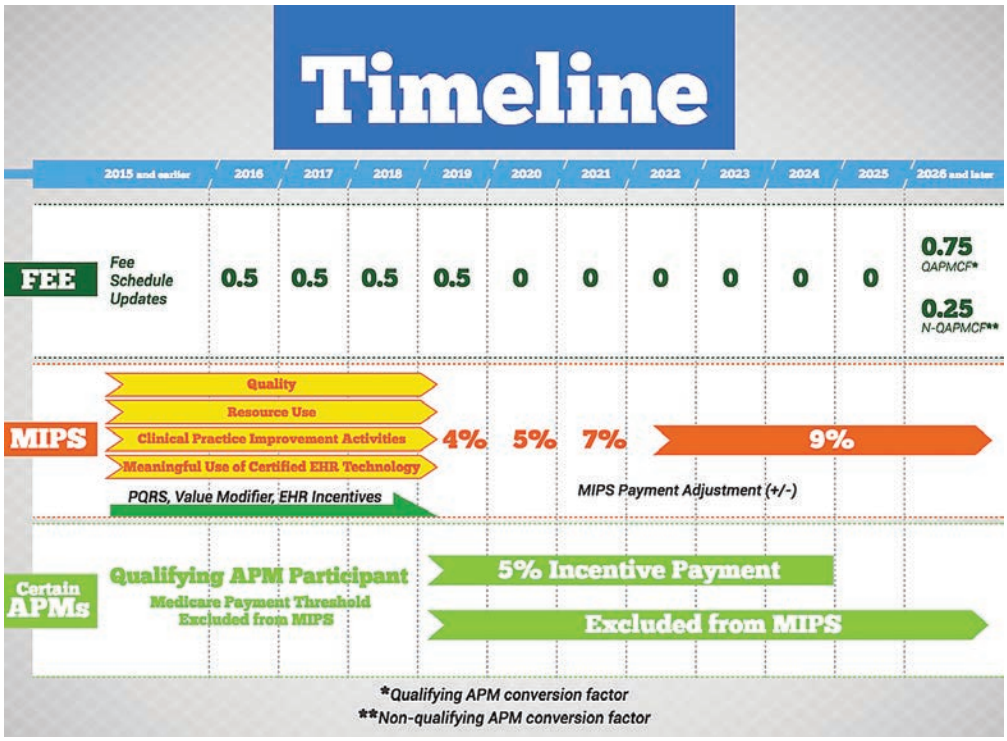
update in 2020 through 2025," Ms. McCune avers. "The only way for physicians to increase their Medicare reimbursement is by being successful with this new MIPS program and potentially qualifying for some bonus money. This could be a problem because the costs of running a practice continue to increase year after year. Another concern is that commercial payers tend to follow Medicare's lead, with regard to increasing reimbursement rates."



The Quality Payment Program from the Department of Health and Human Services has two paths physicians can follow: The Merit-based Incentive Payment System, in which reimbursement will be based on the four areas in the gold arrows; and the more intensive Advanced Alternative Payment Models, in which physicians belong to entities such as Accountable Care Organizations. The diagram shows the timeline for changes to the fee schedule based on the path taken by the physician. *Source: HHS.*

In the past, physicians were paid based on what they did. They saw a patient, submitted a claim, and were paid. "The purpose of these programs is to eliminate the traditional fee-for-service and have a component of a visit or a service provided be fee-for-service, and then link the rest of the payment to quality. So, the existing model that we have had forever is gone," Ms. McCune adds.

APMs

Increasing numbers of Medicare clinicians are participating in alternative payment models, and MACRA has created additional rewards for physicians who choose this path. According to the U.S. Department of Health and Human Services,[2] Medicare clinicians who participate to a sufficient extent in Advanced Alternative Payment Models would be exempt from MIPS reporting requirements and would qualify for financial bonuses. These models include the new Comprehensive Primary Care Plus model, the Next Generation ACO model and other Alternative Payment Models under which clinicians accept both risk and reward for providing coordinated, high-quality care.

However, many physicians who participate to some extent in Alternative Payment Models may not meet the law's requirements for sufficient participation in the most advanced models. The proposed rule is designed to give these health-care providers some benefits within MIPS, as well as to make it easy for physicians to switch between the components of the QPP based on what works best for them and their patients.

The U.S. Department of Health and Human Services expects the number of clinicians who qualify to participate in Advanced Alternative Payment Models to grow as the program matures.

Global Services Data Collection

Another concern is that Section 523 of MACRA requires CMS to develop and implement a process to gather and analyze the necessary data on preoperative and postoperative visits and other services furnished during global surgical periods other than the surgical procedure itself. CMS recently released a draft proposal to collect data on global surgery codes, which represent about half of all physician-provided services under Medicare. The concern is that, if adopted, the proposal could direct more provider resources toward reporting compliance and away from patient care. CMS is proposing to collect data for all 10- and 90-day global services from every physician who

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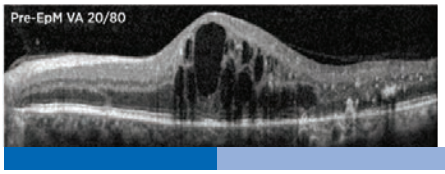

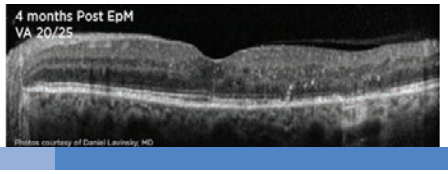

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KEYNOTE SPEAKERS

Francisco J Rodríguez, MD
Scientific Director Fundación Oftalmológica Nacional
Chair Department of Ophthalmology Universidad del Rosario School of Medicine, Bogotá, DC

Victor Hugo Gonzalez, MD
Founder Valley Retina Institute, P.A.
McAllen, Texas USA

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provides these services, rather than from a sample of physicians, as Congress intended under MACRA. Specifically, physicians would be required to report information on every 10-minute increment of care provided before and after each procedure in the hospital, office, or via e-mail or phone, and whether the services were provided by them or their staff.

"If the proposal goes through as planned, it means that, for every postoperative visit, the physician will be scoring the level of complexity of the visit plus the level of complexity for the tech involvement, plus the number of minutes in 10-minute increments. I don't know if doctors will spend the time to do it correctly or if they will forget to do it," Dr. Repka says.

The AAO is opposed to this initiative because it's too broad and inconsistent with what Congress intended when it forced CMS to restore global payments for surgical services last year and study the issue.

According to AAO Health Policy Committee Associate Secretary David B. Glasser, MD, this data collection requirement will affect daily patient care. "Surgeons would be required to keep track of their postop care time in 10-minute increments and report multiples of each postoperative visit code based on time. Literally, this would take a stopwatch. There are approximately 4,200 codes with 10- and 90-day global payments. This would have to be done for every one of these codes, regardless of whether they are frequent or major-dollar codes. The complexity of learning to use the new codes and the data collection burden would guarantee an underestimation of the number of postoperative visits and the time spent delivering postoperative care." REVIEW

1. www.cms.gov
2. http://www.hhs.gov/about/news/2016/04/27/administration-takes-first-step-implement-legislation-modernizing-how-medicare-pays-physicians.html

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***Intermediate, posterior, and panuveitis.**

Indication[1]

Uveitis: HUMIRA is indicated for the treatment of non-infectious intermediate, posterior, and panuveitis in adult patients.

IMPORTANT SAFETY INFORMATION FOR HUMIRA® (adalimumab)[1]

SERIOUS INFECTIONS

Patients treated with HUMIRA are at increased risk for developing serious infections that may lead to hospitalization or death. Most patients who developed these infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids.

Discontinue HUMIRA if a patient develops a serious infection or sepsis.

Reported infections include:

- **Active tuberculosis (TB), including reactivation of latent TB. Patients with TB have frequently presented with disseminated or extrapulmonary disease. Test patients for latent TB before HUMIRA use and during therapy. Initiate treatment for latent TB prior to HUMIRA use.**
- **Invasive fungal infections, including histoplasmosis, coccidioidomycosis, candidiasis, aspergillosis, blastomycosis, and pneumocystosis. Patients with histoplasmosis or other invasive fungal infections may present with disseminated, rather than localized, disease. Antigen and antibody testing for histoplasmosis may be negative in some patients with active infection. Consider empiric anti-fungal therapy in patients at risk for invasive fungal infections who develop severe systemic illness.**
- **Bacterial, viral, and other infections due to opportunistic pathogens, including Legionella and Listeria.**

Carefully consider the risks and benefits of treatment with HUMIRA prior to initiating therapy in patients: 1. with chronic or recurrent infection, 2. who have been exposed to TB, 3. with a history of opportunistic infection, 4. who resided in or traveled in regions where mycoses are endemic, 5. with underlying conditions that may predispose them to infection. Monitor patients closely for the development of signs and symptoms of infection during and after treatment with HUMIRA, including the possible development of TB in patients who tested negative for latent TB infection prior to initiating therapy.

- Do not start HUMIRA during an active infection, including localized infections.
- Patients older than 65 years, patients with co-morbid conditions, and/or patients taking concomitant immunosuppressants may be at greater risk of infection.
- If an infection develops, monitor carefully and initiate appropriate therapy.
- Drug interactions with biologic products: A higher rate of serious infections has been observed in rheumatoid arthritis patients treated with rituximab who received subsequent treatment with a TNF blocker. Concurrent use of HUMIRA with biologic DMARDs (e.g., anakinra or abatacept) or other TNF blockers is not recommended based on the possible increased risk for infections and other potential pharmacological interactions.

MALIGNANCY

Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with TNF blockers, including HUMIRA. Postmarketing cases of hepatosplenic T-cell lymphoma (HSTCL), a rare type of T-cell lymphoma, have been reported in patients treated with TNF blockers, including HUMIRA. These cases have had a very aggressive disease course and have been fatal. The majority of reported TNF blocker cases have occurred in patients with Crohn's disease or ulcerative colitis and the majority were in adolescent and young adult males. Almost all of these patients had received treatment with azathioprine or 6-mercaptopurine concomitantly with a TNF blocker at or prior to diagnosis. It is uncertain whether the occurrence of HSTCL is related to use of a TNF blocker or a TNF blocker in combination with these other immunosuppressants.

- Consider the risks and benefits of HUMIRA treatment prior to initiating or continuing therapy in a patient with known malignancy.
- In clinical trials, more cases of malignancies were observed among HUMIRA-treated patients compared to control patients.
- Non-melanoma skin cancer (NMSC) was reported during clinical trials for HUMIRA-treated patients. Examine all patients, particularly those with a history of prolonged immunosuppressant or PUVA therapy, for the presence of NMSC prior to and during treatment with HUMIRA.
- In HUMIRA clinical trials, there was an approximate 3-fold higher rate of lymphoma than expected in the general U.S. population. Patients with chronic inflammatory diseases, particularly those with highly active disease and/or chronic exposure to immunosuppressant therapies, may be at higher risk of lymphoma than the general population, even in the absence of TNF blockers.

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†Disease flare is defined by an increase in 1 or more inflammatory markers: AC cells, vitreous haze, and/or development of new chorioretinal, and/or retinal vascular lesions.

- Postmarketing cases of acute and chronic leukemia were reported with TNF blocker use. Approximately half of the postmarketing cases of malignancies in children, adolescents, and young adults receiving TNF blockers were lymphomas; other cases included rare malignancies associated with immunosuppression and malignancies not usually observed in children and adolescents.

HYPERSENSITIVITY

- Anaphylaxis and angioneurotic edema have been reported following HUMIRA administration. If a serious allergic reaction occurs, stop HUMIRA and institute appropriate therapy.

HEPATITIS B VIRUS REACTIVATION

- Use of TNF blockers, including HUMIRA, may increase the risk of reactivation of hepatitis B virus (HBV) in patients who are chronic carriers. Some cases have been fatal.
- Evaluate patients at risk for HBV infection for prior evidence of HBV infection before initiating TNF blocker therapy.
- Exercise caution in patients who are carriers of HBV and monitor them during and after HUMIRA treatment.
- Discontinue HUMIRA and begin antiviral therapy in patients who develop HBV reactivation. Exercise caution when resuming HUMIRA after HBV treatment.

NEUROLOGIC REACTIONS

- TNF blockers, including HUMIRA, have been associated with rare cases of new onset or exacerbation of central nervous system and peripheral demyelinating diseases, including multiple sclerosis, optic neuritis, and Guillain-Barré syndrome.
- Exercise caution when considering HUMIRA for patients with these disorders; discontinuation of HUMIRA should be considered if any of these disorders develop.
- There is a known association between intermediate uveitis and central demyelinating disorders.

HEMATOLOGIC REACTIONS

- Rare reports of pancytopenia, including aplastic anemia, have been reported with TNF blockers. Medically significant cytopenia has been infrequently reported with HUMIRA.
- Consider stopping HUMIRA if significant hematologic abnormalities occur.

CONGESTIVE HEART FAILURE

- Worsening or new onset congestive heart failure (CHF) may occur; exercise caution and monitor carefully.

AUTOIMMUNITY

- Treatment with HUMIRA may result in the formation of autoantibodies and, rarely, in development of a lupus-like syndrome. Discontinue treatment if symptoms of a lupus-like syndrome develop.

IMMUNIZATIONS

- Patients on HUMIRA should not receive live vaccines.
- Pediatric patients, if possible, should be brought up to date with all immunizations before initiating HUMIRA therapy.
- The safety of administering live or live-attenuated vaccines in infants exposed to HUMIRA *in utero* is unknown. Risks and benefits should be considered prior to vaccinating (live or live-attenuated) exposed infants.

ADVERSE REACTIONS

- The most common adverse reactions in HUMIRA clinical trials (>10%) were: infections (e.g., upper respiratory, sinusitis), injection site reactions, headache, and rash.

Reference: 1. HUMIRA Injection [package insert]. North Chicago, IL: AbbVie Inc.

Please see Brief Summary of full Prescribing Information on the following page.

 North Chicago, IL 60064 64C-1859319 June 2016 Printed in U.S.A.

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HUMIRA® (adalimumab)

PROFESSIONAL BRIEF SUMMARY
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WARNING: SERIOUS INFECTIONS AND MALIGNANCY

SERIOUS INFECTIONS

Patients treated with HUMIRA are at increased risk for developing serious infections that may lead to hospitalization or death *[see Warnings and Precautions]*. Most patients who developed these infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids.

Discontinue HUMIRA if a patient develops a serious infection or sepsis.

Reported infections include:

- **Active tuberculosis (TB), including reactivation of latent TB. Patients with TB have frequently presented with disseminated or extrapulmonary disease. Test patients for latent TB before HUMIRA use and during therapy. Initiate treatment for latent TB prior to HUMIRA use.**
- **Invasive fungal infections, including histoplasmosis, coccidioidomycosis, candidiasis, aspergillosis, blastomycosis, and pneumocystosis. Patients with histoplasmosis or other invasive fungal infections may present with disseminated, rather than localized, disease. Antigen and antibody testing for histoplasmosis may be negative in some patients with active infection. Consider empiric anti-fungal therapy in patients at risk for invasive fungal infections who develop severe systemic illness.**
- **Bacterial, viral and other infections due to opportunistic pathogens, including Legionella and Listeria.**

Carefully consider the risks and benefits of treatment with HUMIRA prior to initiating therapy in patients with chronic or recurrent infection.

Monitor patients closely for the development of signs and symptoms of infection during and after treatment with HUMIRA, including the possible development of TB in patients who tested negative for latent TB infection prior to initiating therapy *[see Warnings and Precautions and Adverse Reactions]*.

MALIGNANCY

Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with TNF blockers including HUMIRA *[see Warnings and Precautions]*. Post-marketing cases of hepatosplenic T-cell lymphoma (HSTCL), a rare type of T-cell lymphoma, have been reported in patients treated with TNF blockers including HUMIRA. These cases have had a very aggressive disease course and have been fatal. The majority of reported TNF blocker cases have occurred in patients with Crohn's disease or ulcerative colitis and the majority were in adolescent and young adult males. Almost all these patients had received treatment with azathioprine or 6-mercaptopurine (6–MP) concomitantly with a TNF blocker at or prior to diagnosis. It is uncertain whether the occurrence of HSTCL is related to use of a TNF blocker or a TNF blocker in combination with these other immunosuppressants *[see Warnings and Precautions]*.

INDICATIONS AND USAGE

Rheumatoid Arthritis

HUMIRA is indicated for reducing signs and symptoms, inducing major clinical response, inhibiting the progression of structural damage, and improving physical function in adult patients with moderately to severely active rheumatoid arthritis. HUMIRA can be used alone or in combination with methotrexate or other non-biologic disease-modifying anti-rheumatic drugs (DMARDs).

Juvenile Idiopathic Arthritis

HUMIRA is indicated for reducing signs and symptoms of moderately to severely active polyarticular juvenile idiopathic arthritis in patients 2 years of age and older. HUMIRA can be used alone or in combination with methotrexate.

Psoriatic Arthritis

HUMIRA is indicated for reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in adult patients with active psoriatic arthritis. HUMIRA can be used alone or in combination with non-biologic DMARDs.

Ankylosing Spondylitis

HUMIRA is indicated for reducing signs and symptoms in adult patients with active ankylosing spondylitis.

Adult Crohn's Disease

HUMIRA is indicated for reducing signs and symptoms and inducing and maintaining clinical remission in adult patients with moderately to severely active Crohn's disease who have had an inadequate response to conventional therapy. HUMIRA is indicated for reducing signs and symptoms and inducing clinical remission in these patients if they have also lost response to or are intolerant to infliximab.

Pediatric Crohn's Disease

HUMIRA is indicated for reducing signs and symptoms and inducing and maintaining clinical remission in pediatric patients 6 years of age and older with moderately to severely active Crohn's disease who have had an inadequate response to corticosteroids or immunomodulators such as azathioprine, 6-mercaptopurine, or methotrexate.

Ulcerative Colitis

HUMIRA is indicated for inducing and sustaining clinical remission in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to immunosuppressants such as corticosteroids, azathioprine or 6-mercaptopurine (6-MP). The effectiveness of HUMIRA has not been established in patients who have lost response to or were intolerant to TNF blockers.

Plaque Psoriasis

HUMIRA is indicated for the treatment of adult patients with moderate to severe chronic plaque psoriasis who are candidates for systemic therapy or phototherapy, and when other systemic therapies are medically less appropriate. HUMIRA should only be administered to patients who will be closely monitored and have regular follow-up visits with a physician *[see Boxed Warning and Warnings and Precautions]*.

Hidradenitis Suppurativa

HUMIRA is indicated for the treatment of moderate to severe hidradenitis suppurativa.

Uveitis

HUMIRA is indicated for the treatment of non-infectious intermediate, posterior and panuveitis in adult patients.

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Serious Infections

Patients treated with HUMIRA are at increased risk for developing serious infections involving various organ systems and sites that may lead to hospitalization or death *[see Boxed Warning]*. Opportunistic infections due to bacterial, mycobacterial, invasive fungal, viral, parasitic, or other opportunistic pathogens including aspergillosis, blastomycosis, candidiasis, coccidioidomycosis, histoplasmosis, legionellosis, listeriosis, pneumocystosis and tuberculosis have been reported with TNF blockers. Patients have frequently presented with disseminated rather than localized disease.

The concomitant use of a TNF blocker and abatacept or anakinra was associated with a higher risk of serious infections in patients with rheumatoid arthritis (RA); therefore, the concomitant use of HUMIRA and these biologic products is not recommended in the treatment of patients with RA *[see Warnings and Precautions and Drug Interactions]*.

Treatment with HUMIRA should not be initiated in patients with an active infection, including localized infections. Patients greater than 65 years of age, patients with co-morbid conditions and/or patients taking concomitant immunosuppressants (such as corticosteroids or methotrexate), may be at greater risk of infection. Consider the risks and benefits of treatment prior to initiating therapy in patients:

- with chronic or recurrent infection;
- who have been exposed to tuberculosis;
- with a history of an opportunistic infection;
- who have resided or traveled in areas of endemic tuberculosis or endemic mycoses, such as histoplasmosis, coccidioidomycosis, or blastomycosis; or
- with underlying conditions that may predispose them to infection.

Tuberculosis

Cases of reactivation of tuberculosis and new onset tuberculosis infections have been reported in patients receiving HUMIRA, including patients who have previously received treatment for latent or active tuberculosis. Reports included cases of pulmonary and extrapulmonary (i.e., disseminated) tuberculosis. Evaluate patients for tuberculosis risk factors and test for latent infection prior to initiating HUMIRA and periodically during therapy.

Treatment of latent tuberculosis infection prior to therapy with TNF blocking agents has been shown to reduce the risk of tuberculosis reactivation during therapy.

Consider anti-tuberculosis therapy prior to initiation of HUMIRA in patients with a past history of latent or active tuberculosis in whom an adequate course of treatment cannot be confirmed, and for patients with a negative test for latent tuberculosis but having risk factors for tuberculosis infection. Despite prophylactic treatment for tuberculosis, cases of reactivated tuberculosis have occurred in patients treated with HUMIRA. Consultation with a physician with expertise in the treatment of tuberculosis is recommended to aid in the decision whether initiating anti-tuberculosis therapy is appropriate for an individual patient.

Strongly consider tuberculosis in the differential diagnosis in patients who develop a new infection during HUMIRA treatment, especially in patients who have previously or recently traveled to countries with a high prevalence of tuberculosis, or who have had close contact with a person with active tuberculosis.

Monitoring

Closely monitor patients for the development of signs and symptoms of infection during and after treatment with HUMIRA, including the development of tuberculosis in patients who tested negative for latent tuberculosis infection prior to initiating therapy. Tests for latent tuberculosis infection may also be falsely negative while on therapy with HUMIRA.

Discontinue HUMIRA if a patient develops a serious infection or sepsis. For a patient who develops a new infection during treatment with HUMIRA, closely monitor them, perform a prompt and complete diagnostic workup appropriate for an immunocompromised patient, and initiate appropriate antimicrobial therapy.

Invasive Fungal Infections

If patients develop a serious systemic illness and they reside or travel in regions where mycoses are endemic, consider invasive fungal infection in the differential diagnosis. Antigen and antibody testing for histoplasmosis may be negative in some patients with active infection. Consider appropriate empiric antifungal therapy, taking into account both the risk for severe fungal infection and the risks of antifungal therapy, while a diagnostic workup is being performed. To aid in the management of such patients, consider consultation with a physician with expertise in the diagnosis and treatment of invasive fungal infections.

Malignancies

Consider the risks and benefits of TNF-blocker treatment including HUMIRA prior to initiating therapy in patients with a known malignancy other than a successfully treated non-melanoma skin cancer (NMSC) or when considering continuing a TNF blocker in patients who develop a malignancy.

Malignancies in Adults

In the controlled portions of clinical trials of some TNF-blockers, including HUMIRA, more cases of malignancies have been observed among TNF-blocker-treated adult patients compared to control-treated adult patients. During the controlled portions of 39 global HUMIRA clinical trials in adult patients with rheumatoid arthritis (RA), psoriatic arthritis (PsA), ankylosing spondylitis (AS), Crohn's disease (CD), ulcerative colitis (UC) plaque psoriasis (Ps), hidradenitis suppurativa (HS), and uveitis (UV) malignancies, other than non-melanoma (basal cell and squamous cell) skin cancer, were observed at a rate (95% confidence interval) of 0.7 (0.48, 1.03) per 100 patient-years among 7973 HUMIRA-treated patients versus a rate of 0.7 (0.41, 1.17) per 100 patient-years among 4848 control-treated patients (median duration of treatment of 4 months for HUMIRA-treated patients and 4 months for control-treated patients). In 52 global controlled and uncontrolled clinical trials of HUMIRA in adult patients with RA, PsA, AS, CD, UC, Ps, HS and UV, the most frequently observed malignancies, other than lymphoma and NMSC, were breast, colon, prostate, lung, and melanoma. The malignancies in HUMIRA-treated patients in the controlled and uncontrolled portions of the studies were similar in type and number to what would be expected in the general U.S. population according to the SEER database (adjusted for age, gender, and race).

In controlled trials of other TNF blockers in adult patients at higher risk for malignancies (i.e., patients with COPD with a significant smoking history and cyclophosphamide-treated patients with Wegener's granulomatosis), a greater portion of malignancies occurred in the TNF blocker group compared to the control group.

Non-Melanoma Skin Cancer

During the controlled portions of 39 global HUMIRA clinical trials in adult patients with RA, PsA, AS, CD, UC, Ps, HS and UV, the rate (95% confidence interval) of NMSC was 0.8 (0.52, 1.09) per 100 patient-years among HUMIRA-treated patients and 0.2 (0.10, 0.59) per 100 patient-years among control-treated patients. Examine all patients, and in particular patients with a medical history of prior prolonged immunosuppressant therapy or psoriasis patients with a history of PUVA treatment for the presence of NMSC prior to and during treatment with HUMIRA.

Lymphoma and Leukemia

In the controlled portions of clinical trials of all the TNF-blockers in adults, more cases of lymphoma have been observed among TNF-blocker-treated patients compared to control-treated patients. In the controlled portions of 39 global HUMIRA clinical trials in adult patients with RA, PsA, AS, CD, UC Ps, HS and UV, 2 lymphomas occurred among 7973 HUMIRA-treated patients versus 1 among 4848 control-treated patients. In 52 global controlled and uncontrolled clinical trials of HUMIRA in adult patients with RA, PsA, AS, CD, UC, Ps, HS and UV with a median duration of approximately 0.7 years, including 24,605 patients and over 40,215 patient-years of HUMIRA, the observed rate of lymphomas was approximately 0.11 per 100 patient-years. This is approximately 3-fold higher than expected in the general U.S. population according to the SEER database (adjusted for age, gender, and race). Rates of lymphoma in clinical trials of HUMIRA cannot be compared to rates of lymphoma in clinical trials of other TNF blockers and may not predict the rates observed in a broader patient population. Patients with RA and other chronic inflammatory diseases, particularly those with highly active disease and/or chronic exposure to immunosuppressant therapies, may be at a higher risk (up to several fold) than the general population for the development of lymphoma, even in the absence of TNF blockers. Post-marketing cases of acute and chronic leukemia have been reported in association with TNF-blocker use in RA and other indications. Even in the absence of TNF-blocker therapy, patients with RA may be at a higher risk (approximately 2-fold) than the general population for the development of leukemia.

Malignancies in Pediatric Patients and Young Adults

Malignancies, some fatal, have been reported among children, adolescents, and young adults who received treatment with TNF-blockers (initiation of therapy ≤ 18 years of age), of which HUMIRA is a member *[see Boxed Warning]*. Approximately half the cases were lymphomas, including Hodgkin's and non-Hodgkin's lymphoma. The other cases represented a variety of different malignancies and included rare malignancies usually associated with immunosuppression and malignancies that are not usually observed in children and adolescents. The malignancies occurred after a median of 30 months of therapy (range 1 to 84 months). Most of the patients were receiving concomitant immunosuppressants. These cases were reported post-marketing and are derived from a variety of sources including registries and spontaneous postmarketing reports.

Postmarketing cases of hepatosplenic T-cell lymphoma (HSTCL), a rare type of T-cell lymphoma, have been reported in patients treated with TNF blockers including HUMIRA *[see Boxed Warning]*. These cases have had a very aggressive disease course and have been fatal. The majority of reported TNF blocker cases have occurred in patients with Crohn's disease or ulcerative colitis and the majority were in adolescent and young adult males. Almost all of these patients had received treatment with the immunosuppressants azathioprine or 6-mercaptopurine (6–MP) concomitantly with a TNF blocker at or prior to diagnosis. It is uncertain whether the occurrence of HSTCL is related to use of a TNF blocker or a TNF blocker in combination with these other immunosuppressants. The potential risk with the combination of azathioprine or 6-mercaptopurine and HUMIRA should be carefully considered.

Hypersensitivity Reactions

Anaphylaxis and angioneurotic edema have been reported following HUMIRA administration. If an anaphylactic or other serious allergic reaction occurs, immediately discontinue administration of HUMIRA and institute appropriate therapy. In clinical trials of HUMIRA in adults, allergic reactions (e.g., allergic rash, anaphylactoid reaction, fixed drug reaction, non-specified drug reaction, urticaria) have been observed.

