REVIEW® of Ophthalmology

March 2020

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MAKE COMPLICATIONS DISAPPEAR

Surgeons share their bag of tricks for handling tough cataract cases. First in a two-part series. P. 29

ALSO INSIDE:

Change the outlook for dry eye disease

Only CEQUA™ features NCELL™, an innovative technology that helps improve the ocular penetration of cyclosporine[1-3]

Cequa™

(cyclosporine ophthalmic solution) 0.09%

Formulated with NCELL™ TECHNOLOGY

Visit **GetCequa.com** to learn more.

- NCELL helps improve the delivery of cyclosporine to where it is needed[2,3]
- Significant improvement in tear production at 3 months[1]
- Significant improvement in corneal staining as early as 1 month[2,4]
- In a comfort assessment at 3 minutes post instillation, 90% (Day 0) and 85% (Day 84) of patients had no or mild ocular discomfort[4]

INDICATIONS AND USAGE

CEQUA™ (cyclosporine ophthalmic solution) 0.09% is a calcineurin inhibitor immunosuppressant indicated to increase tear production in patients with keratoconjunctivitis sicca (dry eye).

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Potential for Eye Injury and Contamination: To avoid the potential for eye injury and contamination, advise patients not to touch the vial tip to the eye or other surfaces.

Use with Contact Lenses: CEQUA should not be administered while wearing contact lenses. If contact lenses are worn, they should be removed prior to administration of the solution. Lenses may be reinserted 15 minutes following administration of CEQUA ophthalmic solution.

ADVERSE REACTIONS

The most common adverse reactions reported in greater than 5% of patients were pain on instillation of drops (22%) and conjunctival hyperemia (6%). Other adverse reactions reported in 1% to 5% of patients were blepharitis, eye irritation, headache, and urinary tract infection.

Please see brief summary of Full Prescribing Information on the adjacent page.

References: 1. CEQUA [package insert]. Cranbury, NJ: Sun Pharmaceutical Industries, Inc.; 2018. **2.** Data on file. Cranbury, NJ: Sun Pharmaceutical Industries, Inc. **3.** US Patent 9,937,225 B2. **4.** Tauber J, Schechter BA, Bacharach J, et al. A Phase II/III, randomized, double-masked, vehicle-controlled, dose-ranging study of the safety and efficacy of OTX-101 in the treatment of dry eye disease. *Clin Ophthalmol.* 2018;12:1921-1929.

PM-US-CQA-0328 10/2019

SUN
OPHTHALMICS

Brief Summary of Prescribing Information for CEQUA™ (cyclosporine ophthalmic solution) 0.09%, for topical ophthalmic use

CEQUA™ (cyclosporine ophthalmic solution) 0.09%
See package insert for Full Prescribing Information.

INDICATIONS AND USAGE

CEQUA ophthalmic solution is a calcineurin inhibitor immunosuppressant indicated to increase tear production in patients with keratoconjunctivitis sicca (dry eye).

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Potential for Eye Injury and Contamination

To avoid the potential for eye injury and contamination, advise patients not to touch the vial tip to the eye or other surfaces.

Use with Contact Lenses

CEQUA should not be administered while wearing contact lenses. If contact lenses are worn, they should be removed prior to administration of the solution. Lenses may be reinserted 15 minutes following administration of CEQUA ophthalmic solution.

ADVERSE REACTIONS

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 the clinical trials of another drug and may not reflect the rates observed in practice.

In clinical trials, 769 patients received at least 1 dose of cyclosporine ophthalmic solution. The majority of the treated patients were female (83%).

The most common adverse reactions reported in greater than 5% of patients were pain on instillation of drops (22%) and conjunctival hyperemia (6%). Other adverse reactions reported in 1% to 5% of patients were blepharitis, eye irritation, headache, and urinary tract infection.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

There are no adequate and well-controlled studies of CEQUA administration in pregnant women to inform a drug-associated risk. Oral administration of cyclosporine to pregnant rats or rabbits did not produce teratogenicity at clinically relevant doses.

Data

Animal Data

Oral administration of cyclosporine oral solution (USP) to pregnant rats or rabbits was teratogenic at maternally toxic doses of 30 mg/kg/day in rats and 100 mg/kg/day in rabbits, as indicated by increased pre- and postnatal mortality, reduced fetal weight, and skeletal retardations. These doses (normalized to body weight) were approximately 3200 and 21,000 times higher than the maximum recommended human ophthalmic dose (MRHOD) of 1.5 mcg/kg/day, respectively. No adverse embryofetal effects were observed in rats or rabbits receiving cyclosporine during organogenesis at oral doses up to 17 mg/kg/day or 30 mg/kg/day, respectively (approximately 1800 and 6400 times higher than the MRHOD, respectively).

An oral dose of 45 mg/kg/day cyclosporine (approximately 4800 times higher than MRHOD) administered to rats from Day 15 of pregnancy until Day 21 postpartum produced maternal toxicity and an increase in postnatal mortality in offspring. No adverse effects in dams or offspring were observed at oral doses up to 15 mg/kg/day (approximately 1600 times greater than the MRHOD).

Lactation

Risk Summary

Cyclosporine blood concentrations are low following topical ocular administration of CEQUA. There is no information regarding the presence of cyclosporine in human milk following topical administration or on the effects of CEQUA on breastfed infants and milk production. Administration of oral cyclosporine to rats during lactation did not produce adverse effects in offspring at clinically relevant doses. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for CEQUA and any potential adverse effects on the breastfed child from cyclosporine.

Pediatric Use

The safety and efficacy of CEQUA ophthalmic solution have not been established in pediatric patients below the age of 18.

Geriatric Use

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

PATIENT COUNSELING INFORMATION

Handling the Vial

Advise patients to not allow the tip of the vial to touch the eye or any surface, as this may contaminate the solution. Advise patients also not to touch the vial tip to their eye to avoid the potential for injury to the eye.

Use with Contact Lenses

CEQUA should not be administered while wearing contact lenses. Patients with decreased tear production typically should not wear contact lenses. Advise patients that if contact lenses are worn, they should be removed prior to the administration of the solution. Lenses may be reinserted 15 minutes following administration of CEQUA ophthalmic solution.

Administration

Advise patients that the solution from one individual single-use vial is to be used immediately after opening for administration to one or both eyes, and the remaining contents should be discarded immediately after administration.

Rx Only

Distributed by: Sun Pharmaceutical Industries, Inc.
Cranbury, NJ 08512

PLR-00020 2018

SUN OPHTHALMICS

REVIEW NEWS
Volume XXVII • No. 3 • March 2020

Vermont Says No to ODs on Advanced Procedures

A year-long standoff between ophthalmology and optometry over ODs' plans to provide advanced procedures in Vermont has ended with ophthalmology on top.

In February of 2019, the Vermont Optometric Association asked state officials to allow ODs to offer laser procedures, lid injections, lid lesion treatments and other forms of care currently restricted to medical doctors. The Vermont Office of Professional Regulation turned down the request on January 15. "After consulting with stakeholders and conducting extensive and thorough research, the OPR cannot conclude that optometrists are properly trained in and can safely perform the proposed advanced care procedures," the regulatory agency stated in a 40-page report. "Further, OPR finds that there is little need for, and minimal cost savings associated with, expanding optometric scope of practice to include advanced procedures."

Amy A. Gregory, MD, president of the Vermont Ophthalmological Society said her organization was "very pleased" with the regulatory board's decision. "We were also thankful that we had the opportunity to present all of our information and data and that the regulators who made that decision were very thoughtful in reviewing all of the evidence when coming to their decision. Basically, the concern was that patient safety and vision would be put at risk if optometrists who don't have appropriate training were allowed to do lasers and eye surgical procedures."

Besides gathering input from the Vermont Ophthalmological Society, the OPR received input from eight ODs and their patients and asked the state optometric association questions about optometrists' education and training, patient safety, access to care and costs. The OPR asked 21 U.S. optometry schools to provide curricula, course descriptions, syllabi and other information about optometric training and education on the proposed procedures. No school responded, although Elizabeth Hope, OD, MPH, DrPH, president of the Association of Schools of Schools and Colleges of Optometry, contacted the OPR to discuss optometric education and training. Dr. Hope referred questions to the VOA and the American Optometric Association.

"More and more states are taking action to recognize optometry's essential and expanding role in health care, especially with regard to leading-edge treatment of glaucoma, cataracts and other threats to vision and health," said David A. Cockrell, OD, Diplomate of the American Board of Optometry and past president of the AOA. "Although some of my medical colleagues and even some policymakers remain fearful of health care's advancement, the profession of optometry—from our outstanding educational institutions to our forward-looking professional associations to our highly skilled doctors—is embracing and helping to shape the future."

The OPR noted in its report that optometric scope of practice was expanded in Vermont in 1983, 2004 and 2019. ODs in Vermont are permitted to prescribe oral medications, including Schedule II (hydrocodone-combination products), III, IV and V drugs; as well as oral steroids, antibiotics, antivirals and antifungals. Vermont ODs are also permitted to diagnose and treat glaucoma with topical and oral drugs, perform foreign body removal, dilation and irrigation, punctal occlusion and eyelash epilation, as well as order laboratory tests required for the examination, diagnosis, and treatment of a disease or condition related to the eye.

Eye MD in the Vanguard Versus the Coronavirus

While an ophthalmologist may at first appear to be an unlikely epidemic whistleblower, that's just what Li Wenliang, MD, became when he shared some news about a possible re-emergence of SARS with his medical school alumni

friends and warned them to take precautions. "On December 30th, I saw a test report of a patient that detected a high confidence coefficient for SARS coronavirus," he wrote on his Weibo, the Chinese social media website. SARS, or severe acute respiratory syndrome, is the result of a less-powerful coronavirus, but one with many similarities to the current strain. In 2003, a SARS pandemic allegedly covered up by the government killed hundreds in China.[1]

Dr. Li warned his friends on WeChat, the Chinese messaging app, that seven SARS cases were identified at the Huanan Seafood Market, with the suspected patients quarantined in the ER at Wuhan Central Hospital, Tongji Medical College, where he worked and researched genetic influences on diabetic retinopathy. Screenshots of his SARS warnings went viral.

A few days later, the Public Security Bureau tracked down Dr. Li and seven other doctor whistleblowers and accused them of spreading rumors and disturbing the social order. Dr. Li was forced to sign an official letter acknowledging that if he continued with his illegal activity and rumor-spreading he would be brought to justice. Around this time, Chinese authorities were investigating 27 cases of viral pneumonia, but taking careful steps not to mention SARS or coronavirus.

Dr. Li himself contracted the coronavirus while treating a glaucoma patient. Ophthalmologists are more likely to catch a contagious disease from patients than most other doctors because they have to sit or stand so close to their patients.