Hepatitis B Virus Reactivation

Use of TNF blockers, including HUMIRA, may increase the risk of reactivation of hepatitis B virus (HBV) in patients who are chronic carriers of this virus. In some instances, HBV reactivation occurring in conjunction with TNF blocker therapy has been fatal. The majority of these reports have occurred in patients concomitantly receiving other medications that suppress the immune system, which may also contribute to HBV reactivation. Evaluate patients at risk for HBV infection for prior evidence of HBV infection before initiating TNF blocker therapy. Exercise caution in prescribing TNF blockers for patients identified as carriers of HBV. Adequate data are not available on the safety or efficacy of treating patients who are carriers of HBV with anti-viral therapy in conjunction with TNF blocker therapy to prevent HBV reactivation. In patients who develop HBV reactivation, stop HUMIRA and initiate effective anti-viral therapy with appropriate supportive treatment. The safety of resuming TNF blocker therapy after HBV reactivation is controlled is not known.

Neurologic Reactions

Use of TNF blocking agents, including HUMIRA, has been associated with rare cases of new onset or exacerbation of clinical symptoms and/or radiographic evidence of central nervous system demyelinating disease, including multiple sclerosis (MS) and optic neuritis, and peripheral demyelinating disease, including Guillain-Barré syndrome. Exercise caution in considering the use of HUMIRA in patients with preexisting or recent-onset central or peripheral nervous system demyelinating disorders; discontinuation of HUMIRA should be considered if any of these disorders develop. There is a known association between intermediate uveitis and central demyelinating disorders.

Hematological Reactions

Rare reports of pancytopenia including aplastic anemia have been reported with TNF blocking agents. Adverse reactions of the hematologic system, including medically significant cytopenia (e.g., thrombocytopenia, leukopenia) have been infrequently reported with HUMIRA. The causal relationship of these reports to HUMIRA remains unclear. Advise all patients to seek immediate medical attention if they develop signs and symptoms suggestive of blood dyscrasias or infection (e.g., persistent fever, bruising, bleeding, pallor) while on HUMIRA. Consider discontinuation of HUMIRA therapy in patients with confirmed significant hematologic abnormalities.

Use with Anakinra

Concurrent use of anakinra (an interleukin-1 antagonist) and another TNF-blocker, was associated with a greater proportion of serious infections and neutropenia and no added benefit compared with the TNF-blocker alone in patients with RA. Therefore, the combination of HUMIRA and anakinra is not recommended *[see Drug Interactions]*.

Heart Failure

Cases of worsening congestive heart failure (CHF) and new onset CHF have been reported with TNF blockers. Cases of worsening CHF have also been observed with HUMIRA. Exercise caution when using HUMIRA in patients who have heart failure and monitor them carefully.

Autoimmunity

Treatment with HUMIRA may result in the formation of autoantibodies and, rarely, in the development of a lupus-like syndrome. If a patient develops symptoms suggestive of a lupus-like syndrome following treatment with HUMIRA, discontinue treatment *[see Adverse Reactions]*.

Immunizations

In a placebo-controlled clinical trial of patients with RA, no difference was detected in anti-pneumococcal antibody response between HUMIRA and placebo treatment groups when the pneumococcal polysaccharide vaccine and influenza vaccine were administered concurrently with HUMIRA. Patients on HUMIRA may receive concurrent vaccinations, except for live vaccines. No data are available on the secondary transmission of infection by live vaccines in patients receiving HUMIRA.

It is recommended that pediatric patients, if possible, be brought up to date with all immunizations in agreement with current immunization guidelines prior to initiating HUMIRA therapy. Patients on HUMIRA may receive concurrent vaccinations, except for live vaccines.

The safety of administering live or live-attenuated vaccines in infants exposed to HUMIRA *in utero* is unknown. Risks and benefits should be considered prior to vaccinating (live or live-attenuated) exposed infants *[see Use in Specific Populations]*.

Use with Abatacept

In controlled trials, the concurrent administration of TNF-blockers and abatacept was associated with a greater proportion of serious infections than the use of a TNF-blocker alone; the combination therapy, compared to the use of a TNF-blocker alone, has not demonstrated improved clinical benefit in the treatment of RA. Therefore, the combination of abatacept with TNF-blockers including HUMIRA is not recommended *[see Drug Interactions]*.

ADVERSE REACTIONS

The most serious adverse reactions described elsewhere in the labeling include the following:

- Serious Infections *[see Warnings and Precautions]*
- Malignancies *[see Warnings and Precautions]*

Clinical Trials Experience

The most common adverse reaction with HUMIRA was injection site reactions. In placebo-controlled trials, 20% of patients treated with HUMIRA developed injection site reactions (erythema and/or itching, hemorrhage, pain or swelling), compared to 14% of patients receiving placebo. Most injection site reactions were described as mild and generally did not necessitate drug discontinuation.

The proportion of patients who discontinued treatment due to adverse reactions during the double-blind, placebo-controlled portion of studies in patients with RA (i.e., Studies RA-I, RA-II, RA-III and RA-IV) was 7% for patients taking HUMIRA and 4% for placebo-treated patients. The most common adverse reactions leading to discontinuation of HUMIRA in these RA studies were clinical flare reaction (0.7%), rash (0.3%) and pneumonia (0.3%).

Infections

In the controlled portions of the 39 global HUMIRA clinical trials in adult patients with RA, PsA, AS, CD, UC, HS and UV, the rate of serious infections was 4.3 per 100 patient-years in 7973 HUMIRA-treated patients versus a rate of 2.9 per 100 patient-years in 4848 control-treated patients. Serious infections observed included pneumonia, septic arthritis, prosthetic and post-surgical infections, erysipelas, cellulitis, diverticulitis, and pyelonephritis *[see Warnings and Precautions]*.

Tuberculosis and Opportunistic Infections

In 52 global controlled and uncontrolled clinical trials in RA, PsA, AS, CD, UC, Ps, HS and UV that included 24,605 HUMIRA-treated patients, the rate of reported active tuberculosis was 0.20 per 100 patient-years and the rate of positive PPD conversion was 0.09 per 100 patient-years. In a subgroup of 10,113 U.S. and Canadian HUMIRA-treated patients, the rate of reported active TB was 0.05 per 100 patient-years and the rate of positive PPD conversion was 0.07 per 100 patient-years. These trials included reports of miliary, lymphatic, peritoneal, and pulmonary TB. Most of the TB cases occurred within the first eight months after initiation of therapy and may reflect recrudescence of latent disease. In these global clinical trials, cases of serious opportunistic infections have been reported at an overall rate of 0.05 per 100 patient-years. Some cases of serious opportunistic infections and TB have been fatal *[see Warnings and Precautions]*.

Autoantibodies

In the rheumatoid arthritis controlled trials, 12% of patients treated with HUMIRA and 7% of placebo-treated patients that had negative baseline ANA titers developed positive titers at week 24. Two patients out of 3046 treated with HUMIRA developed clinical signs suggestive of new-onset lupus-like syndrome. The patients improved following discontinuation of therapy. No patients developed lupus nephritis or central nervous system symptoms. The impact of long-term treatment with HUMIRA on the development of autoimmune diseases is unknown.

Liver Enzyme Elevations

There have been reports of severe hepatic reactions including acute liver failure in patients receiving TNF-blockers. In controlled Phase 3 trials of HUMIRA (40 mg SC every other week) in patients with RA, PsA, and AS with control period duration ranging from 4 to 104 weeks, ALT elevations ≥ 3 x ULN occurred in 3.5% of HUMIRA-treated patients and 1.5% of control-treated patients. Since many of these patients in these trials were also taking medications that cause liver enzyme elevations (e.g., NSAIDS, MTX), the relationship between HUMIRA and the liver enzyme elevations is not clear. In a controlled Phase 3 trial of HUMIRA in patients with polyarticular JIA who were 4 to 17 years, ALT elevations ≥ 3 x ULN occurred in 4.4% of HUMIRA-treated patients and 1.5% of control-treated patients (ALT more common than AST); liver enzyme test elevations were more frequent among those treated with the combination of HUMIRA and MTX than those treated with HUMIRA alone. In general, these elevations did not lead to discontinuation of HUMIRA treatment. No ALT elevations ≥ 3 x ULN occurred in the open-label study of HUMIRA in patients with polyarticular JIA who were 2 to <4 years.

In controlled Phase 3 trials of HUMIRA (initial doses of 160 mg and 80 mg, or 80 mg and 40 mg on Days 1 and 15, respectively, followed by 40 mg every other week) in adult patients with CD with a control period duration ranging from 4 to 52 weeks, ALT elevations ≥ 3 x ULN occurred in 0.9% of HUMIRA-treated patients and 0.9% of control-treated patients. In the Phase 3 trial of HUMIRA in pediatric patients with Crohn's disease which evaluated efficacy and safety of two body weight based maintenance dose regimens following body weight based induction therapy up to 52 weeks of treatment, ALT elevations ≥ 3 x ULN occurred in 2.6% (5/192) of patients, of whom 4 were receiving concomitant immunosuppressants at baseline; none of these patients discontinued due to abnormalities in ALT tests. In controlled Phase 3 trials of HUMIRA (initial doses of 160 mg and 80 mg on Days 1 and 15 respectively, followed by 40 mg every other week) in patients with UC with control period duration ranging from 1 to 52 weeks, ALT elevations ≥3 x ULN occurred in 1.5% of HUMIRA-treated patients and 1.0% of control-treated patients. In controlled Phase 3 trials of HUMIRA (initial dose of 80 mg then 40 mg every other week) in patients with Ps with control period duration ranging from 12 to 24 weeks, ALT elevations ≥ 3 x ULN occurred in 1.8% of HUMIRA-treated patients and 1.8% of control-treated patients. In controlled trials of HUMIRA (initial doses of 160 mg at Week 0 and 80 mg at Week 2, followed by 40 mg every week starting at Week 4), in subjects with HS with a control period duration ranging from 12 to 16 weeks, ALT elevations ≥ 3 x ULN occurred in 0.3% of HUMIRA-treated subjects and 0.6% of control-treated subjects. In controlled trials of HUMIRA (initial doses of 80 mg at Week 0 followed by 40 mg every other week starting at Week 1) in patients with uveitis with an exposure of 165.4 PYs and 119.8 PYs in HUMIRA-treated and control-treated patients, respectively, ALT elevations ≥ 3 x ULN occurred in 2.4% of HUMIRA-treated patients and 2.4% of control-treated patients.

Immunogenicity

Patients in Studies RA-I, RA-II, and RA-III were tested at multiple time points for antibodies to adalimumab during the 6- to 12-month period. Approximately 5% (58 of 1062) of adult RA patients receiving HUMIRA developed low-titer antibodies to adalimumab at least once during treatment, which were neutralizing *in vitro*. Patients treated with concomitant methotrexate (MTX) had a lower rate of antibody development than patients on HUMIRA monotherapy (1% versus 12%). No apparent correlation of antibody development to adverse reactions was observed. With monotherapy, patients receiving every other week dosing may develop antibodies more frequently than those receiving weekly dosing. In patients receiving the recommended dosage of 40 mg every other week as monotherapy, the ACR 20 response was lower among antibody-positive patients than among antibody-negative patients. The long-term immunogenicity of HUMIRA is unknown.

In patients with polyarticular JIA who were 4 to 17 years of age, adalimumab antibodies were identified in 16% of HUMIRA-treated patients. In patients receiving concomitant MTX, the incidence was 6% compared to 26% with HUMIRA monotherapy. In patients with polyarticular JIA who were 2 to <4 years of age or 4 years of age and older weighing <15 kg, adalimumab antibodies were identified in 7% (1 of 15) of HUMIRA-treated patients, and the one patient was receiving concomitant MTX.

In patients with AS, the rate of development of antibodies to adalimumab in HUMIRA-treated patients was comparable to patients with RA.

In patients with PsA, the rate of antibody development in patients receiving HUMIRA monotherapy was comparable to patients with RA; however, in patients receiving concomitant MTX the rate was 7% compared to 1% in RA.

In adult patients with CD, the rate of antibody development was 3%.

In pediatric patients with Crohn's disease, the rate of antibody development in patients receiving HUMIRA was 3%. However, due to the limitation of the assay conditions, antibodies to adalimumab could be detected only when serum adalimumab levels were < 2 mcg/mL. Among the patients whose serum adalimumab levels were < 2 mcg/mL (approximately 32% of total patients studied), the immunogenicity rate was 10%.

In patients with moderately to severely active UC, the rate of antibody development in patients receiving HUMIRA was 5%. However, due to the limitation of the assay conditions, antibodies to adalimumab could be detected only when serum adalimumab levels were < 2 mcg/mL. Among the patients whose serum adalimumab levels were < 2 mcg/mL (approximately 25% of total patients studied), the immunogenicity rate was 20.7%.

In patients with Ps, the rate of antibody development with HUMIRA monotherapy was 8%. However, due to the limitation of the assay conditions, antibodies to adalimumab could be detected only when serum adalimumab levels were < 2 mcg/mL. Among the patients whose serum adalimumab levels were < 2 mcg/mL (approximately 40% of total patients studied), the immunogenicity rate was 20.7%. In Ps patients who were on HUMIRA monotherapy and subsequently withdrawn from the treatment, the rate of antibodies to adalimumab after retreatment was similar to the rate observed prior to withdrawal.

In subjects with moderate to severe HS, the rate of anti-adalimumab antibody development in subjects treated with HUMIRA was 6.5%. However, because of the limitation of the assay conditions, antibodies to adalimumab could be detected only when serum adalimumab levels were < 2 mcg/mL. Among subjects who stopped HUMIRA treatment for up to 24 weeks and in whom adalimumab serum levels subsequently declined to < 2 mcg/mL (approximately 22% of total subjects studied), the immunogenicity rate was 28%.

In patients with non-infectious uveitis, anti-adalimumab antibodies were identified in 4.8% (12/249) of patients treated with adalimumab. However, due to the limitation of the assay conditions, antibodies to adalimumab could be detected only when serum adalimumab levels were < 2 mcg/mL. Among the patients whose serum adalimumab levels were < 2 mcg/mL (approximately 23% of total patients studied), the immunogenicity rate was 21.1%. Using an assay which could measure an anti-adalimumab antibody titer in all patients, titers were measured in 39.8% (99/249) of non-infectious uveitis patients treated with adalimumab. No correlation of antibody development to safety or efficacy outcomes was observed.

The data reflect the percentage of patients whose test results were considered positive for antibodies to adalimumab or titers, and are highly dependent on the assay. The observed incidence of antibody (including neutralizing antibody) positivity in an assay is highly dependent on several factors including assay sensitivity and specificity, assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to adalimumab with the incidence of antibodies to other products may be misleading.

Other Adverse Reactions

Rheumatoid Arthritis Clinical Studies

The data described below reflect exposure to HUMIRA in 2468 patients, including 2073 exposed for 6 months, 1497 exposed for greater than one year and 1380 in adequate and well-controlled studies (Studies RA-I, RA-II, RA-III, and RA-IV). HUMIRA was studied primarily in placebo-controlled trials and in long-term follow up studies for up to 36 months duration. The population had a mean age of 54 years, 77% were female, 91% were Caucasian and had moderately to severely active rheumatoid arthritis. Most patients received 40 mg HUMIRA every other week.

Table 1 summarizes reactions reported at a rate of at least 5% in patients treated with HUMIRA 40 mg every other week compared to placebo and with an incidence higher than placebo. In Study RA-III, the types and frequencies of adverse reactions in the second year open-label extension were similar to those observed in the one-year double-blind portion.

Table 1. Adverse Reactions Reported by ≥5% of Patients Treated with HUMIRA During Placebo-Controlled Period of Pooled RA Studies (Studies RA-I, RA-II, RA-III, and RA-IV)

	HUMIRA 40 mg subcutaneous Every Other Week	Placebo
Adverse Reaction (Preferred Term)	(N=705)	(N=690)
Respiratory		
Upper respiratory infection	17%	13%
Sinusitis	11%	9%
Flu syndrome	7%	6%
Gastrointestinal		
Nausea	9%	8%
Abdominal pain	7%	4%
Laboratory Tests*		
Laboratory test abnormal	8%	7%
Hypercholesterolemia	6%	4%
Hyperlipidemia	7%	5%
Hematuria	5%	4%
Alkaline phosphatase increased	5%	3%
Other		
Headache	12%	8%
Rash	12%	6%
Accidental injury	10%	8%
Injection site reaction **	8%	1%
Back pain	6%	4%
Urinary tract infection	8%	5%
Hypertension	5%	3%

* Laboratory test abnormalities were reported as adverse reactions in European trials

** Does not include injection site erythema, itching, hemorrhage, pain or swelling

Juvenile Idiopathic Arthritis Clinical Studies

In general, the adverse reactions in the HUMIRA-treated patients in the polyarticular juvenile idiopathic arthritis (JIA) trials (Studies JIA-I and JIA-II) were similar in frequency and type to those seen in adult patients *[see Warnings and Precautions and Adverse Reactions]*. Important findings and differences from adults are discussed in the following paragraphs.

In Study JIA-I, HUMIRA was studied in 171 patients who were 4 to 17 years of age, with polyarticular JIA. Severe adverse reactions reported in the study included neutropenia, streptococcal pharyngitis, increased aminotransferases, herpes zoster, myositis, metrorrhagia, and appendicitis. Serious infections were observed in 4% of patients within approximately 2 years of initiation of treatment with HUMIRA and included cases of herpes simplex, pneumonia, urinary tract infection, pharyngitis, and herpes zoster.

In Study JIA-I, 45% of patients experienced an infection while receiving HUMIRA with or without concomitant MTX in the first 16 weeks of treatment. The types of infections reported in HUMIRA-treated patients were generally similar to those commonly seen in polyarticular JIA patients who are not treated with TNF blockers. Upon initiation of treatment, the most common adverse reactions occurring in this patient population treated with HUMIRA were injection site pain and injection site reaction (19% and 16%, respectively). A less commonly reported adverse event in patients receiving HUMIRA was granuloma annulare which did not lead to discontinuation of HUMIRA treatment.

In the first 48 weeks of treatment in Study JIA-I, non-serious hypersensitivity reactions were seen in approximately 6% of patients and included primarily localized allergic hypersensitivity reactions and allergic rash.

In Study JIA-I, 10% of patients treated with HUMIRA who had negative baseline anti-dsDNA antibodies developed positive titers after 48 weeks of treatment. No patient developed clinical signs of autoimmunity during the clinical trial.

Approximately 15% of patients treated with HUMIRA developed mild-to-moderate elevations of creatine phosphokinase (CPK) in Study JIA-I. Elevations exceeding 5 times the upper limit of normal were observed in several patients. CPK levels decreased or returned to normal in all patients. Most patients were able to continue HUMIRA without interruption.

In Study JIA-II, HUMIRA was studied in 32 patients who were 2 to <4 years of age or 4 years of age and older weighing <15 kg with polyarticular JIA. The safety profile for this patient population was similar to the safety profile seen in patients 4 to 17 years of age with polyarticular JIA.

In Study JIA-II, 78% of patients experienced an infection while receiving HUMIRA. These included nasopharyngitis, bronchitis, upper respiratory tract infection, otitis media, and were mostly mild to moderate in severity. Serious infections were observed in 9% of patients receiving HUMIRA in the study and included dental caries, rotavirus gastroenteritis, and varicella.

In Study JIA-II, non-serious allergic reactions were observed in 6% of patients and included intermittent urticaria and rash, which were all mild in severity.

Psoriatic Arthritis and Ankylosing Spondylitis Clinical Studies

HUMIRA has been studied in 395 patients with psoriatic arthritis (PsA) in two placebo-controlled trials and in an open label study and in 393 patients with ankylosing spondylitis (AS) in two placebo-controlled studies. The safety profile for patients with PsA and AS treated with HUMIRA 40 mg every other

week was similar to the safety profile seen in patients with RA, HUMIRA Studies RA-I through IV.

Adult Crohn's Disease Clinical Studies

HUMIRA has been studied in 1478 adult patients with Crohn's disease (CD) in four placebo-controlled and two open-label extension studies. The safety profile for adult patients with CD treated with HUMIRA was similar to the safety profile seen in patients with RA.

Pediatric Crohn's Disease Clinical Studies

HUMIRA has been studied in 192 pediatric patients with Crohn's disease in one double-blind study (Study PCD-I) and one open-label extension study. The safety profile for pediatric patients with Crohn's disease treated with HUMIRA was similar to the safety profile seen in adult patients with Crohn's disease.

During the 4 week open label induction phase of Study PCD-I, the most common adverse reactions occurring in the pediatric population treated with HUMIRA were injection site pain and injection site reaction (6% and 5%, respectively).

A total of 67% of children experienced an infection while receiving HUMIRA in Study PCD-I. These included upper respiratory tract infection and nasopharyngitis.

A total of 5% of children experienced a serious infection while receiving HUMIRA in Study PCD-I. These included viral infection, device related sepsis (catheter), gastroenteritis, H1N1 influenza, and disseminated histoplasmosis.

In Study PCD-I, allergic reactions were observed in 5% of children which were all non-serious and were primarily localized reactions.

Ulcerative Colitis Clinical Studies

HUMIRA has been studied in 1010 patients with ulcerative colitis (UC) in two placebo-controlled studies and one open-label extension study. The safety profile for patients with UC treated with HUMIRA was similar to the safety profile seen in patients with RA.

Plaque Psoriasis Clinical Studies

HUMIRA has been studied in 1696 subjects with plaque psoriasis (Ps) in placebo-controlled and open-label extension studies. The safety profile for subjects with Ps treated with HUMIRA was similar to the safety profile seen in subjects with RA with the following exceptions. In the placebo-controlled portions of the clinical trials in Ps subjects, HUMIRA-treated subjects had a higher incidence of arthralgia when compared to controls (3% *vs.* 1%).

Hidradenitis Suppurativa Clinical Studies

HUMIRA has been studied in 727 subjects with hidradenitis suppurativa (HS) in three placebo-controlled studies and one open-label extension study. The safety profile for subjects with HS treated with HUMIRA weekly was consistent with the known safety profile of HUMIRA.

Flare of HS, defined as ≥25% increase from baseline in abscesses and inflammatory nodule counts and with a minimum of 2 additional lesions, was documented in 22 (22%) of the 100 subjects who were withdrawn from HUMIRA treatment following the primary efficacy timepoint in two studies.

Uveitis Clinical Studies

HUMIRA has been studied in 464 patients with uveitis (UV) in placebo-controlled and open-label extension studies. The safety profile for patients with UV treated with HUMIRA was similar to the safety profile seen in patients with RA.

Postmarketing Experience

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

Gastrointestinal disorders: Diverticulitis, large bowel perforations including perforations associated with diverticulitis and appendiceal perforations associated with appendicitis, pancreatitis

General disorders and administration site conditions: Pyrexia

Hepato-biliary disorders: Liver failure, hepatitis

Immune system disorders: Sarcoidosis

Neoplasms benign, malignant and unspecified (including cysts and polyps): Merkel Cell Carcinoma (neuroendocrine carcinoma of the skin)

Nervous system disorders: Demyelinating disorders (e.g., optic neuritis, Guillain-Barré syndrome), cerebrovascular accident

Respiratory disorders: Interstitial lung disease, including pulmonary fibrosis, pulmonary embolism

Skin reactions: Stevens Johnson Syndrome, cutaneous vasculitis, erythema multiforme, new or worsening psoriasis (all sub-types including pustular and palmoplantar), alopecia

Vascular disorders: Systemic vasculitis, deep vein thrombosis

DRUG INTERACTIONS

Methotrexate

HUMIRA has been studied in rheumatoid arthritis (RA) patients taking concomitant methotrexate (MTX). Although MTX reduced the apparent adalimumab clearance, the data do not suggest the need for dose adjustment of either HUMIRA or MTX.

Biological Products

In clinical studies in patients with RA, an increased risk of serious infections has been seen with the combination of TNF blockers with anakinra or abatacept, with no added benefit; therefore, use of HUMIRA with abatacept or anakinra is not recommended in patients with RA *[see Warnings and Precautions]*. A higher rate of serious infections has also been observed in patients with RA treated with rituximab who received subsequent treatment with a TNF blocker. There is insufficient information regarding the concomitant use of HUMIRA and other biologic products for the treatment of RA, PsA, AS, CD, UC, Ps, HS and UV. Concomitant administration of HUMIRA with other biologic DMARDS (e.g., anakinra and abatacept) or other TNF blockers is not recommended based upon the possible increased risk for infections and other potential pharmacological interactions.

Live Vaccines

Avoid the use of live vaccines with HUMIRA *[see Warnings and Precautions]*.

Cytochrome P450 Substrates

The formation of CYP450 enzymes may be suppressed by increased levels of cytokines (e.g., TNFα, IL-6) during chronic inflammation. It is possible for a molecule that antagonizes cytokine activity, such as adalimumab, to influence the formation of CYP450 enzymes. Upon initiation or discontinuation of HUMIRA in patients being treated with CYP450 substrates with a narrow therapeutic index, monitoring of the effect (e.g., warfarin) or drug concentration (e.g., cyclosporine or theophylline) is recommended and the individual dose of the drug product may be adjusted as needed.

USE IN SPECIFIC POPULATIONS

Pregnancy

Limited clinical data are available from the Humira Pregnancy Registry. Excluding lost-to-follow-up, data from the registry reports a rate of 5.6% for major birth defects with first trimester use of adalimumab in pregnant women with rheumatoid arthritis (RA), and a rate of 7.8% and 5.5% for major birth defects in the disease-matched and non-diseased comparison groups *[see Data]*. Adalimumab is actively transferred across the placenta during the third trimester of pregnancy and may affect immune response in the *in-utero* exposed infant *[see Clinical Considerations]*. In an embryo-fetal perinatal development study conducted in cynomolgus monkeys, no fetal harm or malformations were observed with intravenous administration of adalimumab during organogenesis and later in gestation, at doses that produced exposures up to approximately 373 times the maximum recommended human dose (MRHD) of 40 mg subcutaneous without methotrexate *[see Data]*.

The estimated background risk of major birth defects and miscarriage for the indicated populations is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and miscarriage is 15-20%, respectively.

Clinical Considerations

Fetal/Neonatal adverse reactions

Monoclonal antibodies are increasingly transported across the placenta as pregnancy progresses, with the largest amount transferred during the third trimester [*see Data*]. Risks and benefits should be considered prior to administering live or live-attenuated vaccines to infants exposed to HUMIRA *in utero [see Use in Specific Populations]*.

Data

Human Data

In a prospective cohort pregnancy exposure registry conducted in the U.S. and Canada between 2004 and 2013, 74 women with RA treated with adalimumab at least during the first trimester, 80 women with RA not treated with adalimumab and 218 women without RA (non-diseased) were enrolled. Excluding lost-to-follow-up, the rate of major defects in the adalimumab-exposed pregnancies (N=72), disease-matched (N=77), and non-diseased comparison groups (N=201) was 5.6%, 7.8% and 5.5%, respectively. However, this study cannot definitely establish the absence of any risk because of methodological limitations, including small sample size and non-randomized study design. Data from the Crohn's disease portion of the study is in the follow-up phase and the analysis is ongoing.

In an independent clinical study conducted in ten pregnant women with inflammatory bowel disease treated with HUMIRA, adalimumab concentrations were measured in maternal serum as well as in cord blood (n=10) and infant serum (n=8) on the day of birth. The last dose of HUMIRA was given between 1 and 56 days prior to delivery. Adalimumab concentrations were 0.16-19.7 µg/mL in cord blood, 4.28-17.7 µg/mL in infant serum, and 0-16.1 µg/mL in maternal serum. In all but one case, the cord blood level of adalimumab was higher than the maternal serum level, suggesting adalimumab actively crosses the placenta. In addition, one infant had serum levels at each of the following: 6 weeks (1.94 µg/mL), 7 weeks (1.31 µg/mL), 8 weeks (0.93 µg/mL), and 11 weeks (0.53 µg/mL), suggesting adalimumab can be detected in the serum of infants exposed *in utero* for at least 3 months from birth.

Lactation

Risk Summary

Limited data from case reports in the published literature describe the presence of adalimumab in human milk at infant doses of 0.1% to 1% of the maternal serum level. There are no reports of adverse effects of adalimumab on the breastfed infant and no effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for HUMIRA and any potential adverse effects on the breastfed child from HUMIRA or from the underlying maternal condition.

Pediatric Use

Safety and efficacy of HUMIRA in pediatric patients for uses other than polyarticular juvenile idiopathic arthritis (JIA) and pediatric Crohn's disease have not been established. Due to its inhibition of TNFα, HUMIRA administered during pregnancy could affect immune response in the *in utero*-exposed newborn and infant. Data from eight infants exposed to HUMIRA *in utero* suggest adalimumab crosses the placenta *[see Use in Specific Populations]*. The clinical significance of elevated adalimumab levels in infants is unknown. The safety of administering live or live-attenuated vaccines in exposed infants is unknown. Risks and benefits should be considered prior to vaccinating (live or live-attenuated) exposed infants.

Post-marketing cases of lymphoma, including hepatosplenic T-cell lymphoma and other malignancies, some fatal, have been reported among children, adolescents, and young adults who received treatment with TNF-blockers including HUMIRA *[see Boxed Warning and Warnings and Precautions]*.

Juvenile Idiopathic Arthritis

In Study JIA-I, HUMIRA was shown to reduce signs and symptoms of active polyarticular JIA in patients 4 to 17 years of age *[see Clinical Studies]*. In Study JIA-II, the safety profile for patients 2 to <4 years of age was similar to the safety profile for patients 4 to 17 years of age with polyarticular JIA *[see Adverse Reactions]*. HUMIRA has not been studied in patients with polyarticular JIA less than 2 years of age or in patients with a weight below 10 kg.

The safety of HUMIRA in patients in the polyarticular JIA trials was generally similar to that observed in adults with certain exceptions *[see Adverse Reactions]*.

Pediatric Crohn's Disease

The safety and effectiveness of HUMIRA for reducing signs and symptoms and inducing and maintaining clinical remission have been established in pediatric patients 6 years of age and older with moderately to severely active Crohn's disease who have had an inadequate response to corticosteroids or immunomodulators such as azathioprine, 6-mercaptopurine, or methotrexate. Use of HUMIRA in this age group is supported by evidence from adequate and well-controlled studies of HUMIRA in adults with additional data from a randomized, double-blind, 52-week clinical study of two dose levels of HUMIRA in 192 pediatric patients (6 to 17 years of age) with moderately to severely active Crohn's disease *[see Clinical Studies]*. The safety and effectiveness of HUMIRA has not been established in pediatric patients with Crohn's disease less than 6 years of age.

Geriatric Use

A total of 519 RA patients 65 years of age and older, including 107 patients 75 years of age and older, received HUMIRA in clinical studies RA-I through IV. No overall difference in effectiveness was observed between these patients and younger patients. The frequency of serious infection and malignancy among HUMIRA treated patients over 65 years of age was higher than for those under 65 years of age. Because there is a higher incidence of infections and malignancies in the elderly population, use caution when treating the elderly.

OVERDOSAGE

Doses up to 10 mg/kg have been administered to patients in clinical trials without evidence of dose-limiting toxicities. In case of overdosage, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions or effects and appropriate symptomatic treatment instituted immediately.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term animal studies of HUMIRA have not been conducted to evaluate the carcinogenic potential or its effect on fertility.

PATIENT COUNSELING INFORMATION

Patient Counseling

Provide the HUMIRA "Medication Guide" to patients or their caregivers, and provide them an opportunity to read it and ask questions prior to initiation of therapy and prior to each time the prescription is renewed. If patients develop signs and symptoms of infection, instruct them to seek medical evaluation immediately.

Advise patients of the potential benefits and risks of HUMIRA.

- **Infections**

  Inform patients that HUMIRA may lower the ability of their immune system to fight infections. Instruct patients of the importance of contacting their doctor if they develop any symptoms of infection, including tuberculosis, invasive fungal infections, and reactivation of hepatitis B virus infections.
- **Malignancies**

  Counsel patients about the risk of malignancies while receiving HUMIRA.
- **Allergic Reactions**

  Advise patients to seek immediate medical attention if they experience any symptoms of severe allergic reactions. Advise latex-sensitive patients that the needle cap of the prefilled syringe contains latex.
- **Other Medical Conditions**

  Advise patients to report any signs of new or worsening medical conditions such as congestive heart failure, neurological disease, autoimmune disorders, or cytopenias. Advise patients to report any symptoms suggestive of a cytopenia such as bruising, bleeding, or persistent fever.

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The KAMRA Corneal Inlay in Practice

Majid Moshirfar, MD, FACS and Ryan T. Wallace
Salt Lake City

Tips and pearls this surgeon has amassed for the KAMRA corneal inlay, now that it's been approved for more than a year.

When the AcuFocus KAMRA corneal inlay was approved last year, it was the first implant of its type, giving surgeons a different angle from which to attack presbyopia. Like any new device or procedure, however, there's a learning curve involved, both in how to implant the KAMRA correctly, as well as the best ways to employ it. In this article, we'll share our tips and techniques for getting the best outcomes with the device, after having surmounted the learning curve over the past 18 months.

Design and Patient Selection

The KAMRA inlay uses the simple pinhole technique to improve reading vision by focusing light as it enters the eye. As a result, unlike monovision LASIK, the KAMRA provides depth of focus. Covered with 8,400 microscopic holes, the 3.8-mm circular inlay is also able to allow oxygen and nutrients to flow into the eye after implantation.

The KAMRA inlay is intended to be placed in the non-dominant eye of patients between the ages of 45 and 60 years old. The Food and Drug Administration states that the inlay works best for those patients who have between +1 and +2 D of presbyopia and who do not already require distance vision contacts or glasses. We aren't aware of any restriction regarding the size of the pupil.[1]

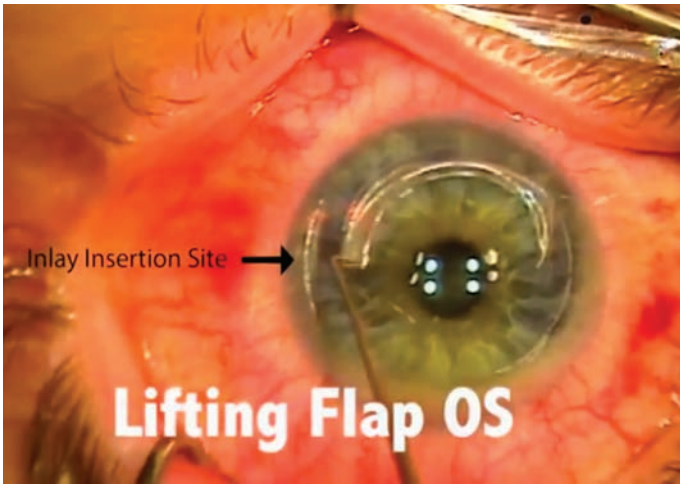
Despite promising results, this device is not a cure-all solution for reading vision, however. Consequently, we wouldn't recommend that this inlay be placed in anyone who will be doing prolonged reading for professional reasons, such as data analytics on a computer, text editing, etc. We do recommend this inlay for patients who would like to do occasional reading while still maintaining a depth of focus, such as reading text on a phone or a newspaper. As a result, before conducting the KAMRA surgery, it is especially important that you give patients a thorough informed consent in order to establish realistic expectations for the KAMRA, including the results of the FDA clinical trials mentioned below.

Implantation Procedure

The standard procedure for KAMRA implantation follows five steps. Here, we've adapted and summarized these steps from the FDA instructions:

First, to prepare the non-dominant eye for implantation, you create a miotic pupil 30 to 60 minutes before

beginning the procedure to allow the full pupil diameter to be visible. Second, using the first Purkinje reflex or the center of the pupil, you mark the cornea with a 4- or 4.5-mm ring marker. There are numerous diagnostic devices that can help you preoperatively identify the center of the pupil vs. the Purkinje reflex. We recommend the use of AcuTarget HD by AcuFocus. However, surgeons may use such devices as the OPD Scan III, iTrace or Vario to help guide them in surgical planning for proper centration. Note that this initial marking of the patient's cornea is essential for centration. The surgeon must use enough marking ink to last through the pocket creation and the eventual inlay implantation; otherwise he may lose the desired landmark during the procedure.



Combining LASIK with KAMRA can allow more patients to receive the inlay. Here the KAMRA insertion site is visible beside the flap.

If the distance between the Purkinje reflex and the center of the pupil is less than 300 µm, you should use the Purkinje image as your center. If the two are more than 300 µm apart, you should center the mark halfway between the center of the pupil and the Purkinje reflex. Although there are studies showing that centration with respect to the pupillary axis or Purkinje may not have a large impact on the visual outcome, a well-done article published last year recommended that we use the first Purkinje reflex for the centration of the KAMRA for the majority of our cases.[2]

In addition, we recommend that for your initial cases you select eyes that have a smaller difference between the Purkinje and the center of the pupil. Eyes in which the Purkinje and the center of the pupil overlap more are better options for surgeons just starting to perform this surgery, as such eyes will provide better results than those with a larger discrepancy. If the discrepancy between the Purkinje and the pupillary center is more than 450 µm, these patients are probably not good candidates due to their large angle kappa.

Third, after centration and marking the cornea, you use a femtosecond laser to create the inlay pocket 225 to 250 µm deep, using a maximum spot-line separation of 6 µm by 6 µm. We prefer to create deeper pockets beyond 40-percent thickness of the cornea, preferably 225 µm or thicker, as long as the residual stromal bed is at least 250 µm. There are three approved laser platforms in the United States that can provide pockets for the implantation of the KAMRA inlay: the Alcon FS200; Ziemer Femto LDV; and the AMO IntraLase iFS.

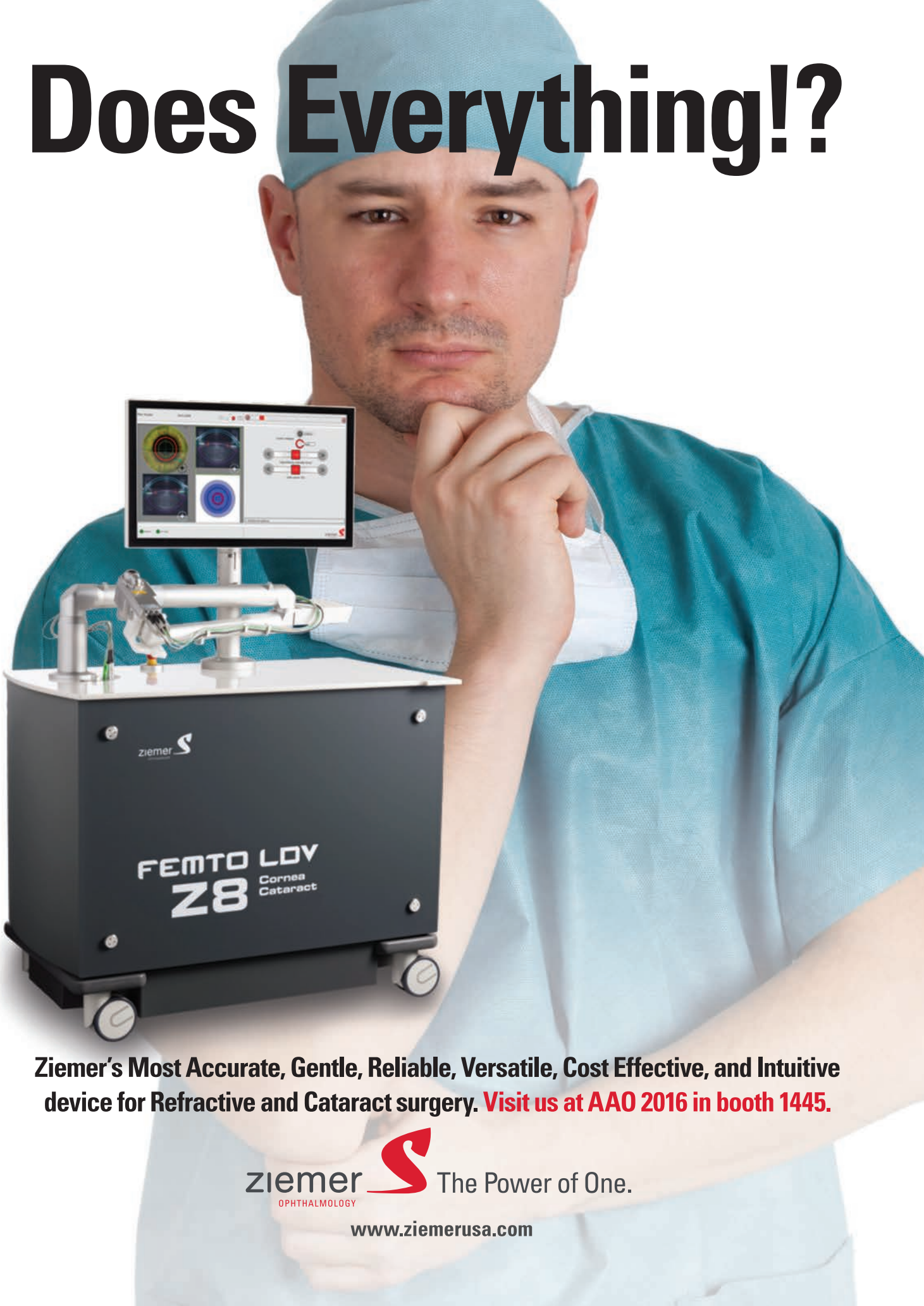
The IntraLase, FS200 and Ziemer lasers create pockets of 4.7 mm, 5.0 mm and 6.5 mm, respectively. Although we have found that 4.7 mm is an ample amount of space for the inlay, compared to the IntraLase, the 5.0 mm FS200 channel is larger and does allow more room and freedom in terms of mobility when the forceps and KAMRA are in the pocket. Another potential advantage the FS200 may provide is that you can place the KAMRA in a meridian desired by the surgeon; it doesn't need to be along the 180-degree axis. Some people may prefer to have the pocket created superiorly for easy accessibility, especially if the surgeon is sitting superiorly.

The Ziemer Femto laser has the largest channel width at 6.5 mm. Although this large size may not be entirely necessary, it's a very friendly platform for surgeons who are used to handling a microkeratome instead of a femtosecond for their laser surgery. You also have the additional advantage of using your desired surgical microscope, which may have better optics and visualization.

When you're docking your femtosecond laser, it's usually recommended that the suction ring be placed more laterally, with a larger amount of temporal scleral show. Such intentional decentration will enable you to place the incision site of the pocket closer to the limbus, reducing the risk of induced astigmatism. It's also strongly recommended that when you are creating your pocket, you size it in such a way that the centration of the inlay is limited by the width of the pocket.

There are some intraoperative centration marking devices such as the Mastel Centration Ring that can help you to choose the proper alignment intraoperatively by having the patient fixate on the centration light. Some surgeons also use the Alcon/WaveLight Allegretto 400Hz or the AMO/VISX S4 platform to aid them with the centration of the KAMRA implantation. However, the WaveLight Allegretto EX 500Hz can't be used for centration. We use the iFS laser for the creation of our pockets, but when it comes to the implantation, we use a surgical microscope combined with the Mastel Ring for better

Does Everything!?



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visualization, as well as for reliable centration.

We strongly recommend that you save the preop planning printout of the image of the distance between the Purkinje reflex and the pupillary center and mount that image on your microscope in the proper orientation to help guide you during the surgery.

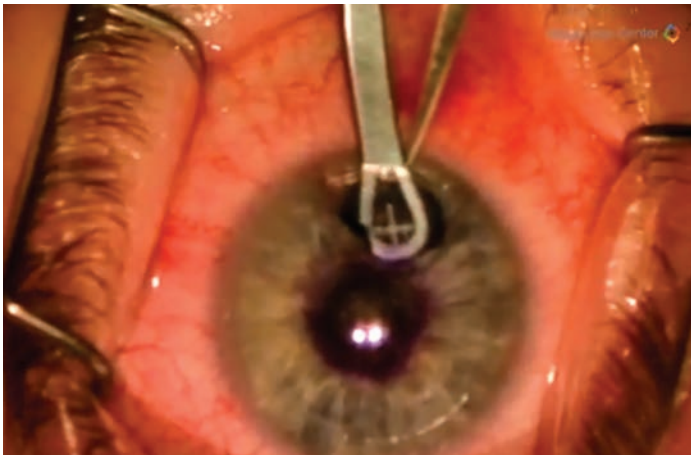
Next, open the pocket using a Sinskey hook and dissect it with the dissector. Make sure the entire pocket is dissected before attempting to implant the KAMRA inlay. After opening the pocket, you insert the KAMRA into the pocket using the forceps. When you're stabilizing the inlay with the forceps, you only want one-quarter of the inlay edge exposed. Move the KAMRA slightly past the centration mark and then pull it back into the necessary alignment. Let the inlay rest for about three seconds before withdrawing the forceps from the eye. You can use a surgical microscope or excimer laser to visualize the implantation, although we believe that a surgical microscope has superior optics.

Based on our initial experience and implanting nearly 90 cases after the FDA approval, we recommend that you make the pockets as deep as possible. This will reduce the risk of hyperopic shift three to six months after the surgery.

Postop Instructions

After you've implanted the inlay, there are some things you can do postop to get the best results.

The original FDA recommendations state that patients be given topical antibiotics four times a day for a minimum of one week, artificial tears q.i.d. for up to a month, as well as topical corticosteroids q.i.d. for the first week, t.i.d. for the second week, b.i.d. for the third week and q.d. for the fourth postoperative week.[3] However, in our experience, we've found that patients need to be on topical corticosteroids longer than was originally recommended. We currently keep them on topical 1% prednisolone q.i.d. for three weeks and subsequently switch the patients to 0.1% fluorometholone q.i.d. for one week. We then taper to t.i.d. for three weeks, b.i.d. for three weeks and q.d. for three weeks, and then once every other day for an additional three weeks. There are also some patients who may need to be on a low dose of steroids twice per week for an extended period of time. These are the KAMRA patients that developed hyperopic shift after four months. We recommend that patients between two and four months postop be followed to target individuals who may need to be on a low dose of steroids to prevent this hyperopic shift.



When inserting the KAMRA, move it slightly past the centration point and pull it back into the proper alignment.

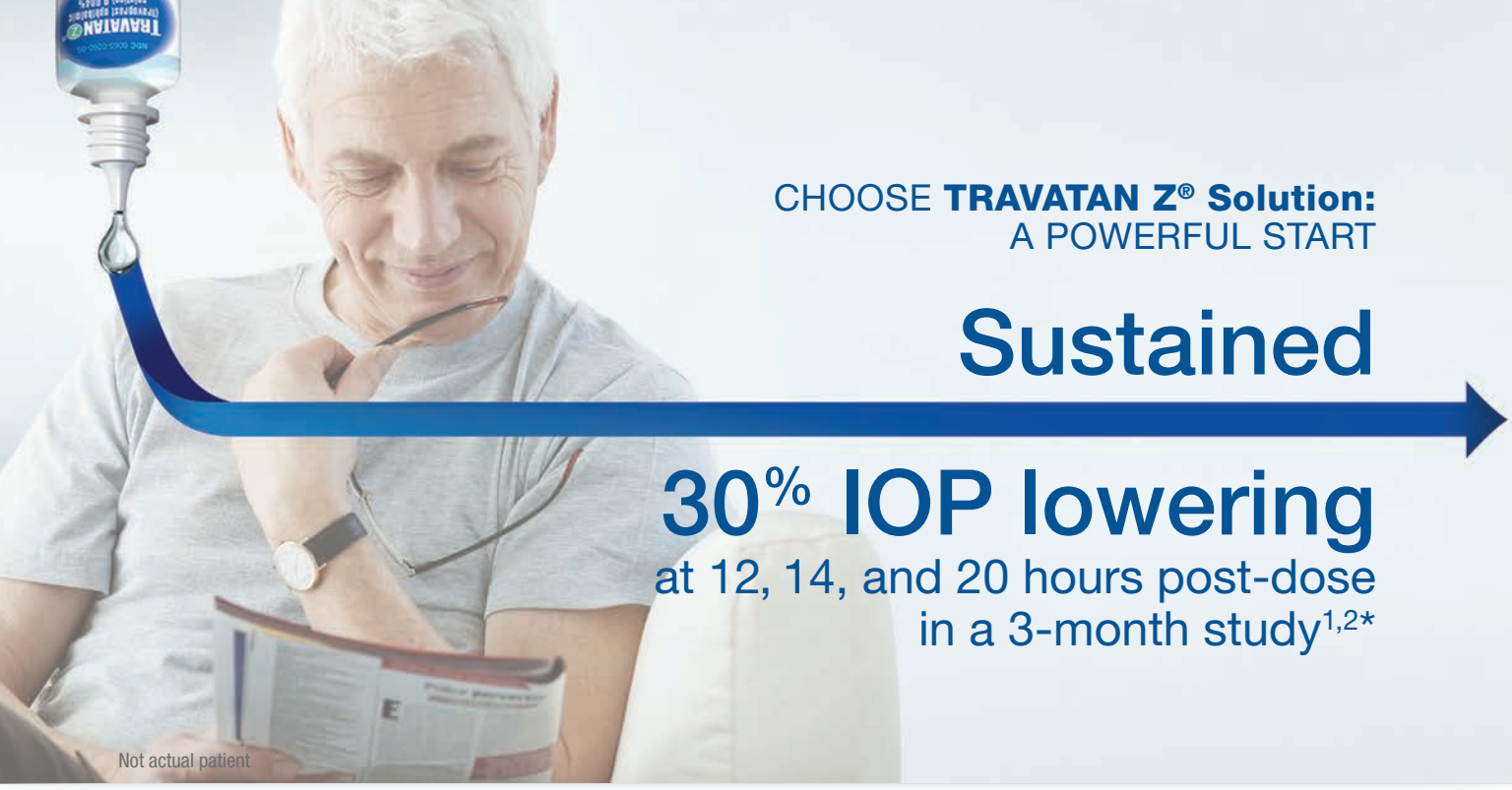
Safety and Efficacy

In the FDA clinical trials for the KAMRA inlay, before surgery, none of the 508 patients were able to see 20/40 uncorrected at near out of the surgery eye. At 12 months after surgery, 83.5 percent (399/478) of the patients saw at that level.[4] Before implantation of the inlay, 43.3 percent (220/508) saw 20/40 at near binocularly, uncorrected. After surgery, 91.8 percent (406/436) were 20/40 or better binocular uncorrected at 12 months.[3]

In the clinical trials, 1.7 percent (8/479) of patients lost one or two lines of best-corrected distance vision at 12 months, and 0.6 percent (3/479) of patients experienced more than two lost lines of vision in the same time frame. After 24 months, 1.2 percent (6/508) of patients had undergone recentration surgeries, and at the end of the 60-month study, 8.9 percent (45/508) of patients had had the inlay explanted.[3] In our initial post-FDA cases, no patient lost more than one line of vision and 81 percent (45/57) of patients had no change in best-corrected distance vision at six months' follow-up. We had five patients that required recentration and one patient that required explantation, citing dissatisfaction with the results.

LASIKamra and PRKamra

Many physicians will recognize that a large number of patients who could benefit from the KAMRA inlay also suffer from myopia or hyperopia with or without astigmatism. For such patients who wish to receive the inlay, consecutive LASIK/KAMRA and PRK/KAMRA could be a justifiable choice. In addition, many practitioners have implemented the simultaneous approach of PRK and KAMRA or LASIK and KAMRA instead of using the two-step approach, and further studies are being conducted as to their predictability and outcomes. These procedures have the potential to be much more convenient for the patients, since patients wouldn't have to go to the operating room twice and combining procedures



Not actual patient

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INDICATIONS AND USAGE

TRAVATAN Z® (travoprost ophthalmic solution) 0.004% is indicated for the reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension.

Dosage and Administration

The recommended dosage is 1 drop in the affected eye(s) once daily in the evening. TRAVATAN Z® Solution should not be administered more than once daily since it has been shown that more frequent administration of prostaglandin analogs may decrease the IOP-lowering effect.

TRAVATAN Z® Solution may be used concomitantly with other topical ophthalmic drug products to lower IOP. If more than 1 topical ophthalmic drug is being used, the drugs should be administered at least 5 minutes apart.

IMPORTANT SAFETY INFORMATION

Warnings and Precautions

Pigmentation—Travoprost ophthalmic solution has been reported to increase the pigmentation of the iris, periorbital tissue (eyelid), and eyelashes. Pigmentation is expected to increase as long as travoprost is administered. After discontinuation of travoprost, pigmentation of the iris is likely to be permanent, while pigmentation of the periorbital tissue and eyelash changes have been reported to be reversible in some patients. The long-term effects of increased pigmentation are not known. While treatment with TRAVATAN Z® Solution can be continued in patients who develop noticeably increased iris pigmentation, these patients should be examined regularly.

Eyelash Changes—TRAVATAN Z® Solution may gradually change eyelashes and vellus hair in the treated eye. These changes include increased length, thickness, and number of lashes. Eyelash changes are usually reversible upon discontinuation of treatment.

Use With Contact Lenses—Contact lenses should be removed prior to instillation of TRAVATAN Z® Solution and may be reinserted 15 minutes following its administration.

Adverse Reactions

The most common adverse reaction observed in controlled clinical studies with TRAVATAN Z® Solution was ocular hyperemia, which was reported in 30 to 50% of patients. Up to 3% of patients discontinued therapy due to conjunctival hyperemia. Ocular adverse reactions reported at an incidence of 5 to 10% in these clinical studies included decreased visual acuity, eye discomfort, foreign body sensation, pain, and pruritus. In postmarketing use with prostaglandin analogs, periorbital and lid changes including deepening of the eyelid sulcus have been observed.

Use in Specific Populations

Use in pediatric patients below the age of 16 years is not recommended because of potential safety concerns related to increased pigmentation following long-term chronic use.

For additional information about TRAVATAN Z® Solution, please see the brief summary of Prescribing Information on the adjacent page.

*__Study Design:__ Double-masked, randomized, parallel-group, multicenter non-inferiority comparison of the efficacy and safety of travoprost 0.004% preserved with benzalkonium chloride (BAK) to TRAVATAN Z® Solution after 3 months of treatment in patients with open-angle glaucoma or ocular hypertension. Baseline IOPs were 27.0 mm Hg (n=322), 25.5 mm Hg (n=322), and 24.8 mm Hg (n=322) at 8 AM, 10 AM, and 4 PM for TRAVATAN Z® Solution. At the end of Month 3, the TRAVATAN Z® Solution group had mean IOPs (95% CI) of 18.7 mm Hg (-0.4, 0.5), 17.7 mm Hg (-0.4, 0.6), and 17.4 mm Hg (-0.2, 0.8) at 8 AM, 10 AM, and 4 PM, respectively. Statistical equivalent reductions in IOP (95% confidence interval about the treatment differences were entirely within ±1.5 mm Hg) were demonstrated between the treatments at all study visits during the 3 months of treatment.

References: 1. Data on file, 2013. **2.** Lewis RA, Katz GJ, Weiss MJ, et al. Travoprost 0.004% with and without benzalkonium chloride: a comparison of safety and efficacy. *J Glaucoma.* 2007;16(1):98-103.

TRAVATAN Z®
(travoprost ophthalmic solution) 0.004%

Alcon®
a Novartis company

TRAVATAN Z®

(travoprost ophthalmic solution) 0.004%

BRIEF SUMMARY OF PRESCRIBING INFORMATION

INDICATIONS AND USAGE
TRAVATAN Z® (travoprost ophthalmic solution) 0.004% is indicated for the reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension.

DOSAGE AND ADMINISTRATION
The recommended dosage is one drop in the affected eye(s) once daily in the evening.
TRAVATAN Z® (travoprost ophthalmic solution) should not be administered more than once daily since it has been shown that more frequent administration of prostaglandin analogs may decrease the intraocular pressure lowering effect.

Reduction of the intraocular pressure starts approximately 2 hours after the first administration with maximum effect reached after 12 hours.

TRAVATAN Z® Solution may be used concomitantly with other topical ophthalmic drug products to lower intraocular pressure. If more than one topical ophthalmic drug is being used, the drugs should be administered at least five (5) minutes apart.