"I started to have cough symptoms on January 10," Dr. Li wrote on his Weibo account page. The next day he had a fever and on January 12, he was hospitalized in the intensive care unit on oxygen support. "I was wondering why [the government's] official notices were still saying there was no human-to-human transmission, and no medical workers infected," he wrote.

"I was wondering why [the government's] official notices were still saying there was no human-to-human transmission, and no medical workers infected," Dr. Li wrote on Weibo.

"I had a nucleic acid test before, but there was no result. After a recent test after treatment, my nucleic acid test was negative, but I still have difficulty breathing and cannot move. My parents are also in the hospital." On February 1, he posted from Wuhan Central Hospital that "Today the nucleic acid test result is positive, the dust has settled, and the diagnosis has finally been confirmed."

On February 7, Dr. Li passed away at Wuhan Central Hospital. He was 34 years old and is survived by his wife and one child, with a second on the way.

In an interview by text with the New York Times, Dr. Li expressed his frustration with China's secrecy and failure to act. "If the officials had disclosed information about the epidemic sooner, I think it would have been a lot better," he said to the Times. "There should be more openness and transparency." REVIEW

1. Learning from SARS: Preparing for the Next Disease Outbreak: Workshop Summary. Institute of Medicine (US) Forum on Microbial Threats. Knobler S, Mahmoud A, Lemon S, et al, eds. Washington, D.C.: National Academies Press (U.S.), 2004.

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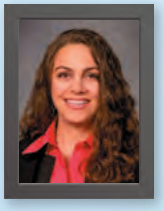
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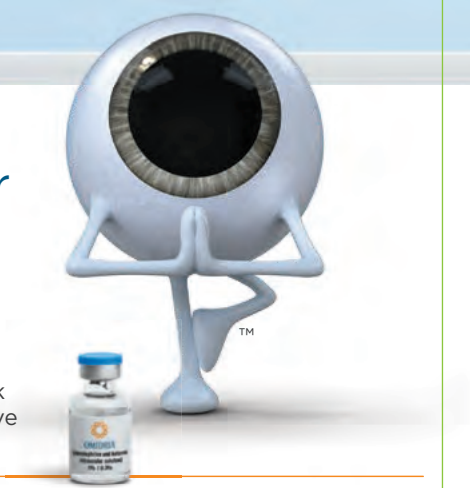
These cataract surgeons use OMIDRIA® (phenylephrine and ketorolac intraocular solution) 1% / 0.3% for **less stress, pure success** in their O.R. day[1]



What about you?

OMIDRIA helps your cataract surgery by inhibiting prostaglandin release to block inflammation and maintain iris tone, preventing miosis and reducing postoperative pain for your patients.[2,3] Experience less stress in your O.R. day with OMIDRIA.[1]

INDICATIONS AND USAGE

OMIDRIA® (phenylephrine and ketorolac intraocular solution) 1% / 0.3% is added to ophthalmic irrigating 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.

IMPORTANT SAFETY INFORMATION

OMIDRIA must be added to irrigating 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% are eye irritation, posterior capsule opacification, increased intraocular pressure, and anterior chamber inflammation.

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

You are encouraged to report Suspected Adverse Reactions to the FDA.
Visit www.fda.gov/medwatch, or call 1-800-FDA-1088.

References: 1. Omeros survey data on file. **2.** OMIDRIA [package insert]. Seattle, WA: Omeros Corporation; 2017. **3.** Al-Hashimi S, Donaldson K, Davidson R, et al; for ASCRS Refractive Cataract Surgery Subcommittee. Medical and surgical management of the small pupil during cataract surgery. *J Cataract Refract Surg*. 2018;44:1032-1041.

The healthcare professionals portrayed in this advertisement are consultants of Omeros Corporation.

OMEROS

OMIDRIA®
(phenylephrine and ketorolac intraocular solution)
1% / 0.3%

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BRIEF SUMMARY OF PRESCRIBING INFORMATION

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

LOTEMAX® SM (loteprednol etabonate ophthalmic gel) 0.38%

For topical ophthalmic use
Initial U.S. Approval: 1998

INDICATIONS AND USAGE

LOTEMAX® SM is a corticosteroid indicated for the treatment of post-operative inflammation and pain following ocular surgery.

DOSAGE AND ADMINISTRATION

Invert closed bottle and shake once to fill tip before instilling drops. Apply one drop of LOTEMAX® SM into the conjunctival sac of the affected eye three times daily beginning the day after surgery and continuing throughout the first 2 weeks of the post-operative period.

CONTRAINDICATIONS

LOTEMAX® SM, as with other ophthalmic corticosteroids, is contraindicated in most viral diseases of the cornea and conjunctiva including epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, and varicella, in mycobacterial infection of the eye and fungal diseases of ocular structures.

WARNINGS AND PRECAUTIONS

Intraocular Pressure (IOP) Increase: Prolonged use of corticosteroids may result in glaucoma with damage to the optic nerve, defects in visual acuity and fields of vision. Steroids should be used with caution in the presence of glaucoma. If this product is used for 10 days or longer, intraocular pressure should be monitored.

Cataracts: Use of corticosteroids may result in posterior subcapsular cataract formation.

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

Bacterial Infections: Prolonged use of corticosteroids may suppress the host response and thus increase the hazard of secondary ocular infections. In acute purulent conditions of the eye, steroids may mask infection or enhance existing infection.

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

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

Contact Lens Wear: Contact lenses should not be worn when the eyes are inflamed.

ADVERSE REACTIONS

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. Adverse reactions associated with ophthalmic steroids include elevated intraocular pressure, which may be associated with infrequent optic nerve damage, visual acuity and field defects, posterior subcapsular cataract formation, delayed wound healing and secondary ocular infection from pathogens including herpes simplex, and perforation of the globe where there is thinning of the cornea or sclera. There were no treatment-emergent adverse drug reactions that occurred in more than 1% of subjects in the three times daily group compared to vehicle.

USE IN SPECIAL POPULATIONS

Pregnancy: Risk Summary: There are no adequate and well controlled studies with loteprednol etabonate in pregnant women. Loteprednol etabonate produced teratogenicity at clinically relevant doses in the rabbit and rat when administered orally during pregnancy. Loteprednol etabonate produced malformations when administered orally to pregnant rabbits at doses 4.2 times the recommended human ophthalmic dose (RHOD) and to pregnant rats at doses 106 times the RHOD. In pregnant rats receiving oral doses of loteprednol etabonate during the period equivalent to the last trimester of pregnancy through lactation in humans, survival of offspring was reduced at doses 10.6 times the RHOD. Maternal toxicity was observed in rats at doses 1066 times the RHOD, and a maternal no observed adverse effect level (NOAEL) was established at 106 times the RHOD. The background risk of major birth defects and miscarriage for the indicated population is unknown. However, the background risk in the U.S. general population of major birth defects is 2 to 4%, and of miscarriage is 15 to 20%, of clinically recognized pregnancies. Data: *Animal Data.* Embryofetal studies were conducted in pregnant rabbits administered loteprednol etabonate by oral gavage on gestation days 6 to 18, to target the period of organogenesis. Loteprednol etabonate produced fetal malformations at 0.1 mg/kg (4.2 times the recommended human ophthalmic dose (RHOD) based on body surface area, assuming 100% absorption). Spina bifida (including meningocele) was observed at 0.1 mg/kg, and exencephaly and craniofacial malformations were observed at 0.4 mg/kg (17 times the RHOD). At 3 mg/kg (128 times the RHOD), loteprednol etabonate was associated with increased incidences of abnormal left common carotid artery, limb flexures, umbilical hernia, scoliosis, and delayed ossification. Abortion and embryofetal lethality (resorption) occurred at 6 mg/kg (256 times the RHOD). A NOAEL for developmental toxicity was not established in this study. The NOAEL for maternal toxicity in rabbits was 3 mg/kg/day. Embryofetal studies were conducted in pregnant rats administered loteprednol etabonate by oral gavage on gestation days 6 to 15, to target the period of organogenesis. Loteprednol etabonate produced fetal malformations, including absent innominate artery at 5 mg/kg (106 times the RHOD); and cleft palate, agnathia, cardiovascular defects, umbilical hernia, decreased fetal body weight and decreased skeletal ossification at 50 mg/kg (1066 times the RHOD). Embryofetal lethality (resorption) was observed at 100 mg/kg (2133 times the RHOD). The NOAEL for developmental toxicity in rats was 0.5 mg/kg (10.6 times the RHOD). Loteprednol etabonate was maternally toxic (reduced body weight gain) at 50 mg/kg/day. The NOAEL for maternal toxicity was 5 mg/kg. A peri-/postnatal study was conducted in rats administered loteprednol etabonate by oral gavage from gestation day 15 (start of fetal period) to postnatal day 21 (the end of lactation period). At 0.5 mg/kg (10.6 times the clinical dose), reduced survival was observed in live-born offspring. Doses ≥ 5 mg/kg (106 times the RHOD) caused umbilical hernia/incomplete gastrointestinal tract. Doses ≥ 50 mg/kg (1066 times the RHOD) produced maternal toxicity (reduced body weight gain, death), decreased number of live-born offspring, decreased birth weight, and delays in postnatal development. A developmental NOAEL was not established in this study. The NOAEL for maternal toxicity was 5 mg/kg.

Lactation: There are no data on the presence of loteprednol etabonate in human milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered, along with the mother's clinical need for LOTEMAX® SM and any potential adverse effects on the breastfed infant from LOTEMAX® SM.

Pediatric Use: Safety and effectiveness of LOTEMAX® SM in pediatric patients 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: Long-term animal studies have not been conducted to evaluate the carcinogenic potential of loteprednol etabonate. Loteprednol etabonate was not genotoxic *in vitro* in the Ames test, the mouse lymphoma tk assay, or in the chromosomal aberration test in human lymphocytes, or *in vivo* in the mouse micronucleus assay. Treatment of male and female rats with 25 mg/kg/day of loteprednol etabonate (533 times the RHOD based on body surface area, assuming 100% absorption) prior to and during mating caused preimplantation loss and decreased the number of live fetuses/live births. The NOAEL for fertility in rats was 5 mg/kg/day (106 times the RHOD).