CONTRAINDICATIONS
None

WARNINGS AND PRECAUTIONS
Pigmentation
Travoprost ophthalmic solution has been reported to cause changes to pigmented tissues. The most frequently reported changes have been increased pigmentation of the iris, periorbital tissue (eyelid) and eyelashes. Pigmentation is expected to increase as long as travoprost is administered. The pigmentation change is due to increased melanin content in the melanocytes rather than to an increase in the number of melanocytes. After discontinuation of travoprost, pigmentation of the iris is likely to be permanent, while pigmentation of the periorbital tissue and eyelash changes have been reported to be reversible in some patients. Patients who receive treatment should be informed of the possibility of increased pigmentation. The long term effects of increased pigmentation are not known.

Iris color change may not be noticeable for several months to years. Typically, the brown pigmentation around the pupil spreads concentrically towards the periphery of the iris and the entire iris or parts of the iris become more brownish. Neither nevi nor freckles of the iris appear to be affected by treatment. While treatment with TRAVATAN Z® (travoprost ophthalmic solution) 0.004% can be continued in patients who develop noticeably increased iris pigmentation, these patients should be examined regularly.

Eyelash Changes
TRAVATAN Z® Solution may gradually change eyelashes and vellus hair in the treated eye. These changes include increased length, thickness, and number of lashes. Eyelash changes are usually reversible upon discontinuation of treatment.

Intraocular Inflammation
TRAVATAN Z® Solution should be used with caution in patients with active intraocular inflammation (e.g., uveitis) because the inflammation may be exacerbated.

Macular Edema
Macular edema, including cystoid macular edema, has been reported during treatment with travoprost ophthalmic solution. TRAVATAN Z® Solution should be used with caution in aphakic patients, in pseudophakic patients with a torn posterior lens capsule, or in patients with known risk factors for macular edema.

Angle-closure, Inflammatory or Neovascular Glaucoma
TRAVATAN Z® Solution has not been evaluated for the treatment of angle-closure, inflammatory or neovascular glaucoma.

Bacterial Keratitis
There have been reports of bacterial keratitis associated with the use of multiple-dose containers of topical ophthalmic products. These containers had been inadvertently contaminated by patients who, in most cases, had a concurrent corneal disease or a disruption of the ocular epithelial surface.

Use with Contact Lenses
Contact lenses should be removed prior to instillation of TRAVATAN Z® Solution and may be reinserted 15 minutes following its administration.

ADVERSE REACTIONS
Clinical Studies Experience
Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice. The most common adverse reaction observed in controlled clinical studies with TRAVATAN® (travoprost ophthalmic solution) 0.004% and TRAVATAN Z® (travoprost ophthalmic solution) 0.004% was ocular hyperemia which was reported in 30 to 50% of patients. Up to 3% of patients discontinued therapy due to conjunctival hyperemia. Ocular adverse reactions reported at an incidence of 5 to 10% in these clinical studies included decreased visual acuity, eye discomfort, foreign body sensation, pain and pruritus. Ocular adverse reactions reported at an incidence of 1 to 4% in clinical studies with TRAVATAN® or TRAVATAN Z® Solutions included abnormal vision, blepharitis, blurred vision, cataract, conjunctivitis, corneal staining, dry eye, iris discoloration, keratitis, lid margin crusting, ocular inflammation, photophobia, subconjunctival hemorrhage and tearing.

Nonocular adverse reactions reported at an incidence of 1 to 5% in these clinical studies were allergy, angina pectoris, anxiety, arthritis, back pain, bradycardia, bronchitis, chest pain, cold/flu syndrome, depression, dyspepsia, gastrointestinal disorder, headache, hypercholesterolemia, hypertension, hypotension, infection, pain, prostate disorder, sinusitis, urinary incontinence and urinary tract infections.

In postmarketing use with prostaglandin analogs, periorbital and lid changes including deepening of the eyelid sulcus have been observed.

USE IN SPECIFIC POPULATIONS
Pregnancy
Pregnancy Category C
Teratogenic effects: Travoprost was teratogenic in rats, at an intravenous (IV) dose up to 10 mcg/kg/day (250 times the maximal recommended human ocular dose (MRHOD), evidenced by an increase in the incidence of skeletal malformations as well as external and visceral malformations, such as fused sternebrae, domed head and hydrocephaly. Travoprost was not teratogenic in rats at IV doses up to 3 mcg/kg/day (75 times the MRHOD), or in mice at subcutaneous doses up to 1 mcg/kg/day (25 times the MRHOD). Travoprost produced an increase in post-implantation losses and a decrease in fetal viability in rats at IV doses > 3 mcg/kg/day (75 times the MRHOD) and in mice at subcutaneous doses > 0.3 mcg/kg/day (7.5 times the MRHOD).

In the offspring of female rats that received travoprost subcutaneously from Day 7 of pregnancy to lactation Day 21 at doses of ≥ 0.12 mcg/kg/day (3 times the MRHOD), the incidence of postnatal mortality was increased, and neonatal body weight gain was decreased. Neonatal development was also affected, evidenced by delayed eye opening, pinna detachment and preputial separation, and by decreased motor activity.

There are no adequate and well-controlled studies of TRAVATAN Z® (travoprost ophthalmic solution) 0.004% administration in pregnant women. Because animal reproductive studies are not always predictive of human response, TRAVATAN Z® Solution should be administered during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers
A study in lactating rats demonstrated that radiolabeled travoprost and/or its metabolites were excreted in milk. It is not known whether this drug or its metabolites are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when TRAVATAN Z® Solution is administered to a nursing woman.

Pediatric Use
Use in pediatric patients below the age of 16 years is not recommended because of potential safety concerns related to increased pigmentation following long-term chronic use.

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

Hepatic and Renal Impairment
Travoprost ophthalmic solution 0.004% has been studied in patients with hepatic impairment and also in patients with renal impairment. No clinically relevant changes in hematology, blood chemistry, or urinalysis laboratory data were observed in these patients.

NONCLINICAL TOXICOLOGY
Carcinogenesis, Mutagenesis, Impairment of Fertility
Two-year carcinogenicity studies in mice and rats at subcutaneous doses of 10, 30, or 100 mcg/kg/day did not show any evidence of carcinogenic potential. However, at 100 mcg/kg/day, male rats were only treated for 82 weeks, and the maximum tolerated dose (MTD) was not reached in the mouse study. The high dose (100 mcg/kg) corresponds to exposure levels over 400 times the human exposure at the maximum recommended human ocular dose (MRHOD) of 0.04 mcg/kg, based on plasma active drug levels. Travoprost was not mutagenic in the Ames test, mouse micronucleus test or rat chromosome aberration assay. A slight increase in the mutant frequency was observed in one of two mouse lymphoma assays in the presence of rat S-9 activation enzymes.

Travoprost did not affect mating or fertility indices in male or female rats at subcutaneous doses up to 10 mcg/kg/day [250 times the maximum recommended human ocular dose of 0.04 mcg/kg/day on a mcg/kg basis (MRHOD)]. At 10 mcg/kg/day, the mean number of corpora lutea was reduced, and the post-implantation losses were increased. These effects were not observed at 3 mcg/kg/day (75 times the MRHOD).

PATIENT COUNSELING INFORMATION
Potential for Pigmentation
Patients should be advised about the potential for increased brown pigmentation of the iris, which may be permanent. Patients should also be informed about the possibility of eyelid skin darkening, which may be reversible after discontinuation of TRAVATAN Z® (travoprost ophthalmic solution) 0.004%.

Potential for Eyelash Changes
Patients should also be informed of the possibility of eyelash and vellus hair changes in the treated eye during treatment with TRAVATAN Z® Solution. These changes may result in a disparity between eyes in length, thickness, pigmentation, number of eyelashes or vellus hairs, and/or direction of eyelash growth. Eyelash changes are usually reversible upon discontinuation of treatment.

Handling the Container
Patients should be instructed to avoid allowing the tip of the dispensing container to contact the eye, surrounding structures, fingers, or any other surface in order to avoid contamination of the solution by common bacteria known to cause ocular infections. Serious damage to the eye and subsequent loss of vision may result from using contaminated solutions.

When to Seek Physician Advice
Patients should also be advised that if they develop an intercurrent ocular condition (e.g., trauma or infection), have ocular surgery, or develop any ocular reactions, particularly conjunctivitis and eyelid reactions, they should immediately seek their physician's advice concerning the continued use of TRAVATAN Z® Solution.

Use with Contact Lenses
Contact lenses should be removed prior to instillation of TRAVATAN Z® Solution and may be reinserted 15 minutes following its administration.

Use with Other Ophthalmic Drugs
If more than one topical ophthalmic drug is being used, the drugs should be administered at least five (5) minutes between applications.

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U.S. Patent Nos. 5,631,287; 5,889,052, 6,011,062; 6,235,781; 6,503,497; and 6,849,253

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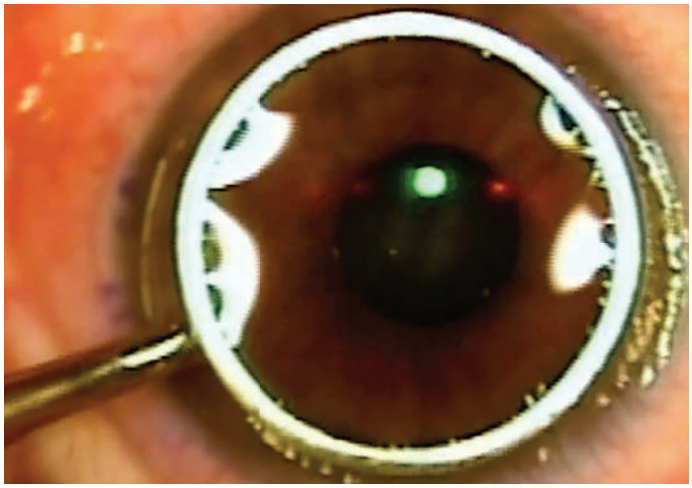
would limit the amount of patients' steroid use to just one treatment course instead of two. In each procedure, it's recommended that the refractive error in the non-dominant eye intentionally be undercorrected for a target of -0.5 to -0.75 D in patients that undergo PRK or LASIK in both eyes. Here is a description of these surgical approaches:



In simultaneous PRK and KAMRA, the surgeon centers and implants the KAMRA as usual, and then follows with epithelial removal (shown here is the alcohol well) and PRK. The inlay is visible in the center of the image.

• ***Consecutive PRKamra and LASIKamra.*** If patients wish, we can correct the refractive error with PRK or LASIK. Then, at another date, usually one to three months after the original surgery, they can undergo KAMRA implantation. This two-step approach to LASIK/KAMRA and PRK/KAMRA has shown good predictability, safety and efficacy in our practice, based on short-term results.

• ***Simultaneous PRKamra.*** Our method for simultaneous PRK and KAMRA involves the same steps of centration and implantation of the KAMRA inlay as before, followed by the alcohol and epithelial removal of PRK (a video of this can be viewed at https://youtu.be/CcWJpFwgS0M). The preliminary results on this simultaneous procedure have been good, but we do not yet have a large enough sample size to evaluate the effectiveness in terms of six- and 12-month data. The scientific literature supports our belief that it should work effectively.

We've come to the conclusion that if you use the KAMRA inlay with PRK in the non-dominant eye, since the patient will require a similar postoperative course of topical corticosteroids for three to four months for both the inlay and PRK surgeries, the treatment will be very similar if we do the procedures simultaneously. Thus, as noted earlier, by combining the two procedures, we save the patient time and he receives steroids for just one period rather than two.

• ***Simultaneous LASIKamra.*** We have found that simultaneous LASIK and KAMRA is also a viable way to bring patients into the range of use for the KAMRA inlay. Previously, physicians would create the corneal flap and place the KAMRA inlay under the flap.[5] However, with our understanding now of deeper insertion's benefits, some physicians have already tested methods of simultaneous KAMRA and LASIK with the inlay implantation in the corneal pocket occurring first, followed by the laser ablation of the eye.

We take a different approach. Our method for this procedure involves the laser ablation of the eye first and the KAMRA implantation second in order to prevent the KAMRA inlay from confounding the pupil tracker on the laser. Because the implantation of the inlay may not always be in the proper position, we think that proceeding with the ablation first prevents any confusion. In addition, we believe that the simultaneous procedure should involve a short waiting period to vent the corneal pocket for the inlay before creating the corneal flap in the same eye, in order to ensure a smooth bed for the laser ablation (to view a video of this, visit https://youtu.be/GZUvXMUyS7M). Like PRKamra, we don't yet have a large enough sample size to evaluate the effectiveness in terms of six- and 12-month data, but the preliminary results have been promising.

Overall, we believe that corneal presbyopic devices such as the KAMRA, and now the recently approved Raindrop, are important approvals for the baby boomer generation's particular vision needs. However, there is still a need for collaboration on studies into such devices' predictability, postoperative care and long-term results, and we look forward to conducting further research studies on these topics. REVIEW

Dr. Moshirfar is an adjunct professor of ophthalmology at the John A. Moran Eye Center at the University of Utah. Mr. Wallace is a clinical research assistant at Hoopes, Durrie, Rivera Research in Draper, Utah. They have no financial interest in the products mentioned.

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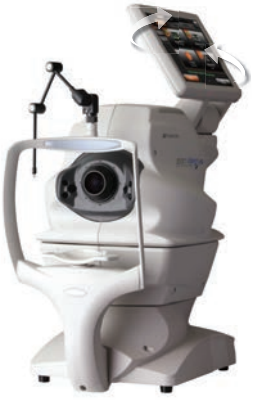

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Questioning NSAIDs For CME Prevention

Kristine Brennan, Senior Associate Editor

This post-cataract practice is being challenged. How are surgeons responding?

Since S. Rodman Irvine, MD, first described cystoid macular edema as a distinct sequela of cataract surgery in a September 1952 lecture, CME has remained stubbornly persistent.[1] Surgical techniques keep evolving, but CME can still take ostensibly low-risk patients by surprise. The postoperative instillation of NSAID drops, together with corticosteroids, is widely considered a preemptive one-two punch against the macular thickening, diminished visual acuity and decreased contrast sensitivity of CME. An Ophthalmic Technology Assessment published in the November 2015 issue of *Ophthalmology*, however, found insufficient high-quality evidence to support the use of NSAIDs.[2] Surgeons nevertheless continue to include NSAIDs in their post-cataract arsenals. Here, the lead author of that controversial study and cataract surgeons who continue prescribing topical NSAIDs share their insights.

The Study

For the OTA, Stephen J. Kim, MD, program director of the vitreoretinal fellowship at Vanderbilt Eye Institute and associate professor of ophthalmology at Vanderbilt University School of Medicine, and his colleagues sought to determine whether previous studies demonstrated the effectiveness of topical NSAIDs in preventing CME-related vision loss after cataract surgery. They estimate that CME detectable by fluorescein angiography occurs in 9 to 19 percent of patients, with the incidence of "visually important" CME occurring in 1 to 4 percent. CME is treatable and often self-limiting, but it can cause permanent vision loss, and its occurrence raises the costs associated with surgery by approximately 50 percent, according to the study's authors. To investigate NSAIDs' effect on CME prevention and long-term visual outcomes, defined as visual acuity at three months postop, the researchers performed comprehensive searches of the Cochrane Library and PubMed databases. They ultimately selected and individually analyzed 15 relevant studies, then collectively summarized them. Dr. Kim and his colleagues concluded that topical NSAIDs hasten visual recovery in routine cataract surgery patients, but they found no gains in visual acuity three months postoperatively compared to patients treated with certain corticosteroids alone or placebos. They also found no support for the conventional wisdom that NSAID drops work synergistically with topical steroids.

"NSAIDs are fine drugs," says Dr. Kim. "But they are a weaker anti-

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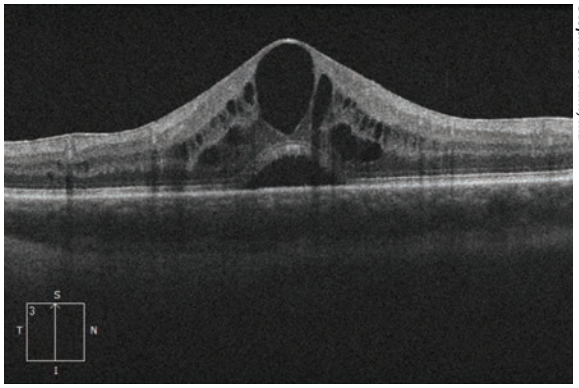
inflammatory than corticosteroids, and their effects are redundant. Their addition may speed visual recovery, but they add nothing to the end result." To help speed attainment of best visual results, he says, surgeons can increase the dosages of topical steroids.

As to why surgeons keep using topical NSAIDs, Dr. Kim says, "It is so ingrained in the culture. It's also driven by industry." He adds that the extant studies haven't looked at the effect of NSAIDs alone in preventing CME. "Historically, all the studies done so far have not been fair studies, in that they've compared patients on two medications [NSAIDs and corticosteroids] to patients taking corticosteroids alone. That's not a one-to-one comparison. A truly fair study would be comparing one patient population using just NSAIDs to one using steroid medication alone, say, four times daily, for both groups. That study has never been done. It has always been a comparison of a corticosteroid group to people who are getting twice as much medication, and the effects of the NSAID are redundant there.

"The evidence we have so far is conflicted," continues Dr. Kim, who emphasizes that his position with a nonprofit teaching hospital precludes any potential financial interest in his findings. He also acknowledges that the community practice of using postop NSAIDs will probably remain in place for the foreseeable future. "It may take 10 or 20 years to move the standard of care," he says.



Stephen J. Kim, MD

OCT image of a retina with CME. Disruption of the blood-retinal barrier due to postop inflammation may contribute to the condition.[2]

Should the Standard Change?

An editorial accompanying the OTA anticipated that it would be "provocative," and disclosed that expert reviewers from the American Society of Cataract and Refractive Surgery had objected to the initial draft because they believed its emphasis on Snellen chart acuity three months postoperatively failed to consider potential problems arising from even transient edema preventable by NSAIDs, such as patient anxiety, diminished productivity and independence, and costs of additional testing.[3] The ASCRS reviewers recommended visual acuity at one month and patient-reported quality of life as better criteria to measure the value of NSAIDs. Because the OTA panel stuck with visual acuity at three months as its metric, the ASCRS experts declined to endorse the OTA.

While there may not be any one-to-one controlled studies comparing NSAIDs and steroids, other research hints at their standalone value in preventing CME. At the ASCRS 2014 Symposium, Keith Walter, MD, presented a paper suggesting that topical NSAID monotherapy may in fact be more effective than corticosteroids—either alone or with NSAIDs—to prevent CME.[4] Dr. Walter's five-year retrospective analysis of 5,000 cataract surgeries showed that name-brand bromfenac drops by themselves prevented CME as well or better than combinations of corticosteroids and NSAIDs.

It's important to emphasize that the above-mentioned paper and the OTA investigated two subtly different things: NSAIDs' efficacy in postoperative CME prevention versus the usefulness and cost-effectiveness of NSAIDs in preventing long-term, CME-related vision loss. Dr. Kim and his co-authors acknowledged this limitation in the OTA. "Although long-term visual acuity (≥ three months) after cataract surgery is an important clinical measure of a therapeutic intervention," they wrote, "this assessment was not designed to comment on the rationale and potential value of NSAID therapy in preventing CME soon after surgery and the patient satisfaction and quality-of-life improvement associated with more rapid visual rehabilitation."[2]

Dissenting Opinions

David R. Hardten, MD, in private practice with Minnesota Eye Consultants and an adjunct professor at the University of Minnesota Department of Ophthalmology and the Illinois College of Optometry, reports that his postop use of NSAIDs for cataract cases remains unchanged after the OTA. "The data has had some articles in favor of NSAIDs, and some articles suggesting that maybe there's no benefit, but I've used them for a very long time and been happy with the results. I think they do provide a little bit better patient comfort after surgery, as well as reducing cystoid macular edema.

"I typically use them twice a day for the first week, and then once a day typically until the bottle's empty or four weeks—whichever comes first," he continues. "I use them in routine eyes, and I use them a little bit longer in patients who have risk factors for cystoid macular edema, like diabetics or folks with epiretinal membrane."

One built-in limitation of the OTA is the historic lack of uniform criteria for identifying CME. However, OCT and fluorescein angiography detect macular thickening during the early postop period, even in the absence of visual

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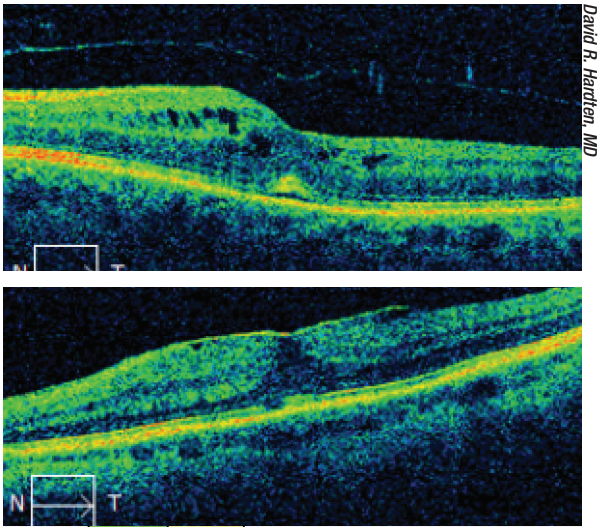
CME symptoms such as loss of visual acuity on a Snellen chart, diminished contrast sensitivity and metamorphopsia.

In the absence of universal endpoints delineating when CME becomes problematic, Dr. Hardten considers NSAIDs a rational choice to speed visual recovery. "I guess the definition of when cystoid macular edema becomes credited as significant is based at least a little bit on the patient's expectations," he observes. "If you know that a patient is extremely sensitive to subtle changes in their vision, if you think that 10 or 15 microns is going to be clinically significant to that specific patient, then you might very well derive more benefit from using an NSAID. Their sensitivity may be a little bit higher, so a margin of just 10 to 15 microns might be apparent to that specific patient. Typically, it's around two to four weeks where even that subtle cystoid macular edema might bother some patients."



David R. Hardten, MD

Top: CME in an eye untreated by NSAIDs at five weeks. Visual acuity was 20/50. Epiretinal membrane was present preoperatively. Bottom: The same eye after a six-week course of treatment combining NSAIDs and steroids. Visual acuity was 20/20.

Those early postop weeks can become especially fraught with high expectations if your patient is set to undergo a second consecutive cataract procedure, Dr. Hardten notes. "Sometimes, that's right when you're trying to get their second eye done. You want them to be pretty happy with that first result, but when they're dealing with even a subtle amount of cystoid macular edema, sometimes it's hard to have them be happy about the prospect of submitting to the surgery for a second time."

Johnny L. Gayton, MD, in private practice at Eyesight Associates in Warner Robins, Ga., and adjunct professor of ophthalmology at Mercer University School of Medicine, also factors in patient expectations when prescribing topical NSAIDs and sees no reason to stop using them. Dr. Gayton concurs that patients want "premium outcomes" in this age of premium IOLs, but opines that the distinction between visually bothersome CME and macular thickening unaccompanied by patient complaint is meaningless when deciding to use NSAIDs: "If you have as little as 10 to 20 microns of macular thickening, which reduces your contrast, whether it bothers somebody or not is actually baseless. There are patients who are not going to complain if you cut their little finger off; there are other patients who are going to complain at just a slight decrease in contrast sensitivity. If you want the absolute best outcome for each patient, why not give them something that's going to make that better outcome more likely?

"There are lots of reasons to use a nonsteroidal, and not just for the prevention of CME," he continues. "Nonsteroidals help with pain. Nonsteroidals help get inflammation under control more quickly, and any time you get inflammation under control more quickly, you get quicker visual recovery. " Dr. Gayton prescribes NSAID drops for four to six weeks postoperatively in patients with no known CME risk factors, and for a minimum of eight weeks in patients with known risks.

Dr. Gayton remains convinced of the synergistic effect of combining topical NSAIDs with steroids, and likens blocking multiple inflammatory pathways with two different eye drops to competing in mixed martial arts. "IN MMA, you get hit with fists, and you get kicked, both. If you have multiple weapons, you're much more likely to be successful than if you only have one. So you use both a steroid and a nonsteroidal," he says.

Dr. Gayton says that he would prescribe NSAIDs if forced to choose between drug classes, because they are specific and less prone to causing side effects. "You don't get pressure spikes with a nonsteroidal: You do with steroids," he says. Still, he routinely uses steroids with NSAIDs. "You use both to start with, and you get the inflammation under good control, then just continue with the nonsteroidal to prevent the long-term sequelae of inflammation, such as CME."

Dr. Kim, however, maintains that combining NSAIDs and corticosteroids is an unnecessary step in routine eyes, because topical steroids alone can safely do the job of preventing CME in low-risk patients. While he acknowledges that there may be a role for NSAIDs in inflammation-prone patients such as those with severe diabetes, he says that topical steroid monotherapy delivers the same long-term outcome and is generally well tolerated. "We are only looking at use of steroid drops for a very limited time, four to six weeks, and any adverse effects tend to be very limited no matter which medication you're using," he

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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.

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BRIEF SUMMARY OF FULL PRESCRIBING INFORMATION

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1 INDICATIONS AND USAGE

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

2 DOSAGE AND ADMINISTRATION

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

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

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

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

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

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

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

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

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

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

After injection, any unused product must be discarded.

3 DOSAGE FORMS AND STRENGTHS

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

4 CONTRAINDICATIONS

EYLEA is contraindicated in patients with

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

Hypersensitivity reactions may manifest as severe intraocular inflammation.

5 WARNINGS AND PRECAUTIONS

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

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

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

6 ADVERSE REACTIONS

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

8 USE IN SPECIFIC POPULATIONS

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

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

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

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

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

17 PATIENT COUNSELING INFORMATION

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

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says. "The potential adverse effects, including corneal haze, corneal melting and increased IOP are similar, whether you use NSAIDs or steroids for CME prevention."

While he acknowledges that not every cataract patient will need postoperative NSAIDs, Dr. Gayton chooses to err on the side of caution. "Sure, there are people in high-risk categories, but we have all seen folks develop problems that you wouldn't expect. Nonsteroidals make that less likely to happen." In his experience, omitting NSAIDS opens the door to higher incidences of CME. Dr. Gayton relates that with the advent of "dropless" cataract surgery, he continued to prescribe NSAID drops postoperatively—and saw CME cases increase in the dropless patients of colleagues who didn't. "I've had cataract surgery myself," he says. "I'm a low-risk guy, but I used my nonsteroidal. My mother is low risk as well, but I used a nonsteroidal on her."

Long-term Outcomes vs. Short–term Value

In addition to valuing NSAIDs as a means of shutting the door to the early development of CME and speeding visual recovery, both Dr. Hardten and Dr. Gayton prescribe them for pain control. "Another thing to consider is that it may provide some comfort to the patient, because the NSAID has a little bit of an anesthetic effect on the ocular surface," notes Dr. Hardten. "So sometimes that incisional discomfort on the first few days is less with an NSAID."

As a former cataract patient, Dr. Gayton gives credence to patient complaints of postoperative pain and says NSAIDs definitely help. "If people don't hurt, they love it," he says.

Pain control, like speed of visual recovery, is a short-term, quality-of-life measure not evaluated in the OTA. Dr. Kim and his colleagues estimated that topical NSAIDs have an average wholesale price of $70 to $130 per bottle, representing up to $180 in added surgery costs.[2] Even in the face of the OTA's finding that these additional costs may well be unnecessary in the long run, surgeons and their patients seem to consider NSAIDs a worthwhile expense for reasons outside the scope of the study: closer alignment of early visual results with patient expectations, comfort, and overall quality of life. REVIEW

Dr. Kim and Dr. Hardten report no relevant financial interests; Dr. Gayton is a paid consultant for Bausch + Lomb, Shire, Sun and Omeros.

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A Deeper Look at Protocols S and T

An experienced clinician and retinal researcher discusses what the trials' findings might mean for clinical practice.

John A. Wells, MD, Columbia, S.C.

The Diabetic Retinopathy Clinical Research Network, since its inception in 2003, has regularly presented us with new information leading to improved treatments for sight-threatening complications of diabetic retinopathy. Given the rapidly increasing prevalence of diabetes mellitus worldwide, there clearly is a need for new therapies to prevent vision loss in these high-risk patients. With the recent publication of the results of Protocols S and T, the DRCRnet has given us new data that will alter our management of proliferative diabetic retinopathy and diabetic macular edema. Protocol S compared intravitreous ranibizumab 0.5 mg injections to panretinal photocoagulation for the treatment of PDR,[1] and Protocol T compared three treatments for DME: intravitreous aflibercept 2 mg; bevacizumab 1.25 mg; and ranibizumab 0.3 mg.[2,3] In this article, we'll examine each trial more closely, with an eye toward putting their findings to use in our practices.

Protocol S

To understand the significance of Protocol S, it helps to discuss PDR and how we've treated it in the past. Untreated, PDR is a leading cause of blindness in the diabetic population. PRP has been an effective but inherently destructive treatment for four decades. Multiple trials of anti-vascular endothelial growth factor therapy for DME have reproducibly demonstrated significant regression of retinopathy severity with VEGF inhibition.[4-6] This observation led to considerable interest in comparing PRP to anti-VEGF therapy for preventing sight-threatening complications of PDR.

In Protocol S, the primary objective was to compare the safety and efficacy of PRP to intravitreous ranibizumab 0.5 mg injections for the treatment of PDR (the 0.5-mg dose was used because at study initiation, the 0.3-mg dose was not yet Food and Drug Administration-approved or available). The primary outcome of the study was that ranibizumab was non-inferior to PRP, with a non-inferiority limit of five letters.

Important secondary outcomes included an area-under-the-curve (AUC) analysis of vision, changes in visual field, development of DME and rates of vitrectomy for complications such as vitreous hemorrhage and traction retinal detachment.

At 55 sites, researchers randomized 394 eyes of 304 patients with active PDR, vision better than or equal to 20/320 and no prior PRP in a 1:1 ratio to receive either six injections of ranibizumab 0.5 mg at monthly intervals (n=191), or immediate PRP in one to three sessions over a maximum eight-week period (n=203). In the ranibizumab group, subsequent injections were given according to a prespecified retreatment algorithm over the initial two years of follow-up, and supplemental PRP was given in the laser group according to similar criteria. The retreatment decision rested on whether the neovascularization of the disc/neovascularization elsewhere was resolved, persistent but stable, or worsening. Center-involving DME at baseline was allowed in both groups and researchers treated it with ranibizumab injections using the DRCR retreatment algorithm from Protocol I.[7]

At baseline, the groups were well balanced in respect to age, sex, duration of diabetes, mean A1C level and no prior PRP. Mean baseline vision was 75 letters (20/32) in both groups,

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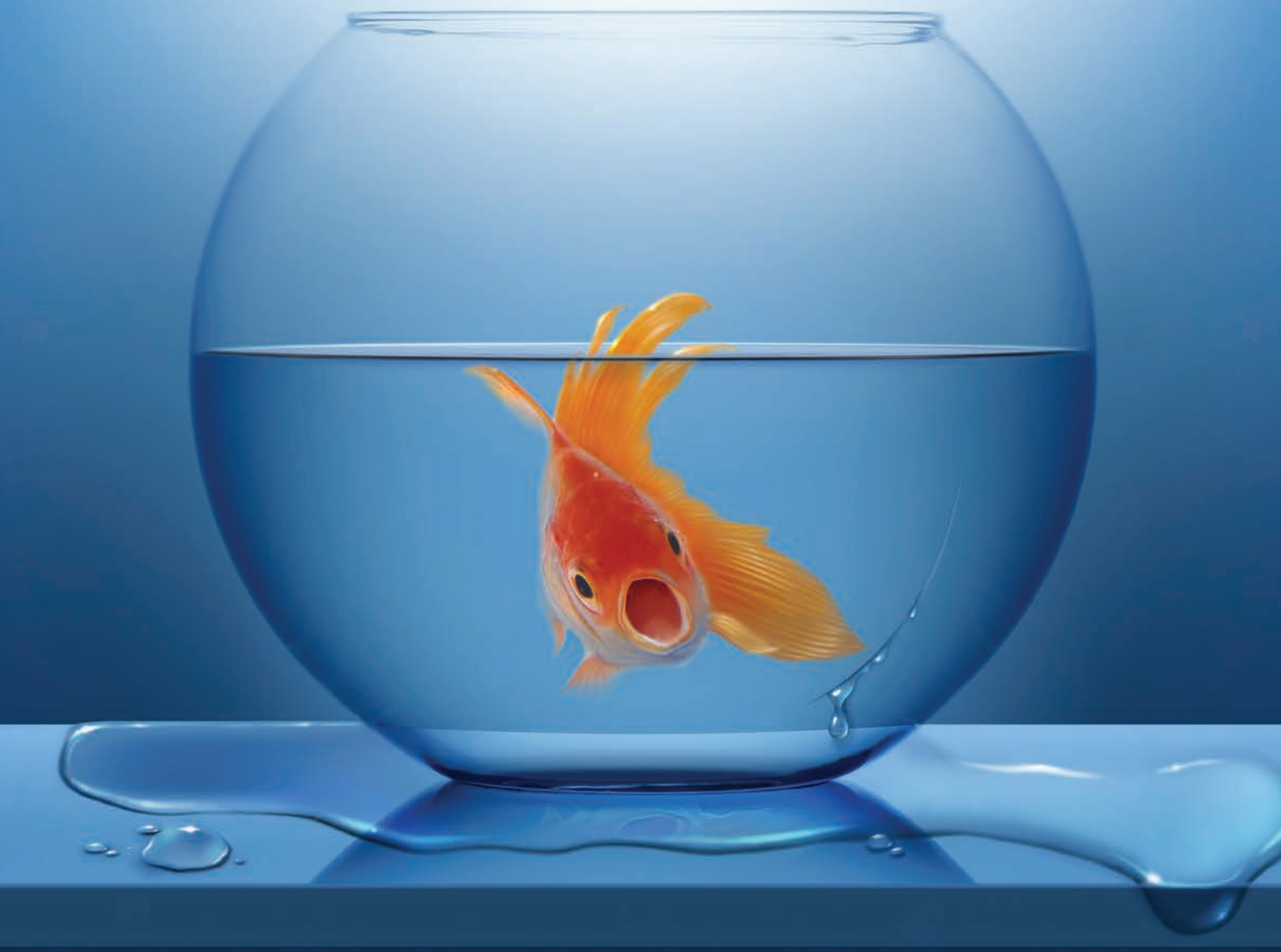

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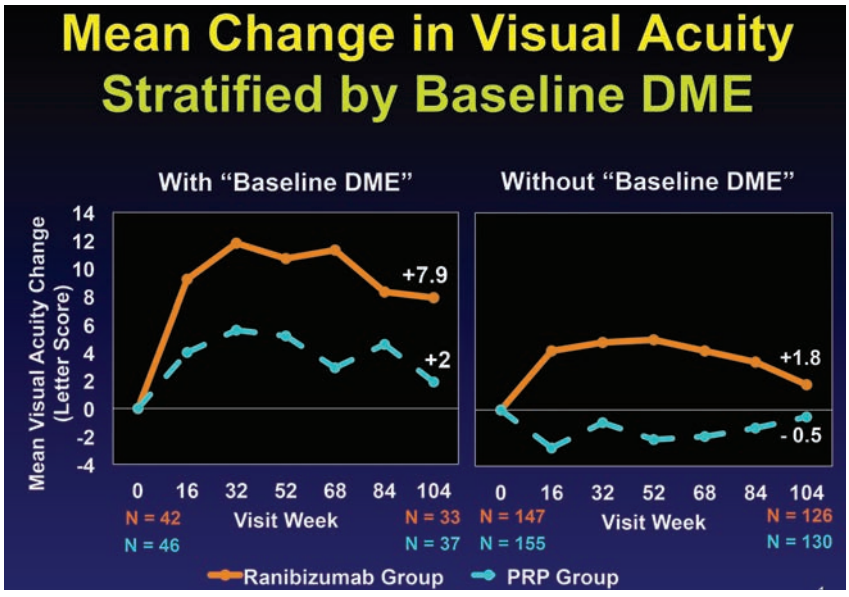

Figure 1. Mean changes in visual acuity at two years in Protocol S in PDR eyes with and without baseline DME. The difference in eyes with baseline DME (left) significantly favors the ranibizumab treatment arm over the panretinal photocoagulation arm, despite both groups receiving ranibizumab injections for DME. The difference in the PRP arm (right) is not significant and met the non-inferiority limit for ranibizumab not being worse than PRP. *All figures provided and copyright owned by the DRCR Network.*

and the mean OCT central subfield thickness was 262 in the ranibizumab group and 249 in the PRP group. Center-involving DME was present at baseline in 22 percent and 23 percent of eyes in the ranibizumab and PRP groups, respectively.

In the ranibizumab group, eyes with baseline DME (n=36) received a median of 14 injections over two years versus a median of 10 injections in eyes without baseline DME (n=133). Only 6 percent of ranibizumab eyes received PRP for rescue treatment over two years, usually during vitrectomy. In the PRP group, 98 percent of eyes received initial PRP according to protocol, and 45 percent received supplemental PRP for worsening PDR at a median of seven months from baseline. In the PRP group, 55 percent of eyes received at least one ranibizumab injection for DME during the two years of follow-up. PRP eyes with baseline DME (n=42) received a median of nine injections, while eyes without baseline DME (n=135) received a median of zero injections through two years.

At the two-year primary endpoint, ranibizumab was non-inferior to PRP with a mean gain of +2.8 letters vs. +0.2 letters in the PRP group. This met the non-inferiority limit of -5 letters. In eyes with central DME at baseline, ranibizumab gave superior improvement in visual acuity with a gain of eight letters versus two letters in the PRP group, despite both arms receiving ranibizumab injections for the DME *(Figure 1)*.

Important secondary outcomes also favored ranibizumab. Visual field loss, measured in decibels by Humphrey analyzers using the 30-2 and 60-4 programs, was significantly less in the ranibizumab arms, with a mean of -23 decibels lost versus -422 decibels in the PRP arm. The pre-planned AUC analysis favored ranibizumab +4.5 letters vs. +0.3 letters for the PRP group. Not surprisingly, given the known effect of ranibizumab on DME, eyes in the ranibizumab group had greater reductions in optical coherence tomography CST, and fewer eyes developed DME during the two years of the study (9 percent vs. 28 percent in the PRP group). Also, rates of vitrectomy were less at 4 percent, vs. 15 percent in the PRP group. Fortunately there were no significant differences between the two treatment arms in ocular or systemic safety events.

So protocol S clearly demonstrated that ranibizumab is at least as effective as PRP in treating PDR (though in both groups about 40 to 45 percent of eyes had active NV at two years). There's significant data that ranibizumab is a better treatment, with superior two-year visual acuity gains, particularly in eyes with baseline DME, and dramatically less visual field loss compared to PRP. Additionally, ranibizumab treated eyes were less likely to develop DME and less likely to require vitrectomy.

However, there are important differences in treatment burden, cost and risk of worsening disease if a patient treated with ranibizumab fails to return for appropriate follow-up. PRP has a proven track record of long-term stability of PDR regression, with most eyes remaining stable for as long as 15 years after laser with no additional treatment.[8] The two-year outcomes thus far don't allow us confidence in the long-term stability of PDR treated with ranibizumab alone. The study is planned for five years, so those ongoing results will inform us as we integrate this data into our clinical practice.

Finally, I believe the most important outcome of this study is the superior vision outcomes with ranibizumab in eyes with PDR and central DME at baseline. Remarkably, eyes in the PRP group that had baseline DME would have received ranibizumab according to the same retreatment algorithm as eyes with DME in the ranibizumab group, yet showed significantly less improvement in vision, suggesting a negative effect of PRP on vision. When adding the benefit to visual field, ra-

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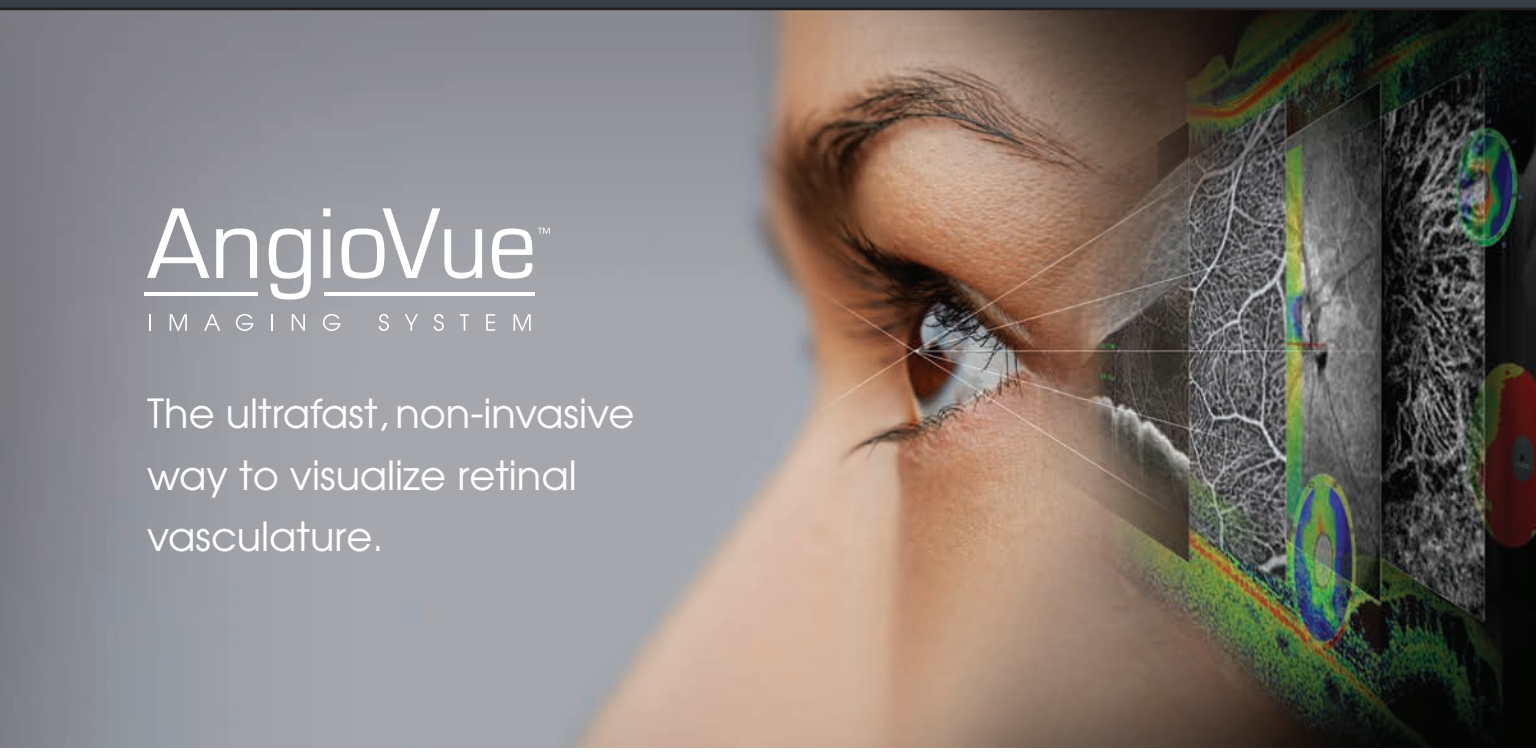

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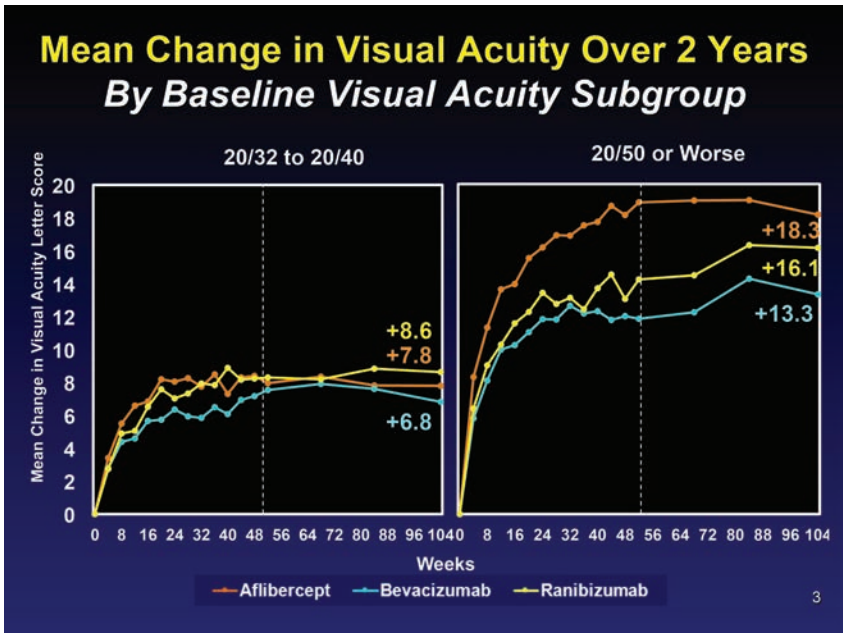

Figure 2. Mean changes in visual acuity by baseline vision subgroup of 20/32 to 20/40 on the left and 20/50 to 20/320 on the right. The difference between aflibercept and ranibizumab seen at one year in the worse vision group wasn't seen at two years.

nibizumab treatment would seem to be the preferred approach in these eyes.

Protocol T

The DRCR Protocol I results, published in 2010, demonstrated the superior visual improvements in eyes with center-involved DME treated with intravitreous ranibizumab 0.5 mg, with prompt or deferred focal/grid laser, over laser alone and intravitreous triamcinolone plus focal/grid laser.[9] This established ranibizumab as the preferred therapy for center-involved DME. Prior to the FDA approval of ranibizumab 0.3 mg for the treatment of DME, bevacizumab 1.25 mg was being widely used off label as a substitute for ranibizumab to treat DME. Similar to the situation with neovascular AMD and the Comparison of AMD Treatments Trials, the DRCRnet organized Protocol T, a non-inferiority study to compare ranibizumab and bevacizumab for DME. Prior to study initiation, aflibercept 2 mg became FDA approved for neovascular AMD treatment. With aflibercept available, the study was changed to a three-way superiority study. The investigators adjusted the ranibizumab dose to 0.3 mg after the FDA approval of that dose for DME in September 2012, shortly after the study began.

In protocol T, 660 eyes with visual acuity of 20/32 to 20/320 and center-involving DME on clinical exam, confirmed by OCT, were enrolled at 89 sites. No prior anti-VEGF therapy in the previous 12 months was allowed, as well as no laser or steroid treatment for DME in the prior four months. The treatment groups were intravitreous injections of aflibercept 2 mg (n=224), bevacizumab 1.25 mg (n=218) or ranibizumab 0.3 mg (n=218). At baseline, the three groups were comparable in terms of visual acuity (68 to 69 letters) and mean OCT central subfield thickness (376 to 390 µm). There was no difference in the percentage of eyes with prior laser for DME (36 to 39 percent) or with prior anti-VEGF therapy (11 to 14 percent). There were also no imbalances in systemic baseline characteristics such as age, duration of diabetes, race or hemoglobin A1C values. Retention in the study was excellent, with more than 95 percent of patients completing the one-year primary outcome visit and more than 90 percent completing the two-year final visit.

Starting at the baseline visit, injections were given as often as every four weeks according to a prespecified retreatment algorithm that was Web-based and determined in real time during the study visit. Essentially, in the first year patients were examined every four weeks and, after the baseline injection, retreatment was given if the eye improved or worsened in vision by five or more ETDRS letters or in OCT CST by 10 percent or more. In the first six months, injections were continued unless the eye achieved 20/20 or better vision and the OCT CST became normal (250 µm or less Stratus equivalent).[10] At or after six months, if the vision and OCT were stable for two consecutive injections and there was persistent edema or vision loss, investigators applied focal grid laser and stopped injections. After that, if the vision or OCT worsened, they resumed the injections. This implies that the protocol tolerated the persistent edema and vision loss after six months and non-protocol treatment for persistent edema wasn't allowed.

In the second year, visits could be extended up to 16 weeks depending on the status of the eye; retreatment in year two was only allowed if the vision or OCT CST worsened. Compliance with protocol treatment was high through two years: Researchers gave 98 percent of required injections, and injections were given when the protocol indicated deferral in only 0.5 percent of visits. Non-protocol alternative treatments were given in three eyes (1 percent), 10 eyes (5 percent) and 1 eye (<1 percent) in the aflibercept, bevacizumab and ranibizumab groups,

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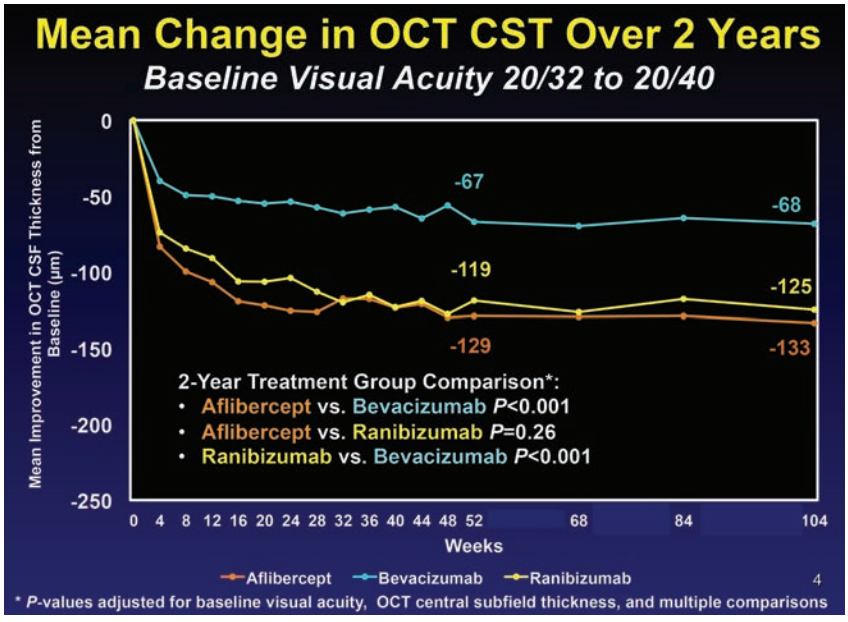

Figure 3. Through two years in Protocol T, bevacizumab-treated eyes had about half as much reduction as the other two treatment groups.

respectively, that met treatment failure criteria.

In the first year, eyes received a median of nine, 10 and 10 injections in the aflibercept, bevacizumab and ranibizumab groups, respectively. In the second year, the number of injections declined by approximately 40 percent, to a median of five, six and six, in the aflibercept, bevacizumab and ranibizumab groups, respectively. The total number of injections was essentially equivalent across the three groups: 15; 16; and 15. So there was no difference in treatment burden between agents.

The decision to apply focal/grid laser was driven by the presence of persistent central DME at six months, and there was a benefit in the aflibercept group compared to the other two agents throughout the two years of the study. In both years, and overall, eyes in the aflibercept group were less likely to require laser. At the end of two years, 41 percent, 50 percent and 64 percent of eyes in the aflibercept, ranibizumab and bevacizumab groups, respectively, received at least one laser treatment, which was statistically significant for all three pairwise comparisons.

The primary outcome of the study was the mean change in visual acuity from baseline at one year. The study was planned for two years to examine longer-term outcomes. For the overall comparison, aflibercept was superior to the other two agents, with a mean of +13.3 versus +11.2 versus +9.7 letters gained for the aflibercept, ranibizumab and bevacizumab groups, respectively. But in year two, the difference between aflibercept and ranibizumab disappeared, while bevacizumab remained inferior to aflibercept but not ranibizumab. But this overall comparison has little clinical utility because there was a very strong interaction with baseline visual acuity.

Prior to the initiation of the study, we hypothesized that eyes with worse vision might have thicker maculae due to higher intraocular VEGF levels, and that the agent with the highest VEGF-binding affinity might be more effective. While there aren't definitive data to support this, at the time the study was planned, it was believed that aflibercept had the greatest binding affinity. So we prespecified a subgroup analysis of eyes with better (20/32 to 20/40) or worse (20/50 to 20/320) baseline vision. Prior DRCRnet studies suggested the median baseline vision in DME was 20/50, so that was chosen as the cut point which put about half of the patients in each subgroup.

In eyes with better baseline vision of 20/32 to 20/40, there was no significant difference between the three agents at one and two years. But in eyes with baseline vision 20/50 or worse, eyes in the aflibercept group gained significantly more vision than either ranibizumab- or bevacizumab-treated eyes. However, in year two, the difference between aflibercept and ranibizumab narrowed and was no longer statistically significant. Bevacizumab remained inferior to aflibercept but not ranibizumab *(Figure 2, p. 78)*.

Gaining three or more lines of vision has historically been considered a clinically significant improvement in clinical trials in ophthalmology. The percentage of eyes gaining three or more lines of vision in the first year of the study was significantly greater with aflibercept than the other two agents: Sixty-seven percent versus 41 percent for bevacizumab versus 50 percent for ranibizumab. But as we have seen previously, these differences disappeared in the second year, with 58 percent, 52 percent and 55 percent of eyes gaining three lines of vision respectively at the two-year final end point. These findings call into question the clinical importance of the differences between the three agents seen at one year.

There were important differences seen in the effectiveness of the three agents in reducing DME as measured by OCT CST. In the eyes with better baseline vision, bevacizumab reduced edema about 50 percent less than the other two agents across the entire two years of the study *(Figure 3)*. In eyes with worse baseline vision, bevacizumab was less effective than the other two agents in the first year, but in year two caught up with ranibizumab but not aflibercept *(Figure 4)*. Addition-

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ally, eyes treated with bevacizumab were half as likely to achieve a normal OCT CST of <250 µm at one year in eyes with better baseline vision. In eyes with worse baseline vision, only 46 percent of bevacizumab eyes versus 66 percent of ranibizumab and 75 percent of aflibercept eyes achieved this degree of anatomic improvement.

In terms of safety, there were no differences between the three agents in rates of ocular adverse events. Rates of endophthalmitis, retinal detachment, inflammation and cataract were low and in keeping with usual clinical experience. There were also no differences found between the three agents in terms of systemic adverse events such as deaths or other serious adverse events. But a prespecified analysis of Antiplatelet Trialists' Collaboration events (non-fatal stroke, non-fatal myocardial infarction and vascular deaths) found a significantly higher rate in the ranibizumab group than bevacizumab and aflibercept: 12 percent vs. 8 percent vs. 5 percent (global p value=0.047; adjusted for baseline variables, p=0.09). This difference has not been seen in multiple previous comparative studies of anti-VEGF agents in either AMD or DME populations, so it's likely that this is a chance finding, recalling that few of these studies, including this one, are sufficiently powered to detect such differences. Additionally, a meta-analysis published in 2014 found no difference in cardiovascular risk between the three anti-VEGF inhibitors.[11]

In summary, Protocol T demonstrated that all three anti-VEGF agents are highly effective treatments for center-involving DME, with significant improvements in vision and reductions in macular edema on OCT at one year that were sustained through two years with fewer injections and lasers than in the first year. In eyes with better baseline vision of 20/32 to 20/40, vision gains of about eight letters were seen in all three groups at one year and maintained at two years. But in eyes with 20/50 or worse baseline vision, aflibercept was superior to the other two agents at one year. In the second year, this superiority was diminished, however, with there being no statistically significant difference between aflibercept and ranibizumab, while bevacizumab remained inferior to aflibercept but not ranibizumab. More interesting is that the percentage of eyes gaining three lines of vision favored aflibercept at one year, but by year two there was no difference seen in the rates of three-line gainers, suggesting that in the long term there may be little clinical difference in the effectiveness of these three agents.

Some important questions remain unanswered. In eyes with better baseline vision, bevacizumab-treated eyes achieved 50 percent less reduction in DME on OCT, and were more likely to require laser. While this didn't result in worse vision through two years, I'm concerned that persistent edema in this group might result in worse vision in the long term unless alternative treatments are given. Because it's more effective at reducing edema and may be more effective at improving vision in eyes with good baseline vision and thicker maculae than bevacizumab,[12] and also is less expensive than aflibercept, I prefer ranibizumab for this subgroup. Although in the worse baseline vision subgroup ranibizumab caught up to aflibercept by two years, I believe that the more rapid improvement seen with aflibercept in the first year cannot be ignored; I still prefer initiating treatment with that agent in this subgroup.