Bausch + Lomb, a division of Valeant Pharmaceuticals North America LLC
Bridgewater, NJ 08807 USA

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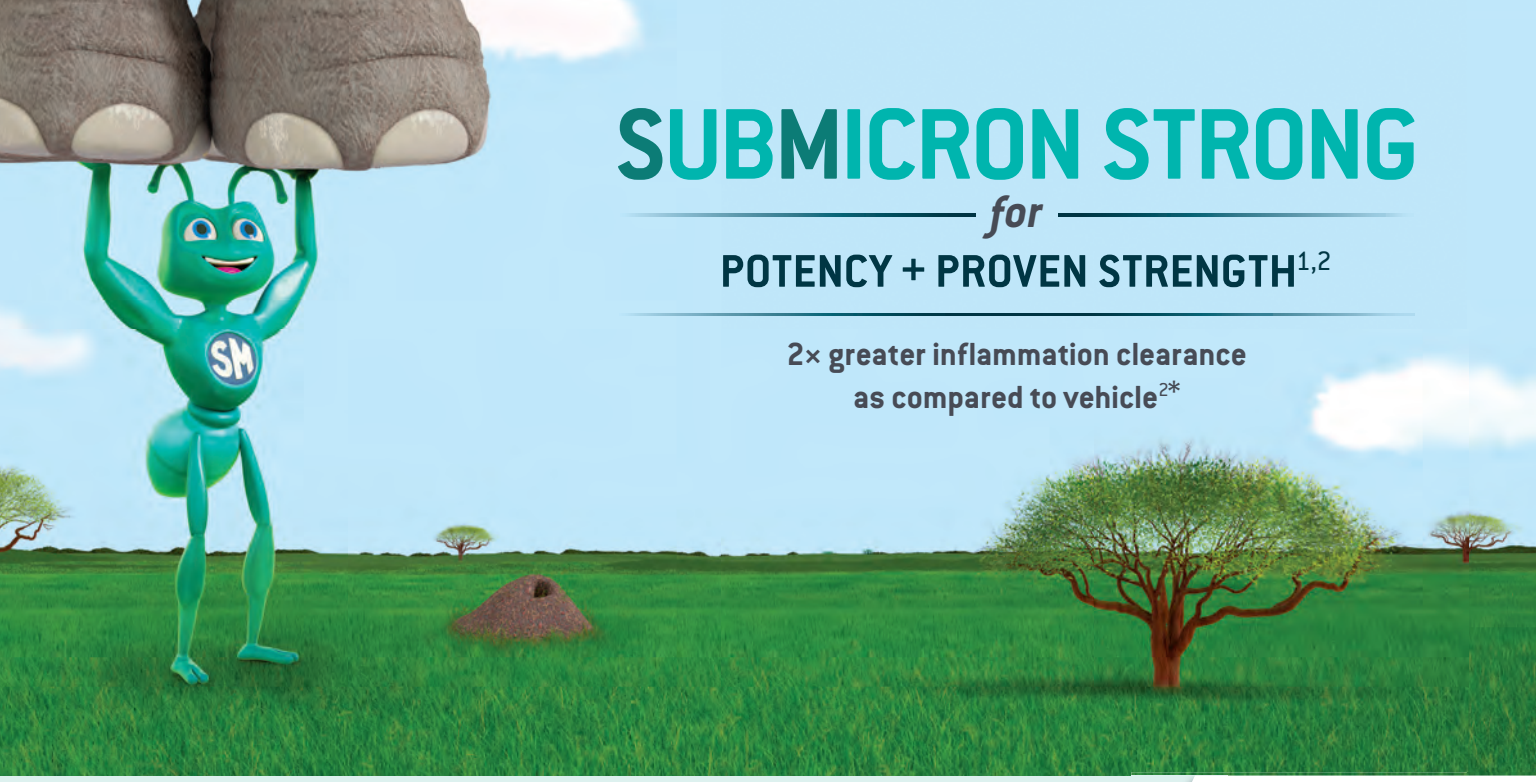
Based on 9669600-9669700 Revised: 02/2019



SUBMICRON STRONG

for

POTENCY + PROVEN STRENGTH[1,2]

2× greater inflammation clearance as compared to vehicle[2]*

SM TECHNOLOGY™

- **Engineered with SM Technology™ for efficient penetration at a low BAK level (0.003%)[1,3]**
- **~2× greater penetration** to the aqueous humor than LOTEMAX® GEL (loteprednol etabonate ophthalmic gel) 0.5%[3]

Clinical significance of these preclinical data has not been established.

LOTEMAX® SM
(loteprednol etabonate ophthalmic gel) 0.38%

SMALL & MIGHTY
SUBMICRON PARTICLES

*PROVEN STRENGTH

- **30% of LOTEMAX® SM patients had complete ACC resolution** vs vehicle (15%) at Day 8 (N=371, *P*<0.0001)[1,2†]
- **74% of LOTEMAX® SM patients were completely pain-free** vs vehicle (49%) at Day 8 (N=371, *P*<0.0001)[1,2‡]

†Pooled analysis of Phase 3 clinical studies. **Study 1:** 29% LOTEMAX® SM (N=171) vs 9% vehicle (N=172). **Study 2:** 31% LOTEMAX® SM (N=200) vs 20% vehicle (N=199); *P*<0.05 for all.

‡Pooled analysis of Phase 3 clinical studies. **Study 1:** 73% LOTEMAX® SM (N=171) vs 48% vehicle (N=172). **Study 2:** 76% LOTEMAX® SM (N=200) vs 50% vehicle (N=199); *P*<0.05 for all.

Indication

LOTEMAX® SM (loteprednol etabonate ophthalmic gel) 0.38% is a corticosteroid indicated for the treatment of post-operative inflammation and pain following ocular surgery.

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- Prolonged use of corticosteroids may result in glaucoma with damage to the optic nerve, defects in visual acuity and fields of vision. Steroids should be used with caution in the presence of glaucoma. If LOTEMAX® SM is used for 10 days or longer, IOP should be monitored.
- Use of corticosteroids may result in posterior subcapsular cataract formation.

Important Safety Information (cont.)

- The use of steroids after cataract surgery may delay healing and increase the incidence of bleb formation. In those with diseases causing thinning of the cornea or sclera, perforations have been known to occur with the use of topical steroids. The initial prescription and renewal of the medication order should be made by a physician only after examination of the patient with the aid of magnification such as slit lamp biomicroscopy and, where appropriate, fluorescein staining.
- Prolonged use of corticosteroids may suppress the host response and thus increase the hazard of secondary ocular infections. In acute purulent conditions, steroids may mask infection or enhance existing infections.
- Employment of a corticosteroid medication in the treatment of patients with a history of herpes simplex requires great caution. Use of ocular steroids may prolong the course and may exacerbate the severity of many viral infections of the eye (including herpes simplex).
- Fungal infections of the cornea are particularly prone to develop coincidentally with long-term local steroid application. Fungus invasion must be considered in any persistent corneal ulceration where a steroid has been used or is in use. Fungal cultures should be taken when appropriate.
- Contact lenses should not be worn when the eyes are inflamed.
- There were no treatment-emergent adverse drug reactions that occurred in more than 1% of subjects in the three times daily group compared to vehicle.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit **www.fda.gov/medwatch** or call **1-800-FDA-1088**.

Please see brief summary of Prescribing Information on adjacent page.

References: 1. LOTEMAX SM Prescribing Information. Bausch & Lomb Incorporated. **2.** Data on file. Bausch & Lomb Incorporated. **3.** Cavet ME, Glogowski S, Lowe ER, Phillips E. Rheological properties, dissolution kinetics, and ocular pharmacokinetics of loteprednol etabonate (submicron) ophthalmic gel 0.38%. *J Ocul Pharmacol Ther.* 2019. doi: 10.1089/jop.2019;35(5):291-300.

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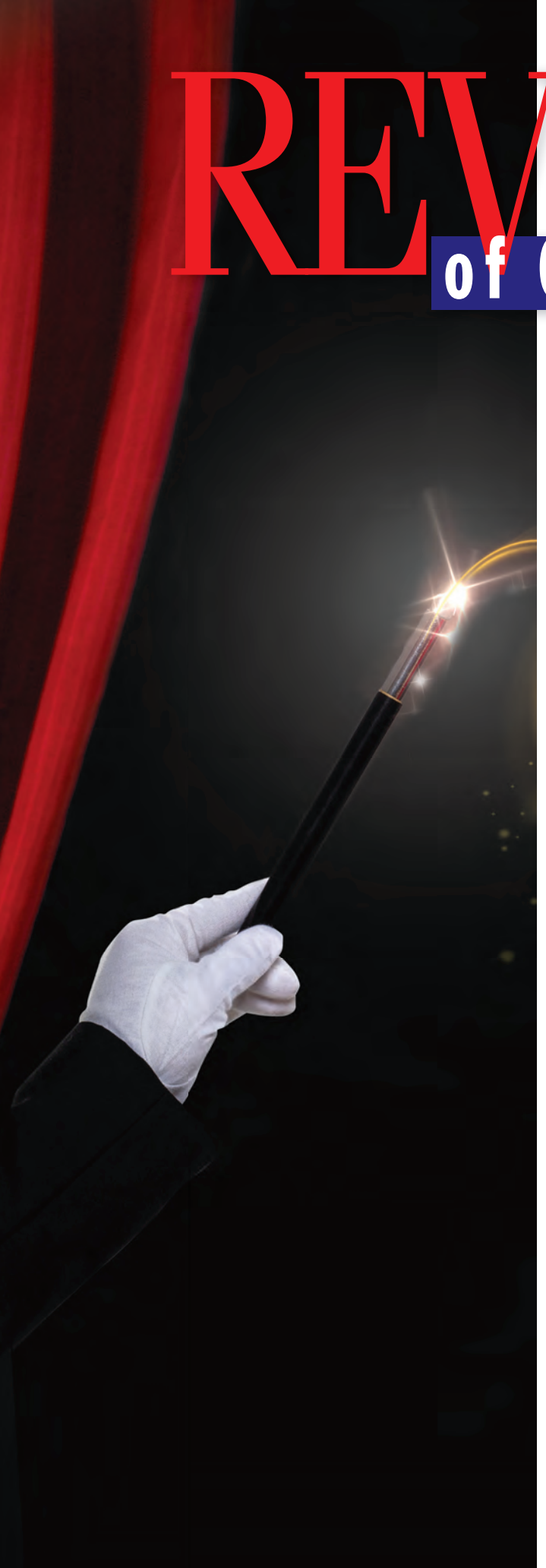

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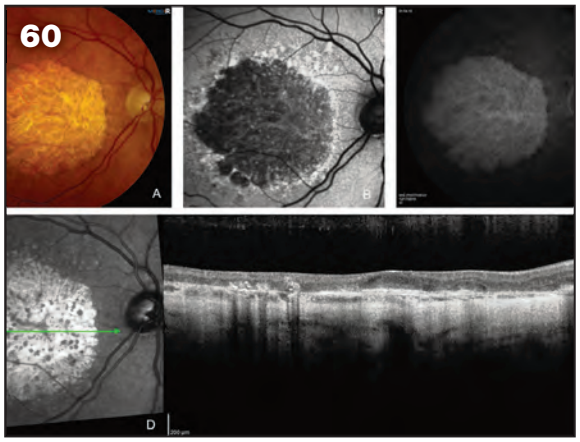

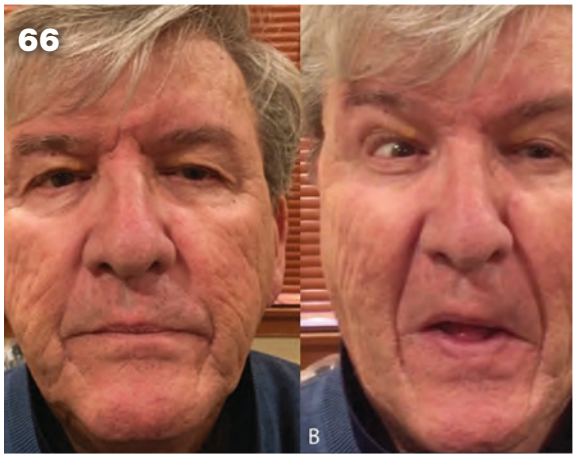

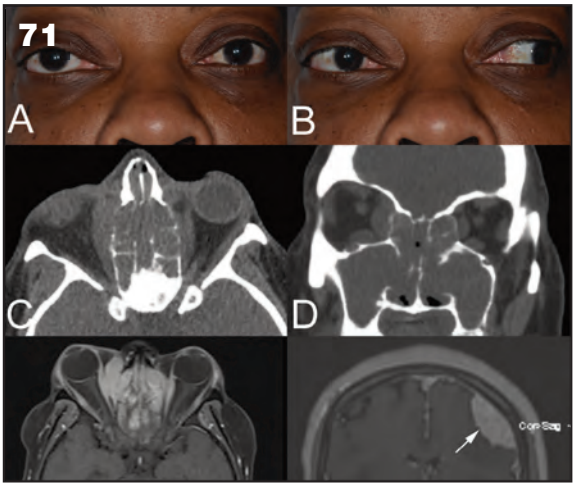

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Indications and Important Safety Information

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INDICATIONS: The TECNIS Symfony® Extended Range of Vision IOL, Model ZXR00, is indicated for primary implantation for the visual correction of aphakia, in adult patients with less than 1 diopter of pre-existing corneal astigmatism, in whom a cataractous lens has been removed. The lens mitigates the effects of presbyopia by providing an extended depth of focus. Compared to an aspheric monofocal IOL, the lens provides improved intermediate and near visual acuity, while maintaining comparable distance visual acuity. The Model ZXR00 IOL is intended for capsular bag placement only. **WARNINGS:** Patients with any of the conditions described in the Directions for Use may not be suitable candidates for an intraocular lens because the lens may exacerbate an existing condition, may interfere with diagnosis or treatment of a condition, or may pose an unreasonable risk to the patient's eyesight. Lenses should not be placed in the ciliary sulcus. May cause a reduction in contrast sensitivity under certain conditions, compared to an aspheric monofocal IOL; fully inform the patient of this risk before implanting the lens. Special consideration should be made in patients with macular disease, amblyopia, corneal irregularities, or other ocular disease. Inform patients to exercise special caution when driving at night or in poor visibility conditions. Some visual effects may be expected due to the lens design, including: a perception of halos, glare, or starbursts around lights under nighttime conditions. These will be bothersome or very bothersome in some people, particularly in low- illumination conditions, and on rare occasions, may be significant enough that the patient may request removal of the IOL. **SERIOUS ADVERSE EVENTS:** The most frequently reported serious adverse events that occurred during the clinical trial of the TECNIS Symfony® lens were cystoid macular edema (2 eyes, 0.7%) and surgical reintervention (treatment injections for cystoid macular edema and endophthalmitis, 2 eyes, 0.7%). No lens-related adverse events occurred during the trial.

TECNIS® MULTIFOCAL FAMILY OF 1-PIECE IOLs

INDICATIONS: The TECNIS® Multifocal 1-Piece intraocular lenses are indicated for primary implantation for the visual correction of aphakia in adult patients with and without presbyopia in whom a cataractous lens has been removed by phacoemulsification and who desire near, intermediate, and distance vision with increased spectacle independence. The intraocular lenses are intended to be placed in the capsular bag. **WARNINGS:** Physicians considering lens implantation should weigh the potential risk/benefit ratio for any conditions described in the Directions for Use that could increase complications or impact patient outcomes. Multifocal IOL implants may be inadvisable in patients where central visual field reduction may not be tolerated, such as macular degeneration, retinal pigment epithelium changes, and glaucoma. The lens should not be placed in the ciliary sulcus. Inform patients about the possibility that a decrease in contrast sensitivity and an increase in visual disturbances may affect their ability to drive a car under certain environmental conditions, such as driving at night or in poor visibility conditions. **PRECAUTIONS:** Prior to surgery, inform prospective patients of the possible risks and benefits associated with the use of this device and provide a copy of the patient information brochure to the patient. Secondary glaucoma has been reported occasionally in patients with controlled glaucoma who received lens implants. **ADVERSE EVENTS:** The rates of surgical re-interventions, most of which were non-lens related, were statistically higher than the FDA grid rate for the ZLB00 (+3.25 D) lens model. The re-intervention rate was 3.3% for both the first and second eyes in the ZLB00 group.

ATTENTION: Reference the Directions for Use for a complete listing of Indications and Important Safety Information.

REFERENCE: 1. DOF2018CT4021. Johnson & Johnson Surgical Vision, Inc; 2018.

See the Passion in Each Patient

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Finding Hyperopia's Surgical Sweet Spot

Experts discuss how to meet the sometimes unrealistic expectations of today's hyperopes.

Sean McKinney, Senior Editor

Like other patients in need of visual correction these days, many hyperopes are eager to find out what the latest laser and lens technologies can do for them. However, surgeons say they've learned from sometimes regrettable experiences to respect the limits of refractive surgery in this cohort of patients.

Nonetheless, by carefully selecting the right candidates and taking advantage of today's full range of procedures—from PRK to refractive lens exchange—experts say you can meet the needs of more hyperopic patients than ever.

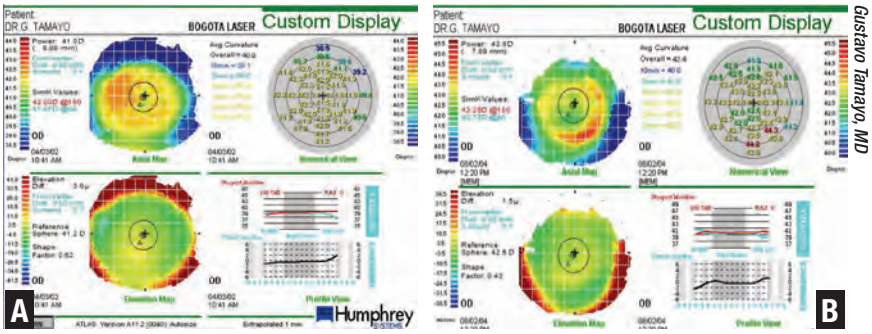
Here, several seasoned surgeons offer advice on choosing the right patients, ruling out inappropriate ones, choosing the best procedures and recognizing risks to avoid.

Choosing the Right Patients

Like most of his colleagues, David R. Hardten, MD, FACS, who is in private practice at Minnesota Eye Consultants in Minneapolis, rules out more hyperopes than not and chooses ideal candidates based on age. "Compared to 10 or 15 years ago, we just don't do as much laser vision correction for higher levels of hyperopia," he says. "The optical quality that corneal refractive surgery provides to these patients isn't as good as we can achieve now with refractive lens exchange because of the availability of today's high quality IOL implants."

Naturally, most of his hyperopic patients are presbyopic, and are starting to explore their options for refractive correction. "At that point, you really should be thinking about what will satisfy your patient five, 10 and 15 years down the line," he says. "That's why RLE procedures represent the vast majority of surgeries I perform on hyperopes."

However, Dr. Hardten says he will still occasionally perform refractive surgery on younger hyperopes who have significant astigmatism. "If you have a patient who is +0.5 D with +2 D astigmatism, you can relieve their astigmatism with a corneal procedure and leave them a little bit hyperopic. They end up being pretty happy—until they become presbyopic in their mid 40s." He recommends against plano corrections. "Usually, a little bit of hyperopia is going to be better because their accommodative tone tolerates this mild hyperopia and they won't be happy with plano or even a -1 D or -0.5 D correction. As they get older and their refractive tone



Gustavo Tamayo, MD

Figure 1. The topography maps above show change after hyperopia treatment with an excimer laser, including a preop flat cornea (A) and a steep postop cornea (B).

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Scott MacRae, MD

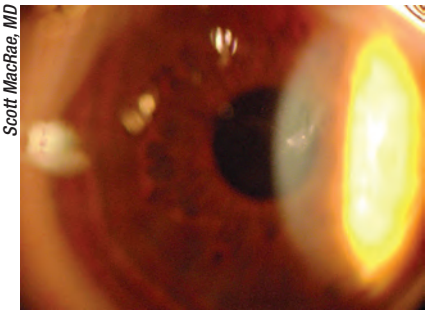

Figure 2. Hyperopic refractive surgery candidates with a history of anterior basement membrane disease, such as anterior basement membrane dystrophy, shown above, should be steered away from LASIK and offered PRK in most cases.

relaxes, you find yourself chasing their changing refractive errors. That's the challenge of correcting younger hyperopes—and why it's better to wait until you can do the lens replacement."

For Scott MacRae, MD, director of refractive services in the department of ophthalmology at the University of Rochester, the ideal hyperope for a corneal refractive procedure is 45 to 55 years old, with a correction that ranges from +1 D to +3 D. "The critical thing is for them to be stable," he says. "I find that these patients do very well with LASIK. Once they get into the 60s, though, they start getting cataracts, and that changes everything." Hyperopes in their 50s or 60s with a refractive error of +4 D or greater are typically what Dr. MacRae considers good candidates for RLE. "However, for any patient in that age group with a progressive, developing cataract, I defer the refractive surgery until they've had their cataract surgery. After cataract surgery, you can fine-tune their refraction with LASIK or PRK."

Gustavo Tamayo, MD, director of the Bogota Laser Ocular Surgery Center in Bogota, Colombia, is an exception to the general rule, making generous allowances for high correction of hyperopes, as long as their keratometry readings don't exceed 49 D. "At 49 D or below, I believe you can effectively correct up to +6 D of hyperopia," he says.

Kathryn M. Hatch, MD, director of the refractive surgery service at Massachusetts Eye & Ear and an assistant professor of ophthalmology at Harvard Medical School, points out that hyperopic laser vision correction isn't always a predictable treatment, especially at higher corrections. This can make patient selection a less-than-exact science. "Low hyperopia and mixed astigmatism patients do fairly well," she notes. "Patients under +2 D or +3 D typically do well."