Finally, it's important to realize that these results give no information on the effectiveness of switching agents when there is persistent edema. As stated earlier, this protocol tolerates persistent edema, but I acknowledge that in clinical practice most retinal specialists won't tolerate persistent swelling and will either switch to a different anti-VEGF agent, add laser or use steroids when there is persistent edema after three to six injections. There are currently no clinical trials to confirm the effectiveness or necessity of switching agents. The treatment protocol used in this study is a useful one that gives

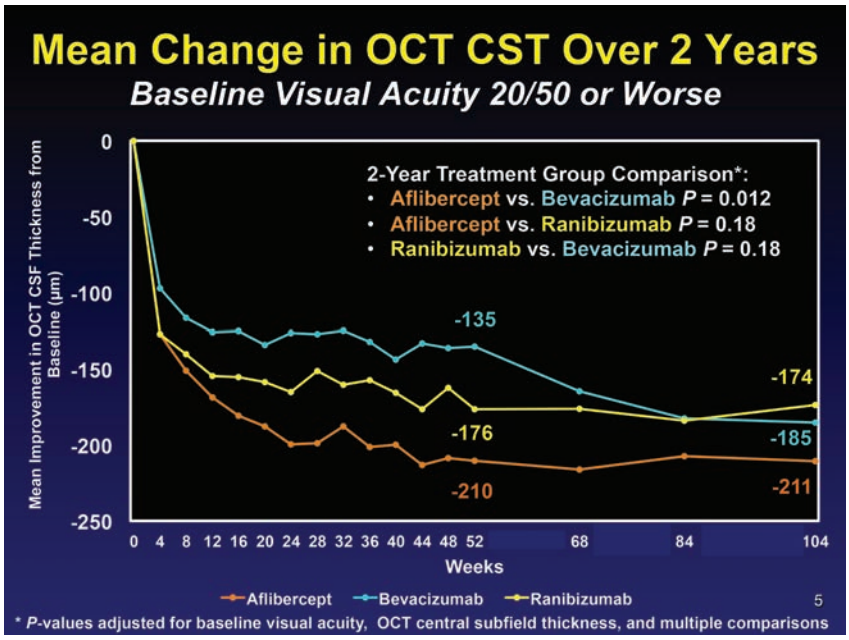

Figure 4. In Protocol T, year one, the bevacizumab group was inferior to the other two groups, but caught up in year two.

excellent results, and can be followed with that knowledge. REVIEW

Dr. Wells is in private practice at Palmetto Retina Center and is chairman of the Department of Ophthalmology of the Palmetto Health-USC Medical Group in Columbia. He can be reached at jackwells@palmettoretina.com. He has received grant support from Genentech and Regeneron. The views expressed by Dr. Wells are his own and not the DRCR Network's.

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Chemical Peels Demystified

A look at the most popular agents for chemical peels and the best ways to employ them.

Teri Kleinberg, MD, Worcester, Mass.

There are so many cosmeceutical products touting universally desirable benefits such as skin tightening, wrinkle reduction and pigment brightening that it can be overwhelming. What's more, the cosmetic representatives that come to my office rattle off lists of exotic-sounding chemicals that I never learned about in medical school or residency. To help get you to that level of proficiency, the following article is the first of a two-part series breaking down well-studied topical agents that have been shown to improve your patients' skin quality and reverse photoaging.

Chemical Peels 101

Chemical peeling is the process of applying chemicals to the skin to destroy the outer, damaged layers, thus accelerating the normal process of exfoliation. The ultimate goals of a chemical peel are to reduce skin dyschromias, eliminate fine rhytids, lighten dark circles and reduce actinic changes.[1] Surgeons have to be careful when approaching peels in the periocular area, as skin thickness in that region can be as little as 0.2 mm. Eyelid skin differs from other skin in that it lacks subcutaneous fat and has a thinner epidermal-dermal junction and a thin but dense dermis.[2] Therefore, it's difficult to extrapolate the effect of chemical peels on the eyelids based on their effect on other skin areas. Chemical peels penetrating much deeper than the superficial dermis are probably best avoided in order to reduce the risk of scarring and cicatricial ectropion. The depth of penetration depends on acid concentration and the timing of application, and is categorized based on histological depth of necrosis.[2] *(See Table 1)*

Types of Peels

There are a multitude of chemical peels available commercially. Two well-studied products that can be titrated to produce superficial to moderate-depth peels, and are safe for Fitzpatrick I to IV skin types *(See Table 2)*,[3] include glycolic acid (GA) and trichloroacetic acid (TCA). *(See Tables 3 and 4)* These products can be combined with botulinum toxin and fillers in order to obtain an overall improvement in wrinkles, skin tone, texture and clarity. Here are their characteristics and risks:

• ***Glycolic acid.*** GA is an alpha hydroxy acid (AHA) found naturally in sugar cane. Other AHAs include citric (from citrus fruit), malic (from apples), tartaric (from grapes) and lactic acid (from milk). It's commercially available in concentrations ranging from 20 to 70% and does require neutralization with an alkaline solution such as 10% sodium bicarbonate solution or water. The gel formulation has a slower penetration time and is easier to control during application.[4] GAs are well tolerated and systemically nontoxic and produce superficial to moderate-depth peels capable of significant effects with few complications.[1] When applied to skin for three to seven minutes, GA can cause epidermolysis and desquamation of epidermal cells. One double-blind, split-face, vehicle-controlled study showed that four weekly treatments of 50% GA improved skin texture, actinic keratoses and fine wrinkling on clinical exam and demonstrated thinning of the stratum corneum, thickening of the epidermal granular layer and increased prominence of collagen

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bundles on histologic exam.[5]

• ***Trichloroacetic acid.*** TCA is a self-limited peel that does not require neutralization, and which has proven to be a relatively safe and effective agent for the periocular region.[3] The concentration of TCA is most predictive of the depth of peel: 10 to 25% for intra-epidermal effect and 30 to 40% for penetration to the papillary dermis.[1] A histopathological study of varying concentrations of TCA applied to eyelid skin in a layered fashion (initial application by cotton-tipped applicator with five minutes of drying time, followed by a second application) demonstrated that even sequential 50% TCA applications failed to penetrate deeper than the papillary dermis.[1] Theoretically, the acid must penetrate to the deep reticular layer of the dermis for scarring and contracture to occur.[1]

• ***Risks to consider.*** It's well worth remembering that increased peel depth, higher acid concentration and longer exposure times increase the risk of scarring and post-inflammatory pigment changes. For GA, experts recommend starting with a lower concentration for the initial peel and gradually increasing the strength over subsequent sessions.[6]

Minor side effects during and immediately after the peel include erythema, stinging sensation, pulling sensation, mild burning, scaling and transient post-inflammatory hyperpigmentation.[5,6]

Patient Selection

It's important to have realistic expectations. Superficial to medium-depth peels produce the best results with mild facial rhytids and minimal dyschromias.[3] Superficial peels are effective for freckles, epidermal melasma (blotchy facial pigmentation) and epidermal hyperpigmentation; moderate-depth peels can reduce senile lentigines (small brown patches).

Table 1: Classes of Chemical Peels[1]

Chemical Peel Level	Histological Level of Necrosis	Description
very superficial	stratum corneum	Exfoliative destruction of the stratum corneum without wound below the stratum granulosum
superficial	epidermal	Destruction of part or all of the epidermis anywhere from stratum granulosum to basal cell layer
medium	papillary dermal	Destruction of epidermis and part or all of the papillary dermis
deep	reticular dermal	Destruction of epidermis and papillary dermis extending into reticular dermis

Nevi, dermal and mixed melasma, dermal post-inflammatory hyperpigmentation and seborrheic keratoses respond poorly to superficial and medium-depth peels.[1] If you need to treat deep rhytids and excessive skin, you should combine a chemical peel with traditional plastic surgery.

Evaluate each patient's skin type using the well-known Fitzpatrick scale, which refers to the ability of skin to acquire a tan or burn after UV light exposure. Skin types I to III don't usually develop post-inflammatory hyperpigmentation and are excellent candidates for undergoing chemical peels.[1] Skin types IV to VI, however, have a much higher risk of hypo- or hyperpigmentation complications. Consider the patient's lifestyle, particularly the ability and motivation to care for the skin in the pre- and post-treatment period. Approach thicker and oilier skin types with more caution, as penetration depths may be more uneven.[1]

Contraindications to chemical peeling include poor healing due to open lesions, radiation, diabetes and photosensitizing medications (e.g., doxycycline, exogenous estrogens). Use of isotretinoin (Accutane) is a strict contraindication for chemical peels for at least one year.[1,3] Oral contraceptives may predispose a patient to hyperpigmentation and should be stopped, if possible, in the peri-peel period.[1] Be sure to pretreat patients with any history of herpes simplex with oral antiviral medications starting one day

Table 2: Fitzpatrick Classification of Skin Types[3]

Fitzpatrick Skin Type	Reaction to UV Light Exposure	Typical Complexion
I	Always burns, never tans	Pale white skin, freckles; blond or red hair; blue eyes
II	Usually burns, tans minimally	White, fair skin; blond or red hair; blue, green, or hazel eyes
III	Sometimes burns, tans uniformly	White skin; any hair or eye color
IV	Rarely burns, always tans well	Moderate brown skin
V	Very rarely burns, tans very easily	Dark brown skin
VI	Never burns, never tans	Deeply pigmented darkest brown skin

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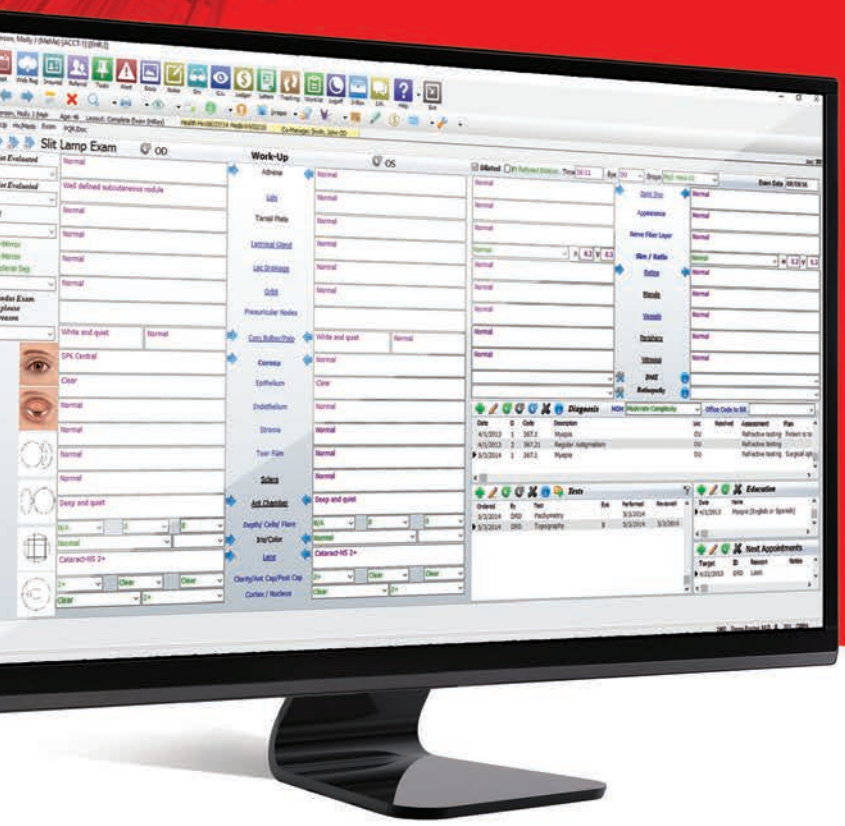

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Table 3: Glycolic Acid and Trichloracetic Acid Peels[1,4]

Peel Depth	Glycolic Acid	Trichloroacetic Acid	Visual Endpoints	Healing Time
Very superficial	30 to 50% for one to two minutes	10% in one coat	Mild erythema	Two to four days
Superficial	50 to 70% for two to five minutes	10 to 30%	Erythema with patches of light frosting	Five days
Medium	70% for three to 15 minutes	35 to 50%	White frosting without visible erythema	A week

prior to the chemical peel and until re-epithelialization is complete.[1,3]

Preparation

Be sure to obtain photos and informed consent prior to performing any chemical peel procedure. Pretreatment of the skin with retinoic acid preparations (which will be covered in more detail in part two of this series) may allow for better penetration of the chemical peel and faster recovery times. However, this may not be necessary in the periocular area unless the skin is unusually sebaceous or hyperkeratotic.[3]

Tell the patient to clean the intended treatment area thoroughly with a facial cleanser or non-residue soap the day before the peel, and to avoid makeup or moisturizers. Immediately prior to the peel, clean the patient's face with acetone or isopropyl alcohol to ensure that any trace of dirt, makeup or oil is removed.[2,3]

Application

First, position the patient's head so that it's tilted at 45 degrees to prevent pooling of the acid.[1] Apply a protective layer of petrolatum ointment or zinc oxide paste to the lateral canthus, nasolabial fold, oral commisures and alar groove—all areas that are particularly prone to acid pooling. A cotton-tip applicator can be used to apply gel solutions; a fan-tip brush may be more appropriate for liquid formulations.[3] The peel should be applied evenly and quickly with a neutralizing agent readily available. If performing a full-face peel, start with areas of thicker skin first, such as the forehead, and then proceed sequentially to the cheeks, nose, chin, and, finally, the perioral and periocular regions to avoid overtreating areas of thinnest skin.[1,3] Skin should be placed on stretch for an even coat, and application should extend through the brow and a little beyond the hair- and jaw-line to avoid clear areas of demarcation.[1]

A fan directed at the treatment area may relieve mild stinging and burning.

Table 4: Advantages/Disadvantages of Acid Peels[4]

	Glycolic Acid	Trichloroacetic Acid
Advantages	-Mild erythema -Mild desquamation -Fast recovery time -Useful in photodamage	-Low-cost -Uniform application and penetration -Self-neutralizing
Disadvantages	-Burning sensation during application -Uniform application difficult -Mandatory neutralization -Skin ulceration if application too long or skin pH reduced	-Stinging and burning during application -High concentrations not recommended for Fitzpatrick V and VI -Hypo/hyperpigmentation can occur

Post-peel Care

The treated areas of skin should be kept moist with a petrolatum-based product. Patients should be counseled to avoid sun exposure, heavy exercise and sweating immediately after a peel.[1] They should also avoid picking at the peeling skin, as this can predispose the underlying skin to increased risk of infection, persistent erythema, hyperpigmentation, and scarring.[1] A medium-depth peel will cause periocular edema, erythema, crusting and pigmentation for approximately one week after the procedure.[1] There's no need for oral antibiotics in superficial to medium-depth peels unless there is evidence of infection. Once re-epithelialization has occurred, skincare regimens, sunscreens and makeup can be restarted. To minimize risks of post-inflammatory hyperpigmentation, the patient should avoid sun exposure for at least six weeks post-peel.[3] Peels should not be repeated any sooner than two weeks, but may be repeated as often as desired as long as you notice evidence of additional benefit.[1,6] REVIEW

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How to Manage Juvenile Open-angle Glaucoma

Early diagnosis and aggressive treatment are paramount, since these patients are often initially asymptomatic.

Alicia Menezes, MD, and Joseph Panarelli, MD, New York City

Juvenile open-angle glaucoma can be a challenging disease to catch early and treat properly, due to the nature of the disease itself as well as the characteristics of some of its younger sufferers. If you know what to look for, however, and respond with prompt, effective treatment, you can help save the JOAG patient's vision. In this article, we'll share our tips for diagnosing JOAG and how to perform a surgical procedure that gives patients the best chance for a successful outcome.

JOAG: What We Know

Juvenile open-angle glaucoma is considered a subset of primary open-angle glaucoma, affecting about 1 in 50,000 persons (males and females equally). The definition has been controversial but generally takes into account the age of onset. The European Glaucoma Society defines JOAG as open-angle glaucoma with onset between the ages of 10 and 35 years.

JOAG demonstrates an autosomal dominant inheritance pattern, and research has found associations between JOAG and gene mutations on chromosome 1-1q21-q23. This locus is known as GLC1A, and contains the gene TIGR (trabecular meshwork induced glucocorticoid response) or MYOC,[1,2] which codes for the myocilin protein. The exact function of this protein and its involvement in glaucoma is currently unknown. Forty mutations of the TIGR/MYOC gene have been identified in both juvenile and adult open-angle glaucoma, and genetic analyses have revealed that 8 to 63 percent of JOAG patients have a TIGR/MYOC mutation. Common findings among JOAG patients include early onset of disease, very high IOP and a strong family history of glaucoma.[3,4] Histopathologic study of the trabecular meshwork in JOAG patients by Kyushu University's Akihito Tawara, MD, and Hajime Inomata, MD, revealed an abnormally compact trabecular meshwork with an accumulation of extracellular material in the trabecular spaces.[5]

Clinical Findings

Juvenile open-angle glaucoma is generally asymptomatic in its early stages. Unlike primary infantile glaucoma, signs such as enlargement of the cornea and globe, breaks in Descemet's membrane, corneal edema, epiphora and photophobia aren't present in patients with the onset of open-angle glaucoma in later childhood or adolescence. Symptoms are rare but may include blurred vision and ocular pain from elevated intraocular pressure. Visual loss accompanies the later stages of the disease and often leads to patients seeking ophthalmic evaluation. Axial myopia has been associated with JOAG. Clinical signs include severe IOP elevation, often in the range of 40 to 50 mmHg. Given the lack of early symptoms, presentation is often late, and advanced cupping of the optic nerve is often noted on initial evaluation. Gonioscopic features include an open anterior chamber angle with high iris insertion and prominent iris processes.[1] Normal-appearing optic discs and angles do not, however, rule out the diagnosis of JOAG.

The diagnosis of JOAG can be straightforward in the setting of a markedly elevated IOP and glaucomatous cupping of the optic disc. The more challenging cases are those teenagers who present with a modest IOP elevation and a healthy-appearing disc. To help diagnose these tougher cases,

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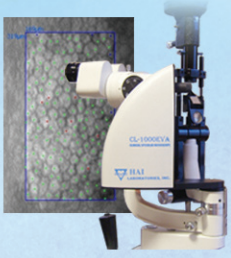

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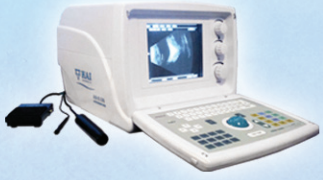

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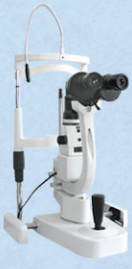

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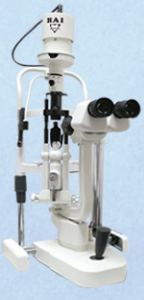

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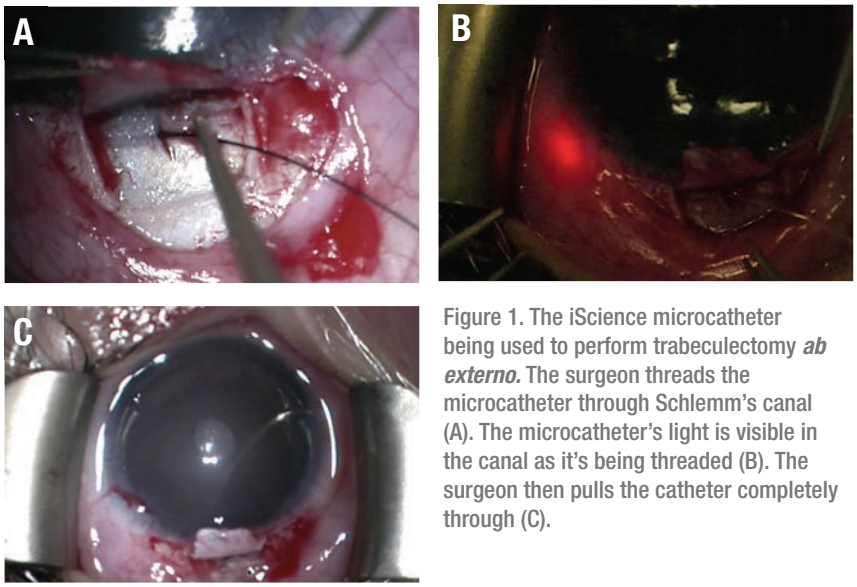

Figure 1. The iScience microcatheter being used to perform trabeculectomy ***ab externo.*** The surgeon threads the microcatheter through Schlemm's canal (A). The microcatheter's light is visible in the canal as it's being threaded (B). The surgeon then pulls the catheter completely through (C).

note that risk factors for JOAG include male gender, myopia and a family history of glaucoma.[1] Monitor teenagers with ocular hypertension closely with periodic assessment of the IOP, optic discs and visual fields. At the time of initial evaluation, obtain baseline visual fields, stereo photographs of the optic disc and a retinal nerve fiber layer thickness assessment with optical coherence tomography. Despite limited normative data, OCT measurements are beneficial for longitudinal assessment and identifying early progression.

Exclude secondary causes of open-angle glaucoma when evaluating young patients with suspected JOAG. Note that pigment dispersion syndrome, uveitis, ocular trauma and steroid use can all result in elevated IOP and glaucoma, and a good clinical exam and review of systems is important to rule out any evidence of these conditions.

Treatment

Although up to 83 percent of JOAG patients eventually require surgical intervention,[7] medical therapy may act as a bridge to more definitive surgical treatment. First-line topical therapy includes beta blockers, prostaglandin analogs and carbonic anhydrase inhibitors. Use alpha agonists with caution, or avoid them altogether, in young patients with JOAG, as potential adverse reactions have been reported in infants and toddlers, including bradycardia, hypotension, hypothermia, hypotonia, apnea and lethargy.[8]

When medications fail to control the IOP, the physician has to turn to surgery. Here's a look at your options:

• ***Angle procedures.*** Angle-based surgical procedures are generally performed first, and are often effective in reducing the IOP and minimizing potential short- and long-term complications. The choice between goniotomy and trabeculotomy depends upon surgeon preference and experience.

Trabeculotomy, via an *ab externo* approach, has been reported to have a success rate of up to 86 percent in treating JOAG, with 14 percent of patients requiring additional surgical intervention to control IOP.[9] Trabeculotomy *ab externo* may be used to incise the trabecular meshwork over 360 degrees using a suture or the iScience microcatheter. *(See Figure 1)*

Newer surgical techniques, such as gonioscopy-assisted transluminal trabeculotomy, have been developed and found to be useful in this patient population, as well. When performing the GATT procedure, the surgeon makes a small, initial 1-to-2 mm nasal goniotomy, and advances a microcatheter circumferentially through Schlemm's canal. The catheter is pulled through to create a 360-degree cleft. The major benefit of *ab interno* procedures such as goniotomy, GATT and Trabectome is that they're performed entirely through a corneal incision, avoiding conjunctival and scleral incisions—and subsequent scarring—altogether.

In cases where angle surgery fails to control IOP, further surgical options include external drainage procedures such as trabeculectomy with mitomycin-C and glaucoma drainage implant surgery, as well as cyclodestructive procedures.

• ***Trabeculectomy.*** Researchers have reported success rates with trabeculectomy ranging from 50 to 87 percent in JOAG patients.[11-14] Obtaining and then maintaining a well-functioning filtering bleb in a child can be difficult, as younger patients have a more robust healing response, often resulting in progressive subconjunctival and episcleral fibrosis. Postop management, including adherence to eye-drop regimens and manipulations such as laser lysis of flap sutures, is complicated in very young children due to their inability to fully cooperate.

Some clinicians have used antifibrosis therapy with MMC to reduce the amount of scarring in young patients, and this approach can result in lower IOPs following trabeculectomy in JOAG patients.[11] However, the use of MMC has also been associated with an increased risk of vision-threatening complications, including hypotony maculopathy and bleb-related infection. The rate of hypotony maculopathy has been reported to be as high as 20 percent, which may be due to the increased incidence of axial myopia in these patients.[11] One study found a 17-percent incidence of bleb-related infections in children with functional blebs.[12] Given these findings, use cau-

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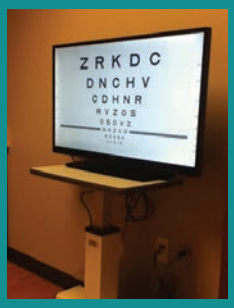

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tion when performing trabeculectomy with MMC in younger children.

• ***Glaucoma drainage implants.*** Due to the higher likelihood of conjunctival scarring in JOAG patients and the increased risk of sight-threatening complications with trabeculectomy (in younger patients), GDI surgery is a reasonable alternative. The most commonly used GDIs are the Ahmed glaucoma valve (New World Medical, Rancho Cucamonga, Calif.) and Baerveldt glaucoma implant (Abbott Medical Optics, Santa Ana, Calif.). Prior studies with at least one year of follow-up have documented success rates following pediatric GDI surgery ranging from 31 percent to 97 percent.[15] There is, however, limited long-term data regarding GDI use in children and young adults.

Another potential issue with GDI in children is that proper positioning of the tube in the anterior chamber can be particularly challenging. Reduced scleral rigidity in these patients makes anterior migration and rotation of the proximal tube tip more common than in adults.[16] Tube migration can result in direct contact or proximity of the tube tip to the posterior corneal surface and may contribute to endothelial cell loss and eventual corneal decompensation. Tube positioning as shown in Figure 2 is preferred; note the longer length and how it's angled away from the corneal endothelium.

Given that patients with JOAG are young and often have very elevated IOPs with advanced disc damage, our preference is to use a 350-mm^2 Baerveldt implant. We use a 7-0 polyglactin suture to temporarily ligate the tube of this non-valved device and allow three to four weeks for a capsule to form around the scleral explant.

For young children, we perform planned ligature release in the operating room between postoperative weeks three and four using a Hoskins lens and green diode laser.[17] We make visualization of the ligature for laser lysis

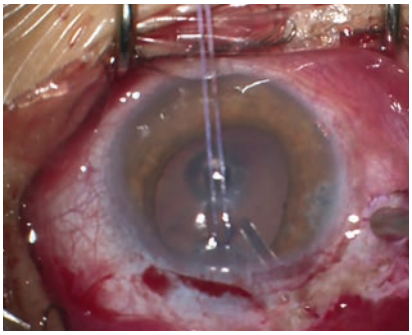

Figure 2. This 13-year-old with JOAG required the placement of a glaucoma drainage device to control his IOP.

easier with the use of corneal tissue as the patch graft material. Fluid elevation of the conjunctiva overlying the scleral plate and profound softening of the globe help confirm ligature release. If you're uncertain if the ligature has been released, you can use B-mode echography to demonstrate the presence of fluid around the drainage plate.

To replace lost volume and provide increased resistance to flow through the tube, you can inject sodium hyaluronate (10 mg/ml) into the anterior chamber immediately following ligature release. This limits the duration and magnitude of hypotony and prevents anterior chamber collapse. For younger children, we often will let the ligature release spontaneously, but will monitor them more closely after the first few postoperative weeks. For older, cooperative children and adults, you can perform planned ligature release by laser lysis followed by an anterior chamber injection of sodium hyaluronate (10 mg/ml) in the office. We prefer to maintain patients on atropine 1% and reduce the number of aqueous suppressant medications whenever possible after the third postoperative week in anticipation of the tube opening. These techniques can help prevent prolonged periods of hypotony and its secondary complications following ligature release.

Although GDI surgery and trabeculectomy have evolved over the years with advances in surgical technique and better ways to modulate wound healing, unique challenges exist in young patients with JOAG as compared to older adults. Careful preop assessment and postoperative monitoring, with frequent follow-up and attention to the early detection and management of adverse events, can improve long-term outcomes. REVIEW

Dr. Menezes is a resident physician at New York Eye and Ear Infirmary of Mt Sinai. Dr. Panarelli is an assistant professor of ophthalmology and associate residency program director at the New York Eye and Ear Infirmary of Mt Sinai. They have no financial interest in any of the products mentioned.

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[1] **Epitropoulos**, **Alice T.**, **Donnenfeld**, **Eric D.**, et al., Effect of Oral Re-esterified Omega-3 Nutritional Supplementation on Dry Eyes. Cornea 2016;0:1-7

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Right Between Your Eyes

A look at ocular/nasal interactions and how they can affect our pharmaceutical therapies.