Patients to Rule Out

Unlike Dr. Tamayo, Dr. MacRae says steep corneas typically put hyperopic refractive surgery prospects on the do-not-operate side of his appointment book. "If their corneas are at 47 D or 48 D, I avoid doing the surgery, especially in a +3 D correction and especially in smaller eyes, because I'm at risk of creating a curvature of more than than 50 D. The patient will likely experience regression."

Dr. MacRae also rules out patients still undergoing refractive changes. "Another red flag goes up for me when patients want near corneal refractive procedures, especially if they've never done monovision," he says. "These patients are probably better off with a trifocal IOL or a mix-and-match biofocal IOL and expanded-depth-of-focus IOL. But it's critical that they have reasonable expectations before you offer them premium IOLs."

He also puts the brakes on refractive surgery when patients have a significant and ongoing shift in hyperopia. "A lot of times that's an indicator that they'll have an early cataract," he says. "I will defer these patients. The second type of patients that I observe more carefully are the younger ones. For example, for people in their early 40s, the manifest refraction may be +1.5 D. Then, when we do their cycloplegic refractions, it might be +2.5 D or +2.75 D. That tells me their hyperopia is latent and that it can get worse over the next few years. You probably want to defer those patients for 18 months to see how they're progressing." When the patients become less latent and more definitively hyperopic, Dr. MacRae says they'll emerge as stronger surgical candidates. "If you treat them before this point, they'll drift after treatment," he adds.

Dr. Hardten avoids patients with refractive errors above the +3 D to +4 D range or—in the under-35 set—even above the +2.5 D to +3 D range. "You can create a lot of optical aberrations when you perform corneal refractive surgery on these patients, so I'd be outside of the range in which I'd offer surgery," he says. "Because a 25-or-30-year-old isn't presbyopic, if you perform an RLE, you'll produce artificial pseudo-accommodation, like you would with a presbyopic IOL, but you'll also get glare and halos."

Once you start using a corneal procedure to correct more than +3 D or

Kathryn M. Hatch, MD

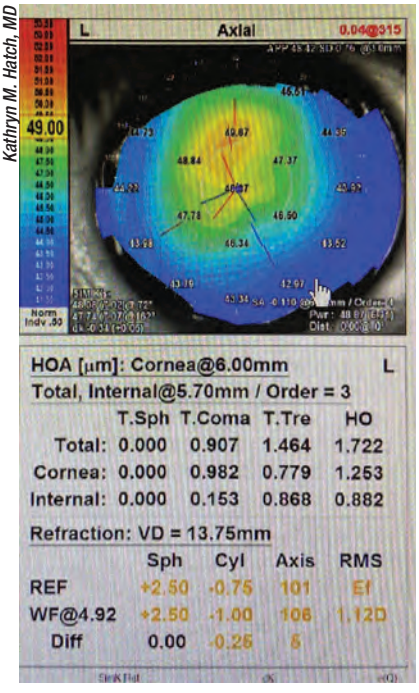

Figure 3. In this corneal topography map, higher-order aberrations are shown after hyperopic LASIK in a patient with cataracts.

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DEXTENZA is a corticosteroid indicated for the treatment of ocular inflammation and pain following ophthalmic surgery.

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

DEXTENZA is contraindicated in patients with active corneal, conjunctival or canalicular infections, including epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, varicella; mycobacterial infections; fungal diseases of the eye, and dacryocystitis.

WARNINGS AND PRECAUTIONS

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

Corticosteroids may suppress the host response and thus increase the hazard for secondary ocular infections. In acute purulent conditions, steroids may mask infection and enhance existing infection.

Use of ocular steroids may prolong the course and may exacerbate the severity of many viral infections of the eye (including herpes simplex).

Fungus invasion must be considered in any persistent corneal ulceration where a steroid has been used or is in use. Fungal culture should be taken when appropriate.

Use of steroids after cataract surgery may delay healing and increase the incidence of bleb formation.

ADVERSE REACTIONS

The most common ocular adverse reactions that occurred in patients treated with DEXTENZA were: anterior chamber inflammation including iritis and iridocyclitis (10%); intraocular pressure increased (6%); visual acuity reduced (2%); cystoid macular edema (1%); corneal edema (1%); eye pain (1%) and conjunctival hyperemia (1%).

The most common non-ocular adverse reaction that occurred in patients treated with DEXTENZA was headache (1%).

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

*73.6% of physicians in Study 1, 76.4% in Study 2, and 79.6% in Study 3 rated DEXTENZA as easy to insert.

References: 1. Sawhney AS et al, inventors; Incept LLC, assignee. US patent 8,409,606 B2. April 2, 2013. **2.** DEXTENZA [package insert]. Bedford, MA: Ocular Therapeutix, Inc; 2019. **3.** Walters T et al. *J Clin Exp Ophthalmol*. 2016;7(4):1-11. **4.** Tyson SL et al. *J Cataract Refract Surg.* 2019;45(2):204-212.

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+4 D, treatments become extremely unpredictable, according to Dr. Hatch. "Patients end up wearing glasses because they regress," she adds. "So I won't do them."

Although Dr. Tamayo's upper limit of acceptable correction (+6 D) is much higher than what the other surgeons interviewed for this article accept, he's conservative when considering a patient's ocular surface. "We have to remember that we're significantly increasing the curvature of the eye and therefore significantly increasing the dryness of the eye because of less-efficient coverage," he notes. "With a more prominent cornea, in terms of how well it's covered by the curvature of the lid, if the patient has dry eye, that could exclude him from refractive surgery."

The typical shallowness of the anterior chamber in hyperopes is another concern. "With some exceptions, many of these patients have an eye that's too shallow or an anterior segment that's too crowded for a phakic IOL," says Dr. Hardten. "They really don't do well with laser vision correction, in my opinion, and they're too young for RLE."

Which Procedures Are Best?

When considering the limited number of good candidates for hyperopic corneal refractive correction, Dr. Hardten says LASIK, SMILE and even PRK are all reasonable choices under the right circumstances. "With LASIK and SMILE, you have a faster recovery, of course, plus the lack of an epithelial defect. However, one of the challenges with LASIK and SMILE for hyperopic patients is that you tend to have larger optical zones and the eyes are smaller. You will have limited room to make a flap for LASIK or a tunnel or interface for SMILE."

He notes that this predicament is even greater in hyperopic astigmatic patients. "Their eyes are shorter in the vertical direction and wider in the horizontal direction, potentially keeping you from blending those ablations way out to the periphery. So, as a result, I find that I provide a higher percentage of PRK procedures to these patients than I do to my standard myopic patients. Your ability to create the optical properties that you want is probably increased with PRK."

Drs. Tamayo, Hatch and MacRae believe that LASIK is the treatment of choice for hyperopes, with some exceptions.

If the patient's cornea is thin or irregular, Dr. Tamayo uses LASEK, which replicates the treatment of PRK once he creates a defect in the epithelium, instead of in the stromal tissue. "I use SMILE for myopic procedures, but more work is needed to develop an accurate nomogram for SMILE if we're to use it well in hyperopic refractive surgery," he adds.

Dr. Hatch is also looking forward to using SMILE. "Right

now, though, I won't use SMILE on hyperopes because it hasn't been approved for this use by the FDA," she adds.

Dr. MacRae says most hyperopes do well with LASIK, except those with a history of anterior basement membrane disease (such as anterior basement membrane dystrophy), which is sometimes found after RK. "These patients tend to do better with PRK," he notes. Also, for older hyperopes who're undergoing corneal refractive procedures, Dr. MacRae recommends "pampering" their epithelium because it tends to be looser. "I've found over the years you may need to stretch the LASIK flap to get it into place for these patients, following up with a bandage lens," he says.

Remember These Risks

Dr. Hardten urges his colleagues to keep in mind that hyperopic refractive surgery patients in general have a greater risk of experiencing optical aberrations, such as glare and halos. "Because, as I mentioned, the flap goes farther into the periphery, these patients actually also have a higher risk of epithelial ingrowth with LASIK and also with SMILE," he observes. "And then, on the PRK side, remember that you're doing a larger-diameter ablation and will probably see slower epithelial recovery than you would in postop myopes."

Although Dr. Hardten typically won't rule out a patient because of ocular surface disease, he encourages preventive and therapeutic vigilance against all conditions that fall under this large umbrella when you perform LASIK, SMILE or PRK. "It's very important to maximize management, using all of the many treatments that are available," he says.

Echoing Dr. Hatch's concern, Dr. MacRae prepares for unpredictable results in hyperopic refractive surgery. "I may have a retreatment rate of less than 5 percent for myopia but it's probably more like 10 percent for hyperopia, and some of that is related to hyperopic shift," he says. "You'll tend to spend less time on the lower hyperopes, but in the higher hyperopes, it's harder to hit the target, because I think the epithelium is trying to fill in and neutralize some of the higher correction. I tell the higher hyperopes they're more likely to need retreatment."

Dr. Hatch says the biggest risks she encounters are undercorrection and regression. "You may find the need to enhance your patients a few years down the line," she adds. "Other complications, such as dry eye, high aberrations, glare and difficulty driving at night, also develop in high corrections," she adds.

Best All-Around Strategy

All of these surgeons agree that close communication with your patients is the best all-around strategy for achieving success when using refractive procedures to manage hyperopia.

"It's a challenge," Dr. Hardten says. "You're taking them somewhere they've never been before and they're very excited. But most of the time, they start thinking unrealistically, that they will end up just like their friend who doesn't wear glasses. You need to tell them this is different. You need to describe something that is impossible to describe and that each patient experiences in a unique fashion.

"After each procedure, pay attention to how well you've understood that unique patient's personality and what the patient had wanted out of the surgery," he continues. "Also, how well the patient understood what you could have reasonably delivered, and if you helped the patient recognize the shortfalls of the technology, as well as the advantages of being less spectacle-dependent. Bringing these patients through this experience while making as few of them unhappy as possible is your best measurement of success." REVIEW

Dr. Hatch is a consultant with Zeiss and Johnson & Johnson Vision. Drs. Tamayo and Hardten are consultants with Johnson & Johnson Vision. Dr. MacRae reports no financial relationships with relevant companies.

1. Choul YP, Sei YO, Roy SC. Measurement of Angle Kappa and Centration in Refractive Surgery. Curr Opin Ophthalmol 23:4:269-75, 2012.

Tips for Maximizing Hyperopic Success

- To best prepare his prototypical hyperopic refractive surgery patient—the ≥50-year-old about to undergo RLE—David Hardten, MD, fits the patient in monovision, distance and multifocal contact lenses. "It's ideal to preoperatively test what these patients would like to do with their vision, given the variety of lens implants that are available," he notes. "Some patients will tolerate distance vision only, using readers. Some will tolerate monovision with their distance eye being plano or emetropic and their near eye being -1 D. Using contact lens trials is a great way to find these things out before surgery."
- Gustavo Tamayo, MD, emphasizes the continuing need to center the hyperopic corneal treatment on the visual axis instead of the pupil.[1] "It's very important to take this approach, most especially in hyperopic procedures," he notes.
- Dr. Tamayo also recommends performing a cycloplegic refraction in all preop patients with hyperopia and hyperopia with astigmatism. "Most of our patients wear glasses or contact lenses that don't correct for the total amount of their hyperopia because they can't tolerate the full correction," he says. "The risk of not doing the cycloplegic refraction would be to undercorrect them." To successfully implement this recommendation, which some surgeons don't follow to avoid upsetting pre-existing accommodative tone, Dr. Tamayo urges you to prepare patients with an intermediate correction of glasses or contact lenses three to four weeks before surgery.

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

How to Handle Noncovered Services

The only thing worse than performing a complicated procedure is performing a complicated procedure for free.

In spite of what your patients want to believe, Medicare does not pay for everything, even care that beneficiaries or their doctors have good reason to think is necessary. You already know that there are many things for which Medicare has no payment, such as upgrading to a presbyopic or astigmatic intraocular lens during cataract surgery. For instance, things that are bundled have coverage but no separate payment. To help shed light on these issues, this month's column deals with those things for which Medicare simply has no coverage. Of course, private payers and Medicare Part C plans (Medicare Advantage) may have different rules and coverage.

Q What does it mean when we say that Medicare has no coverage for a service we deliver?

A For the most part, this means that, due to the circumstances under which you provide a service, the patient has a financial responsibility to pay you.

Q If Medicare has no coverage, what can I charge the patient?

A Generally, you come up with your own charge, which is typically higher than what Medicare might allow.

Q I have a patient who needs something and I'm not sure if it's going to be covered. How can I find out what Medicare doesn't cover?

A There are a few sources you can turn to for that information: the Social Security Act; the Centers for Medicare & Medicaid Regulations and National Coverage Determinations (NCD); and your Medicare Administrative Contractor guidance and its Local Coverage Determinations (LCD) and Local Coverage Articles (LCA).

Q What does the Social Security Act state regarding noncovered services?

A The main noncovered things mentioned in the SSA (Title XVIII and Sections §1862(a)(7) and 1862(s)(8)) are:

- routine eye care;
- glasses (except for the one-time benefit after each cataract surgery);
- cosmetic services (surgery and those services directly related to it, such as drugs, etc.);
- refractive services (refractions and refractive surgery); and
- screening services (unless specially allowed by statute—glaucoma screening, for example, is a covered benefit although it's rarely used).

Q What does Medicare add to the SSA in terms of noncoverage?

A Medicare amplifies the SSA through the use of CMS Rulings

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* In any trabecular bypass MIGS pivotal trial.
† Significant ECL defined as ≥30% ECL.

INDICATION FOR USE. The iStent *inject*® Trabecular Micro-Bypass System Model G2-M-IS is indicated for use in conjunction with cataract surgery for the reduction of intraocular pressure (IOP) in adult patients with mild to moderate primary open-angle glaucoma. **CONTRAINDICATIONS.** The iStent *inject* is contraindicated in eyes with angle-closure glaucoma, traumatic, malignant, uveitic, or neovascular glaucoma, discernible congenital anomalies of the anterior chamber (AC) angle, retrobulbar tumor, thyroid eye disease, or 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 congenital anomalies of the angle, PAS, rubeosis, or conditions that would prohibit adequate visualization of the angle that could lead to improper placement of the stent and pose a hazard. **MRI INFORMATION.** The iStent *inject* is MR-Conditional, i.e., the device is safe for use in a specified MR environment under specified conditions; please see Directions for Use (DFU) label for details. **PRECAUTIONS.** The surgeon should monitor the patient postoperatively for proper maintenance of IOP. The safety and effectiveness of the iStent *inject* have not been established as an alternative to the primary treatment of glaucoma with medications, in children, in eyes with significant prior trauma, abnormal anterior segment, chronic inflammation, prior glaucoma surgery (except SLT performed > 90 days preoperative), glaucoma associated with vascular disorders, pseudoexfoliative, pigmentary or other secondary open-angle glaucomas, pseudophakic eyes, phakic eyes without concomitant cataract surgery or with complicated cataract surgery, eyes with medicated IOP > 24 mmHg or unmedicated IOP < 21 mmHg or > 36 mmHg, or for implantation of more or less than two stents. **ADVERSE EVENTS.** Common postoperative adverse events reported in the randomized pivotal trial included stent obstruction (6.2%), intraocular inflammation (5.7% for iStent *inject* vs. 4.2% for cataract surgery only), secondary surgical intervention (5.4% vs. 5.0%) and BCVA loss ≥ 2 lines ≥ 3 months (2.6% vs. 4.2%). **CAUTION:** Federal law restricts this device to sale by, or on the order of, a physician. Please see DFU for a complete list of contraindications, warnings, precautions, and adverse events.

REFERENCE: 1. Samuelson TW, Sarkisian SR, Lubeck DM, et al. Prospective, randomized, controlled pivotal trial of an *ab interno* implanted trabecular micro-bypass in primary open-angle glaucoma and cataract. *Ophthalmology.* Jun 2019;126(6):811-821.

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and Transmittals as well as National Coverage Determinations. The CMS rulings we are most familiar with are: NCD number 10.1, which notes that with routine cataract surgery, coverage includes one comprehensive eye exam, biometry and sometimes a B-scan if the cataract is dense, and all other things are not likely to be covered; NCD 80.8, which notes that endothelial cell count via specular microscopy is covered as part of the exam and not paid separately unless there's corneal pathology present; and NCD 80.7, which indicates that refractive keratoplasty—such as LASIK, PRK or limbal/corneal relaxing incisions—is likewise not covered except in the rare case where the condition it's being used to treat was surgically induced (e.g., post-trauma corneal repair). There are a few others, but most eye-care NCDs other than 10.1 noted above are in the "80" series. You can view the entire NCD list here: https://www.cms.gov/medicare-coverage-database/indexes/ncd-by-chapter-and-section-index.aspx.

Q What about my Medicare Administrative Contractor? What does it have to help as a supplement to SSA and Medicare to confirm something is not covered?

A MACs write guidance in a number of ways. They all produce Local Coverage Determinations on a variety of services that note which CPT codes have coverage for various indications. They also may have a supplemental document to the LCD, such as Local Coverage Articles, that note which diagnosis codes have coverage. This use of multiple documents is a recent development.

Occasionally there is a link to a Billing and Coding Guide located at the bottom of the LCD or LCA. Of course, if the covered CPT code list in a LCD doesn't comport with a covered diagnosis in the LCA, the service isn't covered for that diagnosis. Many MACs have a Noncovered Services LCD which can help as well.

Q What should we do if something is never covered and we want to explain that to our patients?

A In this case, explain to the beneficiary that Medicare never covers what you believe he needs. Although the official Advance Beneficiary Notice of noncoverage isn't required when something is never covered, to avoid "buyer's remorse," it's a good idea to obtain proof that the beneficiary accepts financial responsibility for noncovered items and services. You can (and should) collect from the patient at the time of service since Medicare will never pay for that service. As noted above, the most common reasons for "never" coverage are that a service is done for screening, cosmetic or refractive purposes.

Q What if something is covered by Medicare only for certain conditions, but my patient has none of them?

A One example of this is blepharoplasty—if it's functional and meets special criteria for coverage, then Medicare will cover and pay, but it won't cover/pay if the criteria in the LCD/LCA are not met. Another example is when you need a test result (e.g., topography) to discuss whether an astigmatic intraocular lens is appropriate; in this case the diagnosis is regular astigmatism, which is refractive, and the test is a patient-pay service.

In this case, you can think of the service you plan to do as a "sometimes-covered" service. In this situation Medicare notes that you must properly execute an ABN before you deliver the planned service(s). Fill out the form describing the planned service(s), note the specific reason why there's no coverage, and your price for the service. Have the beneficiary sign, date and select their choice on the ABN form; keep the original for your files. It can be done on paper or electronically. If it's done on paper, give the patient a copy. If you execute it electronically, you have to offer the patient the option of a paper copy.

Q I have a patient who opted to change insurances before the date of surgery. What should I do?

A First, verify the new insurance, as the rules may be very different for coverage/noncoverage. If it's still noncovered but the patient now has Medicare Part C (a.k.a., Medicare Advantage, or MA), then a determination of benefits is required to identify beneficiary financial responsibility prior to performing the noncovered services. MA Plans have their own waiver processes and aren't permitted to use the ABN form, so you might have to create a similar sort of financial waiver. Since the plans may not all have the same process, you should check with the plans.

Q What about the ABN form itself? Is there anything else I should know?

A Yes. You must always use the most recent version of the form. Use of an older version could mean the notice could be considered invalid and relieve the patient of the responsibility to pay you.

The current form is due to expire at the end of March 2020 and Medicare hasn't released the newest version of the form as of this writing. When the new form is out, be sure to collect all the older versions so that you don't provide free services to patients unintentionally. REVIEW


Low-Vision Devices: The Overt and Covert

A look at four low-vision devices and some tips for modifying smartphones to help those with limited sight.

Christine Leonard, Associate Editor

If you have low-vision patients in your practice who are struggling to find options to help with daily activities, there are numerous accessibility devices with speech features and magnification that can help people use their functioning vision more effectively. However, there's no one-size-fits-all device, since no two patients' low-vision experiences are the same.

Luckily, there are more options than ever today for visual independence. In this article, we'll review some different low-vision devices and offer advice for making the most of smartphone accessibility functions.

Merlin Elite Pro

The Merlin Elite Pro (Enhanced Vision) is a desktop video magnifier (up to 70 x) that features a full HD autofocus camera and text-to-speech capabilities with optical character recognition. The 24-inch LCD screen pivots horizontally and vertically for a comfortable viewing position, and users can toggle between the CCTV camera and a computer. The Merlin Elite Pro also connects to tablets for magnified viewing. This video magnifier is intended for use in a single location. The company says that setup is easy—"just plug in and begin."

The Merlin Elite Pro can read large items, such as newspapers.

A table tray beneath the screen with a user-friendly locking mechanism can move side to side to make reading easier. The company points out that this is especially helpful for reading larger items like newspapers, which won't fit under the camera all at once. The tray helps the user to move on to the next word or sentence once the end of the screen is reached. This tray can be locked so users can write checks, pay bills or do crossword puzzles.

The Merlin Elite Pro's voice feature also allows users to speak commands to choose where they want to begin reading, where to stop or where to add line markers or bookmarks. Both female and male voices are available to choose from, as well as multiple languages. There are three OCR reading formats—full-page text,

This article has no commercial sponsorship.