Mark B. Abelson, MD, CM, FRCSC, FARVO, David A. Hollander, MD, MBA, and Andrew Hertsenberg, PhD
Andover, Mass.

Sometimes, the dual nature of the scientist-physician can pull in opposite directions: Science often adopts a reductionist view to drill down on fundamental mechanisms, while medicine emphasizes more of an integrated, systems-based approach to biological inquiry. In ophthalmology, we often find ourselves on the scientific side of this dichotomy, focusing on the eye as a singular structure. Yet it is, of course, enmeshed in anatomical, vascular and nervous system elements that are critical to healthy ocular physiology. This month, we'll try to bridge this divide by examining the relationships between two neighboring systems, the eye and the nose. Our focus will be the nasolacrimal structures that constitute a shared fluid compartment, as well as the sensory elements common to both structures.

Nasolacrimal Plumbing

The nose and eyes function as complementary sensory organs vital to exploring and understanding our physical world. Though sight and smell are two very different senses, the eye and nose are intimately connected by the nasolacrimal apparatus, the drainage system that carries tears from the ocular surface to the nose and ultimately to the gastrointestinal tract.

The nasolacrimal apparatus is a group of tissues around the eye and nose that are essential to tear production and drainage *(See figure, facing page)*. The apparatus includes the lacrimal gland, the lacrimal canaliculi and the nasolacrimal duct. Lacrimal glands are responsible for the production and secretion of the aqueous portion of the tear film, and are under parasympathetic nervous innervation originating from the pterygopalatine ganglion. Thus, drugs with anticholinergic effects cause both dry mouth and dry eye via attenuation of normal lacrimal gland innervation. The gland is organized into groups of cells that produce and secrete tears onto the ocular surface. The tear film is distributed over the ocular surface by eyelid closure (blink); at the same time, this muscular contraction forces a fraction of the tear volume out and away.

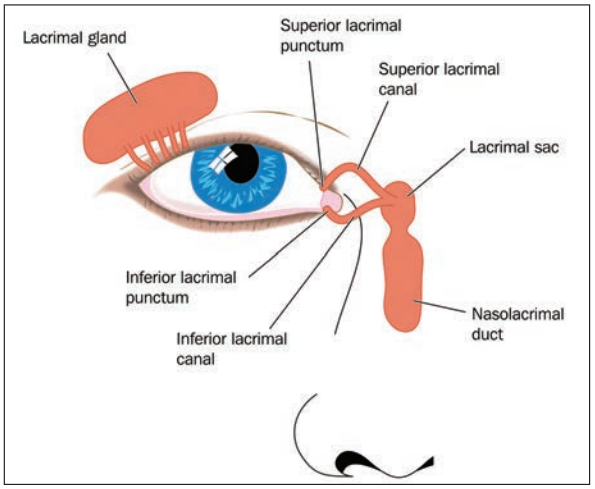
The lacrimal canaliculi are tube-like structures that run from the eye to the lacrimal sac. The ends of the canaliculi, the superior and inferior puncta, are found on the inside of the eyelids adjoining the medial canthus. In addition to spreading tears, blinking causes a transient opening of the lacrimal sac, creating a negative pressure that draws tears in to drain through the puncta and canaliculi. From the lacrimal sac, tears drain via the inferior turbinate and ultimately down the throat. It's not uncommon for patients to associate some eye drop medications with a noticeable taste as the diluted drops travel this route.

The funnels of nasolacrimal drainage are the puncta. A number of conditions, including infections, congenital syndromes and the adverse effects of some drugs (such as the anti-neoplastic docetaxel) can cause punctal stenosis, leading to partial or complete occlusion of the drainage pathway.[1,2] Punctal plugs are used to the same end for patients with dry-eye syndrome; by occluding drainage, the plugs increase the length of time tears remain on the ocular surface. Plugs have also become a popular vehicle for depot drug delivery, a topic covered in previous installments of Therapeutic Topics.

This article has no commercial sponsorship.

Deeper Connections

From the canaliculi, tears drain into the lacrimal sac and then the nasolacrimal duct, emptying into the nasal cavity. This explains why the nose runs when one cries or eyes water excessively. The first division of the trigeminal nerve innervates both the ocular surface and nasal mucosa and is responsible for the nasolacrimal reflex—the tearing that occurs upon stimulation of the nasal mucosa. This response likely occurs, at least in part, to provide additional tear flow to wash away allergens or other noxious stimuli from both the eyes and the nose via the nasolacrimal apparatus. It may also represent a relatively unexplored aspect of dry-eye disease: A 2010 study comparing reflex tearing in normal subjects to dry-eye sufferers found a significant delay in response time in the latter group. (*Maffei C, et al. IOVS 2010;51:ARVO E-Abstract 3398*) This is likely an aspect of the delay seen in the natural compensatory mechanisms in patients with dry eye.[3]



The interconnected nature of the nasolacrimal system. Tears drain through the puncta and canaliculi, and ultimately flow down the throat.

A recent innovative approach to dry eye currently in development from Oculeve and Allergan takes advantage of the reflex using a nasal reflex stimulator. In an open-label, six-month study of patients with moderate to severe dry eye, use of the stimulator resulted in significant improvement in Schirmer's scores, corneal fluorescein staining and symptom scores.[4] This novel technology is a first in terms of implementing device technology as a patient-driven complement to drugs or tear substitutes as therapies for dry eye.

The movement of fluid between the eyes and nose raises important questions and concerns about topical eye drop absorption and potential systemic exposure. As the nose is a highly vascular tissue, drugs administered intranasally are almost certain to be absorbed into the bloodstream and may exert systemic effects. This is important for physicians prescribing topical eye drops that may have negative systemic side effects, as it has been demonstrated that some drugs are absorbed from the tear fluid by the epithelial lining of the nasolacrimal duct.[5] An example of this is the glaucoma drug timolol, which, when absorbed systemically, can cause a number of adverse effects including insomnia, hallucinations and cardiac effects. Similarly, when absorbed through this route, high-dose topical corticosteroids can exert the systemic side effects more commonly seen with oral steroid use.

Pathophysiology

The connection between the eyes, nose and even mouth comes into sharp focus in allergic disease, where the co-morbidity of rhinitis and allergic conjunctivitis is estimated to be 60 to 90 percent.[6] Patients often report symptoms in the eyes, nose and mouth (itchy palate is most common), and it's likely that nasolacrimal drainage of allergens plays at least some part in this.[7] Using the conjunctival allergen challenge model, researchers here at Ora Inc. showed that 82 percent of subjects experienced an itchy palate after allergen was applied directly to the ocular surface via eye drops (*Schoemmell E, et al. IOVS 2016;57:ARVO E-Abstract 310*). This confirms the notion that ocular allergen exposure alone can cause extraocular effects downstream via allergen, histamine and mediator passage through the nasolacrimal apparatus, highlighting the important link between these tissues. Therefore, the nasolacrimal apparatus is of particular importance in the pathophysiology of allergic disease, acting as the interface and conduit between the external and internal milieu that reacts to allergen exposure with rhinitis (runny nose, congestion, post-nasal drip) and conjunctivitis (red, itchy eyes). Therapy follows the same path, as in clinical trials of the ocular antihistamines Bepreve (Bausch + Lomb) or Lastacaft (Allergan), which both reduced symptoms of allergic rhinitis as well as conjunctivitis.[8,9] This dual efficacy holds true for other ophthalmic anti-allergics, as well.[10] One might even make the argument that ocular antihistamines are the superior mode of therapeutic drug delivery for both the eye and the nose, particularly with respect to relief of acute itching.[10]

It's generally thought that retrograde movement of fluid in the nasolacrimal system is negligible or nonexistent. One study examined this question by using a modified Jones Test, wherein drainage from the ocular surface through the nasolacrimal apparatus is assessed by adding fluorescein to the ocular surface and measuring the amount subsequently collected from the nasal cavity. When fluorescein dye was placed on the ocular surface, it was found in the nose within five minutes in every subject tested. Conversely, when fluorescein was administered intranasally via nasal spray, fluorescein was

never detected on the ocular surface in any of the subjects tested.[11] While this study suggests that there is no significant movement of fluid from the nose to the ocular surface, this is proving to not be the whole story. Nasal allergen challenges can induce ocular symptoms,[12] a finding difficult to reconcile with unidirectional movement of fluids through the nasolacrimal apparatus. Interestingly, in a study using Ora's Allergen Biocube, a controlled environmental exposure unit that provides a controlled allergen concentration in the air, subjects treated with an intranasally delivered drug (*Nasapaque; 3E Therapeutics*) saw a significant reduction in rhinorrhea, congestion and nasal and ocular itching. (*Gomes P, et al. IOVS 2016;57:ARVO E-Abstract 305*)

More Than Meets the Eye

These findings are significant for multiple reasons. In general they suggest that both nasal and ocular symptoms of allergic rhinitis or conjunctivitis may be treated with an intranasal or ocular administration of drug, easing disease management for patients. At a more basic level, though, they show that the link between the nose and eye is complex and dynamic. In another study, for example, the researchers suggest that histamine released following nasal allergen exposure could stimulate afferent nasal nerves, which then induce an efferent parasympathetic response, thereby causing a "nasal-ocular" reflex.[13] This response is likely also a target for the selective activity of many H1 histamine receptor antagonists. Inhibiting histamine release in the nose blocks this pathway from the start, reducing or eliminating the conjunctivitis that typically results downstream of antigen challenge.

It is likely that not only allergic but also inflammatory reactions are interconnected in the nose and eye through these same channels. The immunopathology of dry-eye disease has been amply studied, with age-related changes in the ocular and nasal immune system teased out on many levels. One area of interest is nasal-associated lymphoid tissue, or NALT, and its near relation, conjunctiva-associated lymphoid tissue, or CALT. Some researchers have suggested that a deterioration of immune responses of aging NALT contributes to the ocular inflammation observed in dry eye.[14] Surgical closure of the nasolacrimal duct in a rabbit model of dry eye significantly decreases the inflammatory responses of conjunctiva-derived T cells, suggesting that communication with NALT somehow enhances the inflammatory response of this ocular mucosal immune system.

Another connection between the eye and the nose is through secretory IgA. Though this mucosal defense mechanism is predominantly directed against pathogens, for many years dry-eye researchers have been studying a possible role of secretory IgA derived from lacrimal glands and other ocular sources. Intranasal immunization induces IgA not only in the nose and salivary glands but also on the ocular surface,[15,16] indicating that NALT can serve as an inductive site for ocular mucosal IgA responses. The integrated nature of NALT and the ocular mucosal immune system even provides some rationale for intranasal immunotherapeutic targets for inflammatory dry-eye disease.[14] Certainly the notion of intranasal local immunotherapy benefiting ocular allergic disease is attractive, as is the elegant notion of using the ocular or nasal allergic response as a marker for response to systemic immunotherapy.

There's certainly more to learn about the dynamics of ocular-nasal interactions, and future studies are likely to inform and modify future therapeutic development. For example, what role does the local vasculature play in ocular-nasal interactions? How might depot formulations in the eye impact downstream tissues? Understanding this ocular-nasal complex will surely lead to innovation in treatment delivery and multisystem therapies of the future. REVIEW

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Spondyloarthritis and Anterior Uveitis

Researchers for the SENTINEL Working Group looked at the prevalence of spondyloarthritis in patients with anterior uveitis in a multicenter, observational, prospective study. The study's findings demonstrate that a large percentage of patients with clinically significant AU also have undiagnosed SpA.

The study looked at consecutive patients with AU who were human leukocyte antigen-B27 positive or HLA-B27 negative, with more than one episode of AU separated by at least three months. The study excluded patients previously diagnosed with SpA.

Of the 798 patients, most being men with a mean age of 45 years, 60 percent were AU HLA-B27 positive, and 40 percent had recurrent negative AU HLA-B27. A total of 50.2 percent and 17.5 percent of patients presented with axial and peripheral SpA according to ASAS criteria, respectively. Patients with AU who were HLA-B27 positive were more frequently diagnosed with axial (69.8 percent vs. 27.3 percent $p<0.0001$) and peripheral SpA (21.9 percent vs. 11.1 percent $p<0.0001$) than patients with recurrent negative AU HLA-B27. In general, there were no important differences between the groups in terms of ophthalmologic variables.

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Juanola X, Loza E, Cordero-Coma M.

Retinoblastoma Research

Researchers from the Children's Oncology Group Study sought to determine whether insurance status, race and ethnicity correlate with increased retinoblastoma invasiveness as a marker of both risk and time to diagnosis in a retrospective, case-control study. The study's findings suggest a higher rate of more advanced disease associated with non-private insurance, non-white race and Hispanic ethnicity.

Researchers looked at 203 patients from the United States enrolled in the Children's Oncology Group trial ARET0332, a study of patients with unilateral retinoblastoma requiring enucleation. Each surgical participant underwent institutional pathologic review and central pathologic review to determine the presence of well-defined histopathologic features correlating with a higher risk of disease progression. Insurance status, race and ethnicity were compiled from the study record for each patient.

On institutional pathologic review, the results of the study revealed that non-private insurance, non-white race and Hispanic ethnicity all correlated significantly with a greater rate of high-risk pathologic findings. Hispanic ethnicity remained a significant predictor. On central pathologic review, these correlations remained but did not reach statistical significance. The researchers theorize that these differences likely resulted from institutional versus central pathologic reviews, and they also appeared to result from a higher likelihood of patients in minority groups being misclassified as high-risk by institutional pathologists. The researchers note that these findings may also be due to delays in diagnosis for these groups, and say further focus should be on where in the diagnostic process potential delays exist so that these barriers are overcome to care for these groups.

Ophthalmology 2016;123:1817-1823

Green AL, Chintagumplala M, Krailo M, Langholz B, Albert D.

Surgical Management of Boston KPro

In a retrospective chart review, researchers set out to determine the rate of Boston type 1 keratoprosthesis-related corneal melts, leaks and extrusions that required surgical repair. They also evaluated the post-melt repair visual outcomes. The study determined that patients who undergo KPro with severe ocular surface disease are at greater risk for corneal melts, leaks and extrusions.

The researchers examined 110 patients (128 eyes) who received a KPro

between November 2004 and December 2010. They also evaluated the rate of complications, risk factors for melts and post-melt repair visual outcomes.

The study found that 20 eyes from 18 patients developed KPro-related melts that required surgical repair. In total, there were 33 episodes of melt-related complications, the rate of which was 16 percent. The surgical repairs included lamellar patch grafts (15), KPro removal with penetrating keratoplasty (seven), reassembly of KPro onto a new cornea (four), replacement of KPro (three), suturing of a leak (three) and enucleation (one). The majority of eyes (18/20) did not regain their best post-KPro vision at final follow-up. Significant risk factors for melt included previous infectious keratitis ($p<0.0001$, odds ratio: 12.50, 95 percent confidence interval, 4.02-38.9) and conjunctival deficiency (including Stevens-Johnson syndrome, mucous membrane pemphigoid and chemical injury).

Cornea 2016;35:1049-1056
Chan CC, LoVerde L, Qiang J, Nordlund ML, Holland EJ.

Pigmentary Glaucoma and Nuclear Cataracts

In a retrospective, consecutive case series, researchers sought to describe a new association between nonsenile nuclear cataracts and pigmentary glaucoma in patients with controlled intraocular pressure. Investigators say that awareness of the purely nuclear cataract and its clinical presentation can assist the clinician when approaching the patient with pigment dispersion and decreasing vision.

Researchers examined nonsenile nuclear cataracts seen in patients with pigmentary glaucoma with controlled IOP in a single glaucoma specialist practice. The average age of these patients was 50.3 years, a much younger age than the average age seen in senile nuclear sclerotic cataracts. Eight eyes of seven patients with pigmentary glaucoma and visually significant cataract that underwent cataract removal were reviewed.

They found that patients with pigmentary glaucoma developed rapidly progressing, nonsenile nuclear cataracts, with resulting myopic shifts between 4 and 13 D from baseline in less than two years. The patients had controlled IOP, and there were no associations between medication use and cataract development. According to researchers, this is a new association and warrants further investigation.

J Glaucoma 2016;25:547-550
Mosaed S, Haider A, Kim D, Zhang Z.


The Pros and Cons of Using Mitomycin-C

It's a potentially toxic drug that must be used with care—but when managed properly, it can help to protect vision long-term.

Mark B. Sherwood, MD, Gainesville, Fla.

Today, the use of mitomycin-C in glaucoma surgery has become commonplace, and we're happy to use it on almost every patient. Perhaps because we use it so frequently, we tend to get a little blasé about how strong a drug we're using. In reality, mitomycin is a powerful agent with long-term effects, both good and bad. It's an important tool that needs to be used with caution.

Here, I'd like to review some of what we've learned about mitomycin-C over the past 25 years, to help ensure that we use this drug appropriately and safely. I'll also note some of the differences between mitomycin and 5-fluorouracil, another drug in wide use for similar purposes.

Mitomycin-C: An Overview

Mitomycin-C is an alkylating, antitumor antibiotic, generally used in surgery because of its ability to inhibit fibroblast proliferation and suppress vascular ingrowth—two parts of the healing process that can undercut the beneficial effect of a trabeculectomy bleb by producing scarring that stops aqueous outflow. One of mitomycin's active metabolites cross-links with DNA, causing selective interruption of DNA replication, thus inhibiting mitosis and protein synthesis. This makes mitomycin cytotoxic for both fibroblasts and microvascular endothelial cells, so it not only reduces the production of fibroblasts, but also the microvascular blood supply to the area treated.

One reason mitomycin is so effective is that it's not dependent on the cell-cycle phase. In contrast, 5-FU is only effective at certain phases of the cell's life cycle. You can see the results of this difference in studies that compare the effectiveness of the two agents. For example, in a study done in 1993, researchers took cells from eyes that had been treated with distilled H_2O, 5-FU or mitomycin and then grew them in culture to reveal their relative state of health.[1] *(See charts, top of page 104.)* They took the cells after different periods of time postoperatively—at one hour, five days and 30 days postop. The cells were then cultured for 15 days.

The left-hand graph shows the relative impact on cell growth when the cells were taken from the treated area one hour after surgery. The cells treated with water show a fairly exponential growth rate over the following 15-day period. The cells that were exposed to 5-FU show delayed growth for seven to nine days, but then they resume growing at about the same rate as those treated with water. The third line in the graph shows that when treated with mitomycin, even after 15 days the cells' growth rate is still very slow compared to the other two treatments.

The middle graph shows the growth when the cells were taken for culturing five days after treatment. As you can see, after a short delay of two or three days, the water- and 5-FU-treated cells' growth rates are almost the same, suggesting that the cells treated with 5-FU are approaching normal condition by about seven days postop. With the mitomycin-treated cells, you see a fairly significant delay and much slower growth rate compared to the other treatments thereafter. The third graph shows the impact on growth rate when the cells were cultured 30 days postoperatively. At this point, the growth rates of the water- and 5-FU-treated cells are

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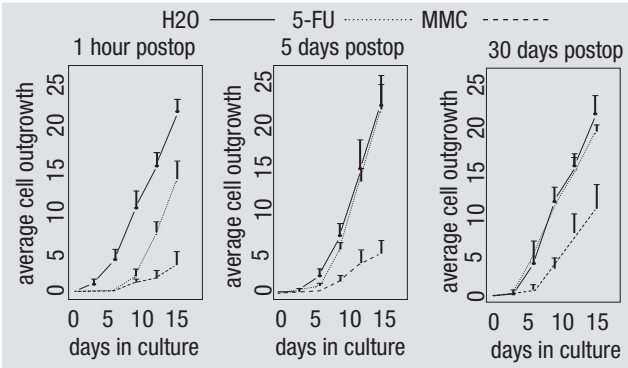
overlapping and essentially identical, while the mitomycin-treated cells still show a slowed growth rate.

The bottom line of this experiment is that you can almost think of the 5-FU as having a temporary effect on the fibroblasts. After that temporary effect—lasting five to seven days—wears off, the cells pretty much resume growing as if they had not been treated. In contrast, mitomycin has a long-term effect on the fibroblasts; even 30 days after treatment the cells' growth rate is still reduced.

Tissue Growth after Trabeculectomy



The growth rate of scleral fibroblast cells in culture after treatment with H_2O, 5-FU or MMC in a rabbit model. Cells were taken from the treated area at the times indicated and then cultured. In each case, MMC-treated cells grew more slowly than those treated with 5-FU after 15 days in culture. Cells treated with 5-FU that were cultured five or 30 days after treatment exhibited growth curves similar to cells treated with water. (Khaw PT, Doyle JW, et al, 1993)[1]

Another 1993 study compared bleb survival rates following the application of water, 5-FU and two different strengths of mitomycin over a 30-day postoperative period in a rabbit model.[2] *(See graph below.)* The control blebs (treated with water) were almost all gone by day 14; the ones treated with topically applied 5-FU lasted until day 25; about 60 percent of the blebs treated with mitomycin 0.2 survived until day 30; and virtually all of the blebs treated with mitomycin 0.4 survived to day 30. (One takeaway from this is that we have the ability to titrate this effect; we don't have to choose between no effect and maximum effect—with all of the potential side effects potentially accompanying the latter.)

Given these data, it's reasonable to ask why anyone would still use 5-FU. For one thing, 5-FU produces good results in many patients. If you can control the scarring response early on and get a good bleb established, you often can go on to get a very good long-term result. 5-FU can accomplish that in many patients. In addition, two studies comparing the use of mitomycin versus 5-FU in normal-tension glaucoma patients found that outcomes were often better when 5-FU was used instead of mitomycin.[3,4]

Minimizing Toxicity

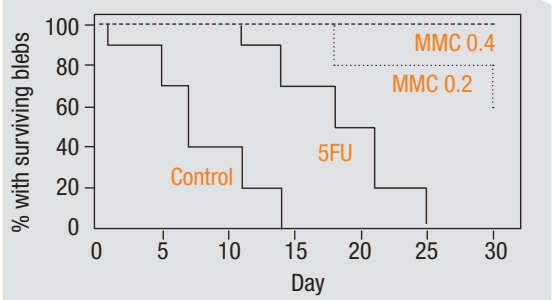
Mitomycin is clearly effective at prolonging the life of a bleb, but it creates this effect by interfering with DNA replication, so it's not hard to imagine how this can backfire. The side effects of treatment with mitomycin were well-illustrated by a 1991 study involving four New Zealand white rabbits.[5] In this study, 50 µl of 0.5 mg/ml mitomycin—a fairly strong formulation—was injected into the anterior chamber. Within 24 hours the eyes showed severe inflammation; within 72 hours the researchers found corneal opacification. By two weeks post-injection, the iris and ciliary body were necrotic and the cornea was distressed; the endothelium was basically gone. Clearly, full-strength mitomycin in the anterior chamber is highly toxic.

Other studies have demonstrated similar damaging effects:

- One study reported limbal stem cell deficiency after subconjunctival injection of 0.1 to 0.2 ml of 0.2 mg/ml mitomycin, a delivery method that more and more surgeons are using.[6]
- Another study found greater corneal endothelial cell loss at three months in patients getting trabeculectomies with mitomycin than in those undergoing trabeculectomy without mitomycin.[7]
- A third study using a relatively low 0.1 to 0.2 mg/ml dose to treat the intact sclera in a rabbit model found pathologic changes in the ciliary epithelium, nerves within the ciliary body and the ciliary body capillaries even six to 12 months postoperatively.[8]

In clinical practice, we rarely see problems that are clearly connected to the use of mitomycin. However, as these studies demonstrate, mitomycin may cause limbal cell deficiency, corneal endothelial cell loss, changes in the ciliary body and

Bleb Survival After Different Treatments



Blebs treated with water, 5-FU and two different strengths of mitomycin-C (in a rabbit model) show dramatically different survival rates. (Khaw PT, Doyle JW, et al, 1993)[2]

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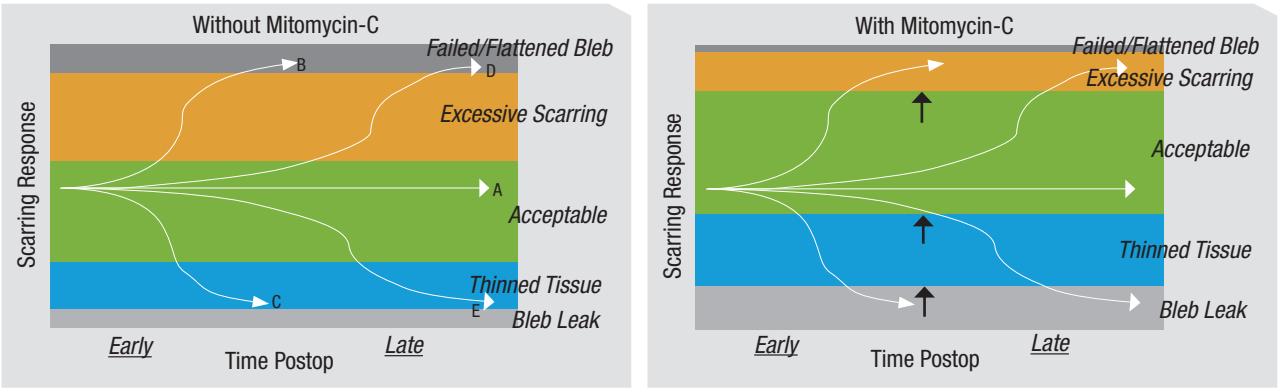
Likelihood of Scarring Responses With and Without Mitomycin-C



Using mitomycin-C alters the likelihood of different outcomes following trabeculectomy. The green zones represent acceptable capsule thickness; the orange zones represent excessive scarring, leaving the capsule too thick and pressure higher than desired; the upper dark grey zones, blebs that have scarred over completely and failed; the blue zones, blebs with thin tissue and possibly too low a pressure or leakage; and the lower light grey zones, leaky, thin, avascular blebs. The curving lines running across the charts represent different patients. Even without MMC, 60 or 70 percent of trabeculectomy patients will do beautifully (like patient A). Some, like patient B, will get excessive scarring and a failed bleb early on, while others, like patient D, will get that result sometime later. Some patients, like patient C, will develop thinning tissue early on, while others, like patient E, will have this outcome late in the postoperative course—possibly even years after the surgery. The differences between the left and right charts show how the likelihood of different outcomes shifts when mitomycin-C is used. Using mitomycin shifts the likely scarring response away from excessive scarring and towards thinned tissues.

reduced aqueous production.

Obviously, mitomycin-C is not something we should be using carelessly. Fortunately, we have a number of ways to titrate the impact of the drug. We can control:

- the concentration we use;
- the method of application (e.g., via sponge or injection);
- the duration of application;
- the surface area treated; and
- the amount of rinsing we do after the application is complete.

A study published in 1997 demonstrated the impact of the amount of surface area treated with mitomycin.[9] The study involved 24 New Zealand white rabbits; one-third of them were treated over a large 8x10-mm surface area, one-third over a smaller 4x2-mm area, and a no-treatment group acted as a control. At 21 days researchers found that the large treatment area led to improved bleb survival ($p<0.039$), larger bleb area ($p<0.009$), better bleb height ($p<0.005$) and a more diffuse bleb that wasn't as thin-walled or localized as that seen in the other two groups.

The reason for wanting to create a large, diffuse bleb—which may sound counterintuitive to the uninitiated—is that a small, localized bleb tends to generate a "ring of steel" around the area you've treated. This leads to thinning of the tissues that you've treated, because the aqueous has nowhere to go beyond that localized area. To avoid this, you want to create a wide, diffuse bleb with a large surface area, perhaps using a lower concentration and shorter duration to limit toxicity.

The amount of irrigation we apply has also been shown to affect how much mitomycin makes it into the anterior chamber, which (as already noted) can have negative effects. In one 1995 study, researchers put a 6x4-mm cellulose sponge, soaked in mitomycin 0.5 mg/ml, on the eyes of a rabbit for five minutes.[10] Then, one eye was irrigated with 10 ml of saline for one minute; the other eye was left without irrigation. Then they looked at the aqueous levels of mitomycin over the course of an hour. The eyes which received irrigation to wash off the mitomycin had much lower mitomycin concentrations at all time points, and a continuous drop in concentration after 15 minutes. The eye not irrigated showed a continuous rise in aqueous mitomycin level over the course of the hour.