The Compact 10 HD Speech device from Optelec USA.

full-page picture and single-line text—so users can choose their preferred reading experience. Documents, pictures and files can be saved and exported to a computer. For more information, visit enhancedvision.com.

Compact 10 HD Speech

The Compact 10 HD Speech is a portable visual magnifier from Optelec USA. This magnifier features a 10-inch screen, large command touchscreen buttons, text-to-speech capabilities and customizable contrast features. A built-in stand props the magnifier at an angle for easy viewing of pages. In addition to a reading camera for documents and an overview camera for seeing objects or text from a short distance, the device also features a compact swing-out camera that folds out from the top of the device, extending the range of magnification and making writing or viewing medications easier.

In Easy Mode, users can adjust the contrast and magnification on the device. In Advanced Mode, users can access a menu, a clock and extra options. You can also save snapshots.

The company says that this device starts up quickly so it's ready when you need it. An indicator at the foot of the Compact 10 tells you where to position the document you wish to read. After placing the document, capture an image and the device will read it aloud with the accompanying magnified text display. It's portable, and at around 10 x 7 inches and weighing two pounds, it fits in most purses and is easily transported in its case. The Compact 10 comes with a rechargeable lithium-ion battery that provides three and a half hours of continuous use as well as a reversible USB-C connector for charging. "It's inconspicuous; it doesn't create a scene," says a company representative. For more information, visit us.optelec.com.

iZoom USB

TrySight's iZoom screen magnifier and reader software comes on a convenient USB drive. Since it's not locked down to a particular machine, users can insert the iZoom program into any computer with a compatible USB port. The software saves your settings, so there's no need to reconfigure it with each new machine you access. No administrative access or installation is required either. "It's really useful for students who want to access computers to study, for those going back to work or anyone accessing a library," adds a company representative. "It doesn't leave anything on the computer when you unplug it."

iZoom works only with Windows computers and requires a mouse pointer to direct the software for magnification. The software magnifies up to 32X and uses a special font-smoothing technology to maintain a clear image. Seventeen natural-voice languages are available for the reading functions, and users can adjust contrast and colors and enhance pointers and cursors for ease of viewing. To learn more, visit trysight.com.

The iZoom USB magnifies text on screens.

eSight

eSight Corporation says its medical device-classed eSight glasses improve low vision through high-speed camera technology, optimization algorithms and video processing software. The glasses feature two OLED screens—one for each eye—and are compatible with HDMI, Bluetooth, Wi-Fi and removable SD cards. Sensors on the glasses note distance, temperature and the wearer's orientation.

The camera in the glasses captures live footage, which is then optimized and enhanced by computer algorithms. The user can enhance image quality further with a remote control; zoom and magnify up to 24X; adjust contrast, focus and color settings; take photos and stream content directly to the device screens in front of their eyes. There's even access to peripheral vision.

In a 2018 study sponsored by eSight, researchers measured the effect of this head-mounted low-vision device on visual function.[1] Data was recorded for 51 participants ages 13 to 75 with stable vision at baseline (no device), at fitting (with device) and after three months of daily use. Immediate improvements in distance VA (0.74 ±0.28 logMAR), contrast sensitivity (0.57 ±0.53 logMAR) and critical print size (0.52 ±0.43 logMAR) were seen with no further change after three months; reading acuity, based on the MNREAD chart, improved at fitting (0.56 ±0.35 logMAR) and by one additional line after three months (all $p<0.001$). Reading speed

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eSight eyewear is a head-worn device that helps to improve low vision with the aid of high-speed camera technology and video processing software.

increased only slightly from baseline to three months. The researchers concluded that using eSight led to immediate improvement in visual ability, including face recognition and reading. For information, visit esighteyewear.com.

Smartphone Mods

Today's smartphones can also act as discrete aids to the visually impaired. Equipped with cameras and AI technology, smartphones or tablets make ideal personal assistants for tech-savvy people of all ages. To access built-in accessibility features, patients can go to their phones' Settings and select Accessibility. There, they'll find options like Android's Screen Magnifier or Screen Reader and Apple's VoiceOver and Magnifier. There are also a number of free apps available for iPhone and Android that provide large-text keyboards, larger home screen icons and swipe gesture-calling. Some apps for business like Office Lens (Microsoft) allow users to scan whiteboards, business cards, photos and single-page items. Intelligent cropping and OCR technology convert these images into MS Office files or PDFs that can be imported to OneDrive.

Smartphone AIs such as Siri and Google Assistant allow users to search for information, call and text, manage calendars, schedule meetings, set reminders and alarms, play music and get weather updates—all with voice commands. Amazon's Alexa smart speaker can create shopping lists, to-do lists or gift lists, read out the latest news, play a game of Jeopardy!, call for help in case of an accident, act as a home intercom or shop online.

The Google Assistant Camera, Google Lens, and Google Lookout apps all allow users to learn more about their environment by taking a photo of something (e.g., currencies, labels, signs). Google can analyze the photo, translate, read text and provide information about its contents. The information about the image can be displayed in large text. Users can identify plants, scan barcodes to display large-print nutrition facts or find ISBN numbers, find and shop for similar décor or clothing and learn about landmarks, restaurants, shops and their ratings and hours of operation. Google Lookout was specifically designed to assist people who are blind or have low vision. It's available on devices running Android 5 and above, like Google Pixel phones, LG 7-8 and Samsung Galaxy S6-10.

Siri, Google Assistant and Alexa can also help the visually-impaired manage everyday tasks and gain more independence. With the appropriate compatible technologies, using voice commands, users can adjust door locks and security, appliances, lights, window shades, sound systems or climate controls. Non-tech-savvy individuals may find the initial setup daunting, but once integrated, they may find the voice-activated technology very useful.

Devices for low vision and disability often cost thousands of dollars, and while smartphones aren't perfect solutions for all socioeconomic situations, many smartphone-based options for those with low vision are free or come with the phone. Assistive intelligent home technologies from Amazon, Apple and Google are becoming more mainstream and therefore more affordable. When it comes to dealing with the emotional and psychological aspects of vision loss and blindness, advanced technologies can help light the way ahead. REVIEW

1. Wittich W, Lorenzini MC, Markowitz S, et al. The effect of a head-mounted low vision device on visual function. Optom Vis Sci 2018;95:9:774-84.

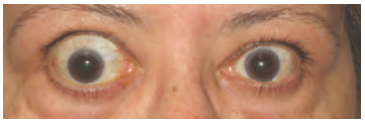
NOW APPROVED

The first and only FDA-approved treatment for Thyroid Eye Disease (TED)

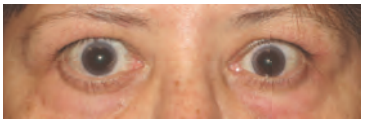
TEPEZZA™
teprotumumab-trbw

TEPEZZA decreases proptosis, diplopia, and the signs and symptoms of TED without concomitant steroids[1-3]

SEE THE DIFFERENCE[4]



BASELINE
Proptosis: 25 mm



POST-TREATMENT (WEEK 24)
Proptosis: 21 mm

Real TEPEZZA patient treated in a clinical trial. Results shown are with no surgical intervention. Individual results may vary. TEPEZZA met its primary endpoint vs placebo in 2 randomized, placebo-controlled trials (P<0.01), defined as proptosis responder rate at Week 24 (percentage of patients with ≥2-mm reduction in proptosis in the study eye from baseline).[1-3,5]

Learn more at TEPEZZAhcp.com

INDICATION

TEPEZZA is indicated for the treatment of Thyroid Eye Disease.

IMPORTANT SAFETY INFORMATION

Warnings and Precautions

Infusion Reactions: TEPEZZA may cause infusion reactions. Infusion reactions have been reported in approximately 4% of patients treated with TEPEZZA. Reported infusion reactions have usually been mild or moderate in severity. Signs and symptoms may include transient increases in blood pressure, feeling hot, tachycardia, dyspnea, headache, and muscular pain. Infusion reactions may occur during an infusion or within 1.5 hours after an infusion. In patients who experience an infusion reaction, consideration should be given to premedicating with an antihistamine, antipyretic, or corticosteroid and/or administering all subsequent infusions at a slower infusion rate.

Preexisting Inflammatory Bowel Disease: TEPEZZA may cause an exacerbation of preexisting inflammatory bowel disease (IBD). Monitor patients with IBD for flare of disease. If IBD exacerbation is suspected, consider discontinuation of TEPEZZA.

Hyperglycemia: Increased blood glucose or hyperglycemia may occur in patients treated with TEPEZZA. In clinical trials, 10% of patients (two-thirds of whom had preexisting diabetes or impaired glucose tolerance) experienced hyperglycemia. Hyperglycemic events should be managed with medications for glycemic control, if necessary. Monitor patients for elevated blood glucose and symptoms of hyperglycemia while on treatment with TEPEZZA. Patients with preexisting diabetes should be under appropriate glycemic control before receiving TEPEZZA.

Adverse Reactions

The most common adverse reactions (incidence ≥5% and greater than placebo) are muscle spasm, nausea, alopecia, diarrhea, fatigue, hyperglycemia, hearing impairment, dysgeusia, headache, and dry skin.

Please see Brief Summary of Prescribing Information for TEPEZZA on adjacent pages.

References: 1. TEPEZZA (teprotumumab-trbw) [prescribing information] Horizon. **2.** Data on File. Horizon, April 2019. **3.** Smith TJ, Kahaly GJ, Ezra DG, et al. Teprotumumab for thyroid-associated ophthalmopathy. *N Engl J Med.* 2017;376(18):1748-1761. **4.** Data on File. Horizon, January 2020. **5.** Data on File. Horizon, December 2019.

HORIZON

TEPEZZA™
teprotumumab-trbw

For injection, for intravenous use

Brief Summary - Please see the TEPEZZA package insert for full prescribing information.

INDICATIONS AND USAGE

TEPEZZA is indicated for the treatment of Thyroid Eye Disease.

WARNINGS AND PRECAUTIONS

Infusion Reactions

TEPEZZA may cause infusion reactions. Infusion reactions have been reported in approximately 4% of patients treated with TEPEZZA. Signs and symptoms of infusion-related reactions include transient increases in blood pressure, feeling hot, tachycardia, dyspnea, headache and muscular pain. Infusion reactions may occur during any of the infusions or within 1.5 hours after an infusion. Reported infusion reactions are usually mild or moderate in severity and can usually be successfully managed with corticosteroids and antihistamines. In patients who experience an infusion reaction, consideration should be given to pre-medicating with an antihistamine, antipyretic, corticosteroid and/or administering all subsequent infusions at a slower infusion rate.

Exacerbation of Preexisting Inflammatory Bowel Disease

TEPEZZA may cause an exacerbation of preexisting inflammatory bowel disease (IBD). Monitor patients with IBD for flare of disease. If IBD exacerbation is suspected, consider discontinuation of TEPEZZA.