Given all of these factors that are within our control, it would be convenient to have a formula to guide us, in terms of which concentration to use, how large an area to cover, how long to apply it and how long to rinse the eye after application. Unfortunately, such a formula doesn't exist, because different eyes react differently to the same use of mitomycin (in the same surgery performed by the same surgeon). The results of seemingly identical treatment can range from a thick, encapsulated bleb to a nice diffuse, not-too-thin bleb to a very thin, avascular bleb. In fact, our inability to predict how a given patient will respond to mitomycin undoubtedly accounts—at least in part—for the less-than-100-percent rate of excellent outcomes associated with trabeculectomy.

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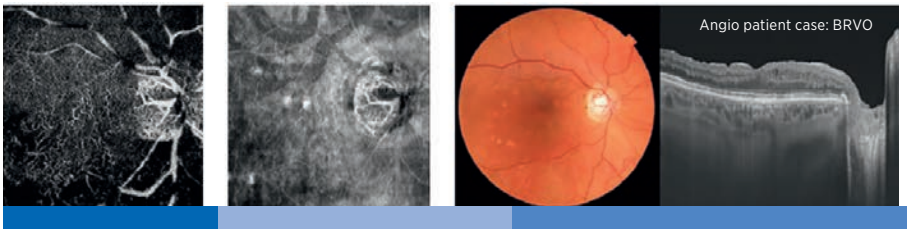

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We do know a few things. We know that younger, fitter patients heal better than older, less-well patients. We know that patients of African ancestry tend to scar more than Caucasian patients. We know that patients with one eye that develops an encapsulated bleb have more risk of developing one in the other eye. But on the whole, we're partly guessing; we really don't know how a patient is going to respond to a trabeculectomy surgery. The best we can do is make an educated guess, based on our experience and the limited data that's available.

The Impact of MMC

As surgeons, we tend to think of mitomycin-C as a positive agent, which in general it is. However, it's not a cure-all. What it does is shift the likelihood of certain types of outcomes in a direction that is more favorable to our patients' long-term vision and comfort *(as illustrated in the charts at the top of page 106)*. Essentially, by using mitomycin, we've shifted the likely response away from excessive scarring and towards thinned tissues.

Of course, these responses—too much or little scarring—will sometimes occur whether we use mitomycin or not. Mitomycin simply changes the relative postoperative risks toward less risk of excessive scarring and a failed bleb, and greater risk of thin tissues and bleb leaks. Again, mitomycin is not a cure-all; you have to pick your poison.

My intention here is not to minimize the value of mitomycin. We do tend to get better outcomes when we use it than when we don't, and there's no question that reducing excessive scarring is a significant change. But it's easy to focus on the potential complications that can result from the use of mitomycin. We all think about the potential for bleb leaks, endophthalmitis and blebitis. There is reason for concern, but it's also important to keep your perspective.

Consider a study published in 1997 that compared the number of patients developing endophthalmitis each year at the Bascom Palmer Eye Institute, divided into two groups based on whether or not mitomycin was used during the surgery.[11] From 1989 to 1991 there was no mitomycin use; on average, three patients per year developed endophthalmitis. Then, as mitomycin became part of some surgeries in '94 and '95, the number jumped. In 1995 in particular, the group receiving mitomycin had a

significantly higher number of cases of endophthalmitis than the non-mitomycin group—five, compared to one. This clearly suggests that using mitomycin may lead to more endophthalmitis. On the other hand, we're talking about one to six cases of endophthalmitis per year out of a very large number of patients undergoing trabeculectomy surgery at Bascom Palmer during this period. Furthermore, these numbers only present one side of the story; they don't tell us how many blebs would have failed, but didn't because of the mitomycin.

The reality is, use of mitomycin dramatically increases the number of blebs that continue to function for many years—blebs that may not have continued to work if we hadn't used mitomycin. That's the reason we use it. If we get an extra 15 patients to do well long-term out of every 100, adding one extra patient with a problem out of that 100 might be considered to be a reasonable trade-off, especially since glaucoma is potentially vision-threatening if not adequately controlled. Remember: People with glaucoma most commonly go blind because of a lack of pressure control—not because of the complications of surgery.

Making the Best of It

Back in the early 1990s, many surgeons were reluctant to use mitomycin. Today, however, very few glaucoma surgeons fail to use mitomycin on the vast majority of their surgical patients. Mitomycin is a very useful and effective tool, but it's not a perfect solution to the problem of scarring. It's very effective at decreasing fibrosis and improving bleb survival, but it increases bleb thinning and side effects, especially long-term. Sometimes it's too effective; sometimes it's not effective enough. It's a potentially toxic agent, and individual variations make the results of using it unpredictable. We get better at using it as a result of experience, but we have to recognize that the outcome for any given patient is beyond our ability to predict.

A few basic tenets for its use have held up. Because the effects are localized to the area treated, it's important to treat a large surface area to decrease the risk of a "ring of steel" forming, with a thin ischemic anterior bleb. Rinsing the eye thoroughly with BSS is helpful in minimizing the damaging effects described earlier. Some surgeons use more intense mitomycin treatment on

younger patients because of their superior healing, but it's important to remember that the younger the patient, the longer the bleb has to last and the greater the risk that, over time, a thin bleb will allow an infection to get inside the eye. For example, if the infection rate is half a percent per year, a 90-year-old patient who survives five years has a 2.5 percent total risk. But if the patient is 30 and may live another 50, 60 or 70 years, that half-percent-per-year risk becomes much more significant. So you always have to weigh the effectiveness of your treatment against the possible risks.

People have been trying to develop alternative surgeries that don't require a bleb, such as the minimally invasive glaucoma surgeries, but as everyone knows, the weakness of those pro-cedures is their less-dramatic reduc-tion in pressure. At the same time, people have spent many years trying to develop better agents for getting an antifibrosis effect when creating a bleb, but they haven't found any-thing else that works as well as mito-mycin—at least so far. That's the conundrum: Even though there are risks associated with using mitomycin, the risk of losing vision is far greater if our surgery fails to lower the patient's pressure over the long run. REVIEW

Dr. Sherwood is a professor of ophthalmology and director of the Center for Vision Research at the University of Florida. He is a past recipient of the American Academy of Ophthalmology's Honor Award.

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Topcon Unveils a New OCT System

Topcon has introduced the newly designed 3D OCT-1 Maestro, with the focus on automation and ease of access. Topcon says Maestro simplifies the process of capturing the optic nerve and macula by imaging both in a single scan. The new design boasts a 50,000 A-scans/sec spectral domain OCT with color fundus camera, fully automatic operation (alignment, focus and capture), 12 x 9- mm wide-field OCT scan with reference database and automatic layer segmentation analysis of total retina; nerve fiber layer; ganglion cell layer + inner plexiform layer; and GCL + IPL + RNFL.

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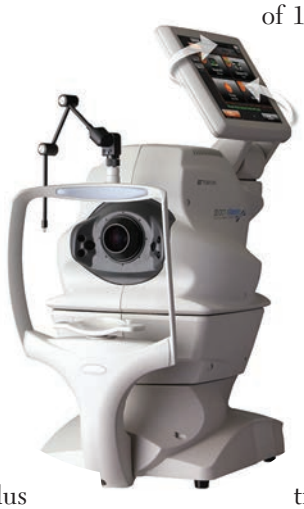

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Volk Optical Adds Gonio Lenses

Volk has introduced single-use gonio lenses to provide maximum convenience and safety to patients, without compromising image quality for visualization, diagnosis and laser treatment, the company says. Volk specifically uses single-use three- and four-mirror gonio lenses, which provide high image resolution of the anterior chamber angle, peripheral retina and posterior pole, similar to the images captured with Volk's glass gonio lenses.

Both the three- and four-mirror lenses have an image magnification of 1x and 1x laser spot. The three-mirror gonio lens has mirrors angled at 60, 66 and 76 degrees, eliminating gaps in the visualized fundus. The four-mirror gonio lens's mirrors are equally angled at 63 degrees for visualization of the entire anterior chamber.

Volk claims that the new single-use lenses eliminate the potential for cross-contamination of infectious disease, as well as the costly reprocessing of reusable lenses.

For more information, visit volk.com.

LENSTAR Gets Hill-RBF Calculator

Haag-Streit's newly introduced Hill-Radial Basis Function calculator, included in the next EyeSuite software cycle available to LENSTAR users, provides a new system for intraocular lens power selection.

The Hill-RBF uses pattern recognition and data interpolation to determine IOL power. Haag-Streit believes that the advantage of pattern recognition for selecting an IOL power is its use of adaptive learning. In this system, short, normal and long eyes are viewed as patterns. The Hill-RBF IOL power selection system also uses the boundary model, which indicates to the user when the calculator is performing within a defined area of accuracy.

Haag-Streit notes that unlike older, static theoretical formulas, this approach will be updated on a regular basis.

For more information, visit rbfcalculator.com.

Bausch + Lomb Launches EZ-24

Bausch + Lomb says its new EZ-24 Easy-Load lens delivery system provides smooth and easy delivery of the SofPort IOL through a 2.4-mm incision, resulting in a simple procedure and minimal postprocedural irritation.

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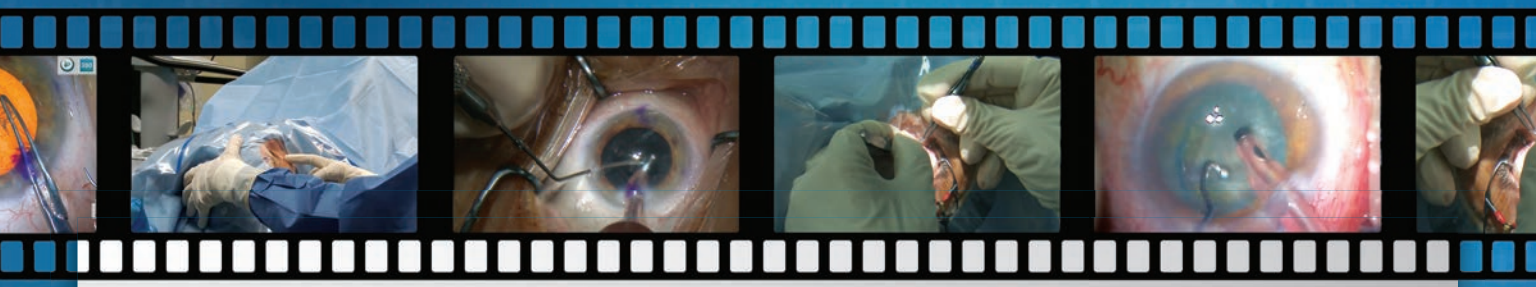

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Richard Mackool, MD, a world renowned anterior segment ophthalmic microsurgeon, has assembled a web-based video collection of surgical cases that encompass both routine and challenging cases, demonstrating both familiar and potentially unfamiliar surgical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

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

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

1. Present a method of preventing iris prolapse during phacoemulsification in eyes with floppy iris
2. Present techniques to accurately position a toric IOL in eyes with a small pupil

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Zeiss recently announced the wireless integration of its Essential Line of digital refraction instruments with popular electronic medical record software systems such as Compulink, Crystal, OfficeMate, ExamWriter, My Vision Express, OD Link, Practice Director and Revolution EHR.

Now Zeiss customers can send data wirelessly from EL instruments to the now compatible EMR software. This allows data from the Zeiss instruments to be loaded into the EMR software as the patient undergoes the exam process, ensuring that relevant data is immediately accessible to the doctor.

The Zeiss EL instruments that work with the EMRs include: Visulens 500 Auto Lensmeter; i.Profiler plus Aberrometer/Topographer; Visuref 100 Autorefractor/Keratometer; Visuscreen 100/500 Acuity Systems and Visuphor 500 Digital Phoropter.

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Review of Ophthalmology®

A 49-year-old woman presents with eye pain that's resistant to pain medications.

Cindy X. Zheng, MD, Carol L. Shields, MD
Ocular Oncology Service, Wills Eye Hospital, Philadelphia

Presentation

A 49-year-old Caucasian female was managed by a general ophthalmologist for intermittent pain and redness of her right eye. The patient had initially presented to the general ophthalmologist eight months prior, at which time it was noted that she had sectoral injection of her superficial and deep episceral blood vessels with a normal dilated fundus examination, suggestive of episcleritis or scleritis. She was advised to take oral naproxen, but there was minimal improvement of her signs and symptoms, despite compliance with her medication.

The ophthalmologist tried several other regimens over the next few months, including topical prednisolone acetate 1%, topical difluprednate 0.05%, topical olpatadine 0.2% and topical cyclosporine 0.05%. However, none of these medications helped to relieve her symptoms. Approximately one month prior to presentation, she developed a constant, severe headache, lasting more than five hours per day. Repeat dilated fundus examination at that time demonstrated a mass in her right eye, suspicious for ring melanoma despite best-corrected visual acuity of 20/20 in both eyes. As part of her workup, she had magnetic resonance imaging of her brain and orbits, which was concerning for an intraocular mass *(Figure 1)*. Based on these findings, she was referred to Wills Eye Hospital's ocular oncology service for further evaluation.

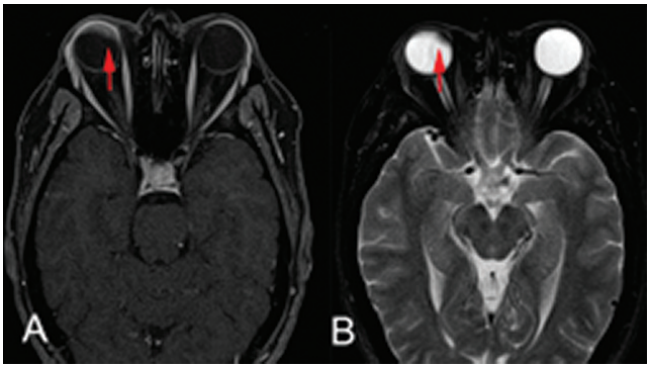
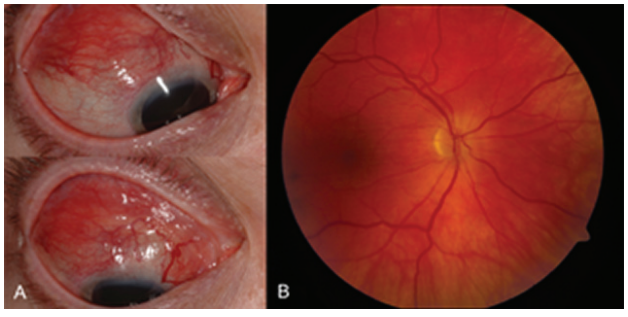


Figure 1. Post-contrast (A) T1-weighted magnetic resonance imaging with fat suppression and gadolinium enhancement, and (B) T2-weighted magnetic resonance imaging of brain and orbits showing an intraocular mass in the right eye, as indicated by arrow.



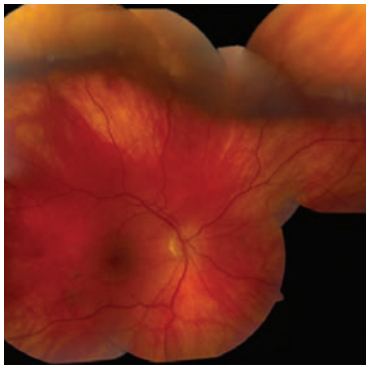


Figure 2. (A) Right eye revealing sectoral injection and engorgement of episcleral and underlying scleral blood vessels. (B) Right fundus showing horizontal retinal striae throughout macula and blunted foveal reflex. Figure 3. Montage of right fundus showing large elevated mass superiorly.

Medical History

The patient had a past medical history of seasonal allergies for which she took loratadine as needed. She did not have any additional ocular history or chronic medications. There was no personal or family history of cancer. She had no history of tobacco smoking or excessive alcohol intake. The review of systems was unremarkable.

Examination

Ocular examination revealed best-corrected visual acuity of 20/20 in each eye. The pupils were equal, round and reactive bilaterally without afferent pupillary defect. Extraocular motility and confrontation visual field exam were full OU. Intraocular pressure by Goldmann applanation tonometry was 18 mmHg OD and 17 mmHg OS. Anterior segment and dilated fundus examination OS were unremarkable.

The anterior segment OD revealed sectoral injection of the superficial and deep episcleral blood vessels from 9 to 3 o'clock *(Figure 2A)*. On dilated fundus examination the optic nerve and blood vessels were within normal limits, but there were horizontal retinal striae throughout the macula, a blunted foveal reflex and a large elevated mass measuring approximately 25 mm at its base and 5 mm in thickness and without subretinal fluid *(Figures 2B and 3)*.

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

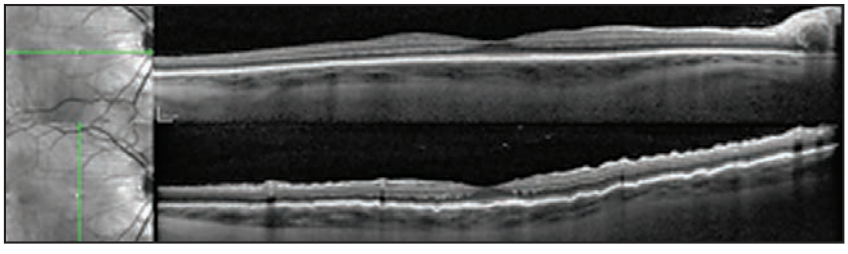
Diagnosis, Workup and Treatment

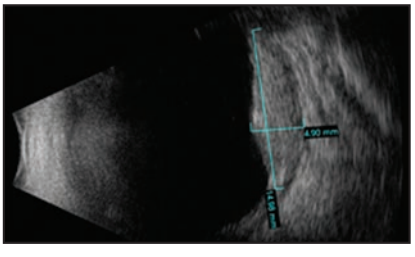
Differential diagnosis of the mass included a neoplastic process such as amelanotic choroidal melanoma or metastases with overlying thinning of the sclera. Additional considerations included an inflammatory process, such as posterior scleritis or granulomatous disease, or a structural process, such as choroidal effusion or exudative retinal detachment.

Further workup was directed at imaging the mass and macula. Optical coherence tomography of the macula of the right eye showed internal limiting membrane irregularity with retinal folds *(Figure 4)*, consistent with retinal striae seen on examination. B-scan ultrasonography documented echodense thickening of the eye wall with high internal reflectivity and a thickness of 4.9 mm, consistent with scleritis *(Figure 5)*. Transillumination of the mass revealed complete transmission of light, more suggestive of scleritis rather than solid melanoma. Review of previous MRI images revealed no extension of the mass into the optic nerve or orbit.

Given the patient's examination, a diagnosis of anterior and posterior scleritis was made. The diagnosis was based on several factors: First, she had symptoms of pain and anterior segment signs consistent with anterior scleritis. In addition, there was an elevated mass with normal-appearing overlying choroidal and retinal vessels and orange color, lacking pigmentation, that was similar to the surrounding fundus. Furthermore, B-scan ultrasonography showed dense thickening of the eye wall and transillumination revealed complete passage of light, consistent with posterior scleritis. At this time, the patient was started on oral prednisone 80 mg daily with a slow taper. She was also referred to the rheumatology department for further workup of a possible systemic autoimmune etiology, but all of her lab results were unrevealing.

At one-month and three-month follow-up, she had improvement in her pain and the fundus abnormalities *(Figure 6)*. However, there was mild recurrence of her symptoms during the prednisone taper, so she was started on mycophenolate mofetil 1,500 mg twice daily by the rheumatologist.





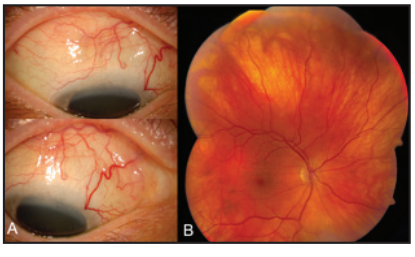


Figure 4 (top). Optical coherence tomography of the right eye showing internal limiting membrane irregularity with retinal folds on vertical orientation.
Figure 5 (bottom left). B-scan ultrasonography of the right eye showing echodense diffuse posterior thickening with high internal reflectivity, consistent with posterior scleritis.
Figure 6 (bottom right). Three months following initiation of oral prednisone, the episclera (A) showed improvement and the fundus (B) demonstrated reduction in scleral thickening, with nearly complete resolution of symptoms.

Discussion

Posterior scleritis is a rare disease and confirming the diagnosis can be challenging. It can mimic many other disease processes;[1] among these is choroidal melanoma or metastasis, as seen in our patient. Although all age groups can be affected, one study of 99 patients with posterior scleritis found the mean age at onset to be 49.[2] This condition also has a predilection for women and is twice as common in females compared to males. Posterior scleritis is associated with systemic disease in 30 percent of cases, including rheumatoid arthritis, systemic vasculitis and granulo-

matosis with polyangitis.[2]

The most common presenting symptoms are unrelenting periocular pain, headache, decreased vision and epibulbar redness.[2,5] There is clinical evidence of anterior scleritis in one-third of cases at the time posterior scleritis is diagnosed, and anterior involvement is present in 60 percent of cases at some point on follow-up.[2] On examination, patients most commonly manifest deep scleral thickening with overlying serous retinal detachment, and occasionally optic disc edema. Other findings can include retinal striae, choroidal folds and choroidal detachment.[5] Vision loss occurs in approximately 33 percent of cases, most commonly secondary to exudative retinal detachment, macular distortion from a scleral mass, and cystoid macular edema.[2,5,6] Although rare, 1 to 3 percent of patients can develop permanent vision loss.[2] Rarely, patients may have deep ocular pain without objective findings. In fact, in a study of 99 patients with posterior scleritis, 17 percent had no clinical abnormalities,[2] and therefore required an even higher index of suspicion to make the diagnosis.

B-scan ultrasonography is helpful in diagnosing posterior scleritis. Characteristic findings include diffuse, echodense thickening of the posterior sclera as well as the classic "T sign."[5,7] This is due to squaring off of a normally rounded optic nerve along with edema in Tenon's capsule extending along the posterior aspect of the eye forming a "T" shape. On MRI, the sclera in posterior scleritis has a low signal with a small degree of retinal/choroidal enhancement, the surrounding orbital tissues may show greater enhancement.[8]

Of particular interest in this case, posterior scleritis can masquerade as other disease processes, including choroidal melanoma.[9-12] Of the 12,000 cases of posterior uveal melanoma referred to a tertiary care center, 1,739 (14 percent) were pseudomelanomas and 5 cases (<1 percent) were due to posterior scleritis.[13] B-scan ultrasonography greatly aids in distinguishing posterior scleritis from melanoma, as it will show an echo-dense mass with scleritis, whereas melanoma is echolucent. Posterior scleritis also reveals complete transmission of light on transillumination, whereas melanoma would likely block transmission. Additionally, presence of pain is more common in cases of scleritis, although it can be present in cases of tumor necrosis. If the findings are equivocal,

(continued on page 121)

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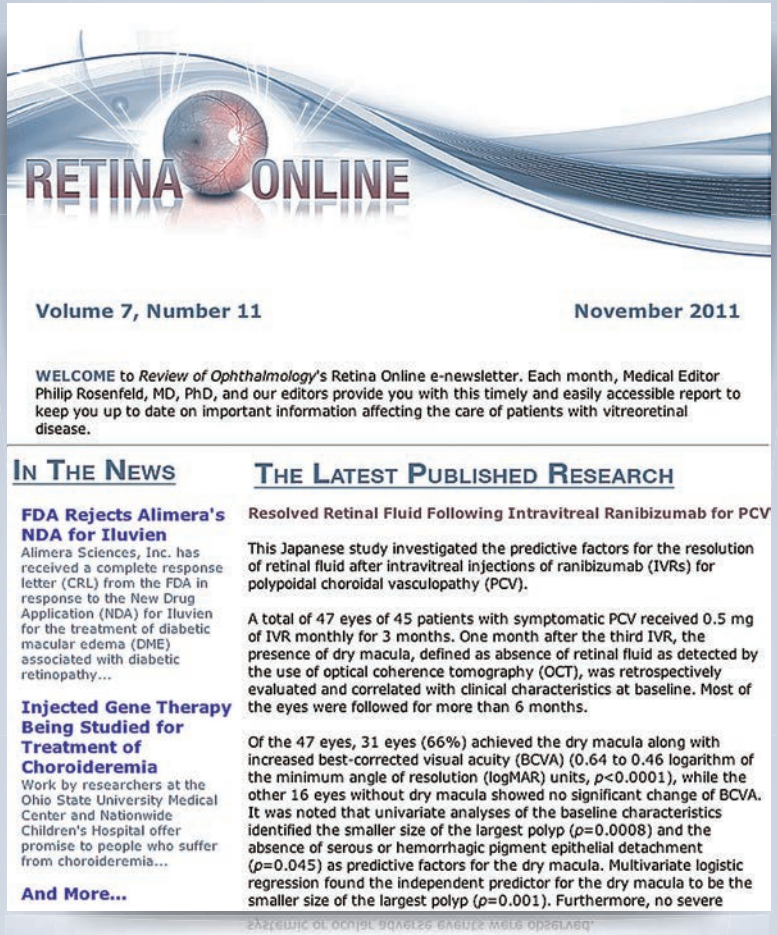

RETINA ONLINE

Volume 7, Number 11 November 2011

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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FDA Rejects Alimera's NDA for Iluvien
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Resolved Retinal Fluid Following Intravitreal Ranibizumab for PCV

This Japanese study investigated the predictive factors for the resolution of retinal fluid after intravitreal injections of ranibizumab (IVRs) for polypoidal choroidal vasculopathy (PCV).

A total of 47 eyes of 45 patients with symptomatic PCV received 0.5 mg of IVR monthly for 3 months. One month after the third IVR, the presence of dry macula, defined as absence of retinal fluid as detected by the use of optical coherence tomography (OCT), was retrospectively evaluated and correlated with clinical characteristics at baseline. Most of the eyes were followed for more than 6 months.

Of the 47 eyes, 31 eyes (66%) achieved the dry macula along with increased best-corrected visual acuity (BCVA) (0.64 to 0.46 logarithm of the minimum angle of resolution (logMAR) units, $p<0.0001$), while the other 16 eyes without dry macula showed no significant change of BCVA. It was noted that univariate analyses of the baseline characteristics identified the smaller size of the largest polyp ($p=0.0008$) and the absence of serous or hemorrhagic pigment epithelial detachment ($p=0.045$) as predictive factors for the dry macula. Multivariate logistic regression found the independent predictor for the dry macula to be the smaller size of the largest polyp ($p=0.001$). Furthermore, no severe

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REVIEW® of Ophthalmology

(continued from page 119)

fine-needle aspiration biopsy can be performed for a definitive diagnosis.[8]

Patients with posterior scleritis may respond well to nonsteroidal anti-inflammatory drugs.[2] However, systemic prednisone is often necessary for resolution of symptoms and findings. In more severe cases with vision loss from optic nerve or macular involvement, intravenous corticosteroids can be initiated, followed by oral prednisone taper for complete resolution.[2] Long-term dependency on corticosteroids may require adjustment to a steroid-sparing agent, such as mycophenolate mofetil, cyclophosphamide or cyclosporine A.[2]

Posterior scleritis is a rare inflammatory disease associated with pain, headache, redness and vision loss that can masquerade as other entities. In presenting this case we hope to highlight this rare entity along with the accompanying testing that can be instrumental in establishing the correct diagnosis. REVIEW

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

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

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

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

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

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

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

Shire

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

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

US Patents: 8367701; 9353088; 7314938; 7745460; 7790743; 7928122; 9216174; 8168655; 8084047; 8592450; 9085553 and pending patent applications.
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xiidra™ (lifitegrast ophthalmic solution) 5%

NiiCE TO MEET YOU

The only prescription eye drop FDA-approved to treat both the signs and symptoms of Dry Eye Disease

Xiidra improved patient-reported symptoms of eye dryness and improved signs of inferior corneal staining. So help your patients get to know Xiidra.

Check it out at Xiidra-ECP.com

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

The safety of lifitegrast was evaluated in a total of 5 clinical studies. 1401 patients received at least one dose of lifitegrast (1287 of which received Xiidra). The most common adverse reactions (5-25%) were instillation site irritation, dysgeusia, and reduced visual acuity.

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

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

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

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

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

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

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