Hyperglycemia

Hyperglycemia or increased blood glucose may occur in patients treated with TEPEZZA. In clinical trials, 10% of patients (two-thirds of whom had preexisting diabetes or impaired glucose tolerance) experienced hyperglycemia. Hyperglycemic events should be controlled with medications for glycemic control, if necessary.

Monitor patients for elevated blood glucose and symptoms of hyperglycemia while on treatment with TEPEZZA. Patients with preexisting diabetes should be under appropriate glycemic control before receiving TEPEZZA.

ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Infusion Reactions [see Warnings and Precautions]
- Exacerbation of Inflammatory Bowel Disease [see Warnings and Precautions]
- Hyperglycemia [see Warnings and Precautions]

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 the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of TEPEZZA was evaluated in two randomized, double-masked, placebo-controlled clinical studies (Study 1 [NCT:01868997] and Study 2 [NCT:03298867]) consisting of 170 patients with Thyroid Eye Disease (84 received TEPEZZA and 86 received placebo). Patients were treated with TEPEZZA (10 mg/kg for first infusion and 20 mg/kg for the remaining 7 infusions) or placebo given as an intravenous infusion every 3 weeks for a total of 8 infusions. The majority of patients completed 8 infusions (89% of TEPEZZA patients and 93% of placebo patients).

The most common adverse reactions (≥5%) that occurred at greater incidence in the TEPEZZA group than in the control group during the treatment period of Studies 1 and 2 are summarized in Table 1.

Table 1. Adverse Reactions Occurring in 5% or More of Patients Treated with TEPEZZA and Greater Incidence than Placebo

Adverse Reactions	TEPEZZA N=84 N (%)	Placebo N=86 N (%)
Muscle spasms	21 (25%)	6 (7%)
Nausea	14 (17%)	8 (9%)
Alopecia	11 (13%)	7 (8%)
Diarrhea	10 (12%)	7 (8%)
Fatigue[a]	10 (12%)	6 (7%)
Hyperglycemia[b]	8 (10%)	1 (1%)
Hearing impairment[c]	8 (10%)	0
Dysgeusia	7 (8%)	0
Headache	7 (8%)	6 (7%)
Dry skin	7 (8%)	0

a - Fatigue includes asthenia
b - Hyperglycemia includes blood glucose increase
c - Hearing impairment (includes deafness, eustachian tube dysfunction, hyperacusis, hypoacusis and autophony)

Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay.

In a placebo-controlled study with TEPEZZA, 1 of 42 patients treated with placebo had detectable levels of antidrug antibodies in serum. In the same study, none of the 41 patients treated with TEPEZZA had detectable levels of antidrug antibodies in serum.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

Based on findings in animals and its mechanism of action inhibiting insulin-like growth factor-1 receptor (IGF-1R), TEPEZZA may cause fetal harm when administered to a pregnant woman. Adequate and well-controlled studies with TEPEZZA have not been conducted in pregnant women. There is insufficient data with TEPEZZA use in pregnant women to inform any drug associated risks for adverse developmental outcomes. In utero teprotumumab exposure in cynomolgus monkeys dosed once weekly with teprotumumab throughout pregnancy resulted in external and skeletal abnormalities. Teprotumumab exposure may lead to an increase in fetal loss [see Data]. Therefore, TEPEZZA should not be used in pregnancy, and appropriate forms of contraception should be implemented prior to initiation, during treatment and for 6 months following the last dose of TEPEZZA.

If the patient becomes pregnant during treatment, TEPEZZA should be discontinued and the patient advised of the potential risk to the fetus.

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

Data

Animal Data

In an abridged pilot embryofetal development study, seven pregnant cynomolgus monkeys were dosed intravenously at one dose level of teprotumumab, 75 mg/kg (2.8-fold the maximum recommended human dose [MRHD] based on AUC) once weekly from gestation day 20 through the end of gestation. The incidence of abortion was higher for the teprotumumab treated group compared to the control group. Teprotumumab caused decreased fetal growth during pregnancy, decreased fetal size and weight at caesarean section, decreased placental weight and size, and decreased amniotic fluid volume. Multiple external and skeletal abnormalities were observed in each exposed fetus, including: misshapen cranium, closely set eyes, micrognathia, pointing and narrowing of the nose, and ossification abnormalities of skull bones, sternebrae, carpals, tarsals and teeth. The test dose, 75 mg/kg of teprotumumab, was the maternal no observed adverse effect level (NOAEL).

Based on mechanism of action inhibiting IGF-1R, postnatal exposure to teprotumumab may cause harm.

Lactation

Risk Summary

There is no information regarding the presence of TEPEZZA in human milk, the effects on the breastfed infant or the effects on milk production.

Females and Males of Reproductive Potential

Contraception

Females

Based on its mechanism of action inhibiting IGF-1R, TEPEZZA may cause fetal harm when administered to a pregnant woman (see Use in Specific Populations). Advise females of reproductive potential to use effective contraception prior to initiation, during treatment with TEPEZZA and for 6 months after the last dose of TEPEZZA.

Pediatric Use

Safety and effectiveness have not been established in pediatric patients.

Geriatric Use

Of the 171 patients in the two randomized trials, 15% were 65 years of age or older; the number of patients 65 years or older was similar between treatment groups. No overall differences in efficacy or safety were observed between patients 65 years or older and younger patients (less than 65 years of age).

OVERDOSAGE

No information is available for patients who have received an overdosage.

PATIENT COUNSELING INFORMATION

Embryo-Fetal Toxicity

Advise females of reproductive potential that TEPEZZA can cause harm to a fetus and to inform their healthcare provider of a known or suspected pregnancy.

Educate and counsel females of reproductive potential about the need to use effective contraception prior to initiation, during treatment with TEPEZZA and for 6 months after the last dose of TEPEZZA.

Infusion-related reactions

Advise patients that TEPEZZA may cause infusion reactions that can occur at any time. Instruct patients to recognize the signs and symptoms of infusion reaction and to contact their healthcare provider immediately for signs or symptoms of potential infusion-related reactions.

Exacerbation of Inflammatory Bowel Disease

Advise patients on the risk of inflammatory bowel disease (IBD) and to seek medical advice immediately if they experience diarrhea, with or without blood or rectal bleeding, associated with abdominal pain or cramping/colic, urgency, tenesmus or incontinence.

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HORIZON

Make Complications Disappear

Christopher Kent, Senior Editor

In the first of a two-part series, surgeons share their bag of tricks for handling tough cataract cases.

Cataract surgery may be the most frequently performed surgery in the world, but it's still a complex procedure that—like the eyes cataract surgeons are operating on—is a little different every time. Given the vast number of patients presenting for surgery, surgeons are certain to encounter challenges.

Here, in the first of a two-part series, surgeons who've performed thousands of cataract surgeries share their advice regarding what to do when facing obstacles—expected or unexpected—during cataract surgery. Challenges discussed this month include uncooperative pupils; poor visualization through the cornea; lack of a red reflex; and weak or missing zonular fibers.

Visualization: Problematic Pupil

One of the first challenges a cataract surgeon may encounter is a small pupil, despite preoperative dilating drops. Options for addressing this include stretching the pupil with viscoelastic; stretching the iris manually with a tool; using iris hooks to hold the iris back during the surgery; and using a ring to keep the pupil enlarged.

Richard Mackool, MD, medical director at The Mackool Eye Institute and Laser Center in Astoria, New York, and senior attending surgeon at the Mt. Sinai New York Eye and Ear Infirmary and New York University Medical Center, says that when dilation becomes an issue, the surgeon should first ask if there's a chemical way to dilate it. "Don't be in a hurry to use mechanical stretching without trying other steps first," he says.

Dr. Mackool notes that in many eyes, especially those with a somewhat floppy iris, you may be able to get the pupil to enlarge just by injecting viscoelastic. "I normally use a dispersive viscoelastic for this because it will retain its position against the sphincter of the iris during the procedure much better than a cohesive viscoelastic," he says. "In many cases, that's all that's needed. However, in some eyes you may also want to inject an adrenergic drug such as epinephrine or phenylephrine. If that's the case, you need to inject that drug before you inject the OVD. If you inject the OVD first, it will prevent the drug from reaching the iris.

"During the case, avoid aspirating the OVD from the region of the pupillary margin," he adds. "And, don't hesitate to re-inject OVD during the case if the pupil starts to come down."

In terms of mechanical devices for managing the iris, Dr. Mackool notes that some devices aren't designed to

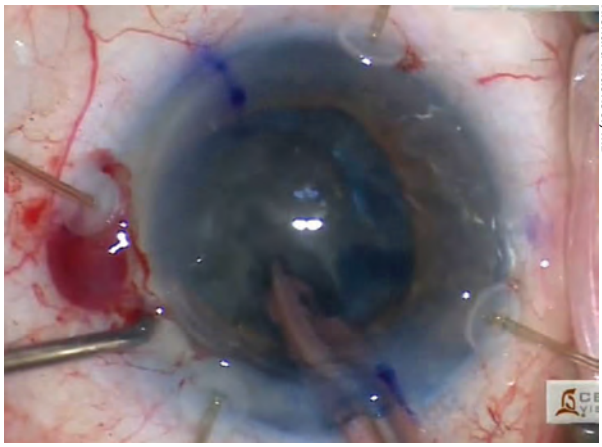
This article has no commercial sponsorship.

be left in the eye. "My favorite in this category is the two-pronged Beehler pupil dilator [Moria Surgical]," he says. "It stretches the pupil, and in the vast majority of cases, that's adequate to resolve the problem."

Elizabeth Yeu, MD, currently in private practice at Virginia Eye Consultants in Norfolk, Virginia, an assistant professor in the department of ophthalmology at Eastern Virginia Medical School, and medical director of the Virginia Surgery Center, notes that to some extent, choosing to work with a pupil between 4 and 6 mm is a matter of the surgeon's skill set and comfort level. "For me, getting Omidria [keterolac and 1.5% phenylephrine] onboard in that situation has been a huge advantage," she says. "It allows me to avoid having to do a physical manipulation of the pupil to enlarge it with a Beehler device, iris hooks or a Malyugin Ring.

"However, if the pupil is very small—say under 4 mm—and it's not responding to the initial dilating drops, it's not going to dilate because of Omidria or any other drug," she continues. "In that situation, mechanical manipulation becomes a necessity. Which type of device you should use depends partly on factors such as the presence of posterior synechiae and partly on what the surgeon is comfortable with. If the patient hasn't been using Flomax [tamsulosin], my go-to is using the Beehler dilator."

Dr. Mackool says the third way to manage a small pupil is with iris retractors. "These are typically less expensive than the rings, but are a bit more time-consuming to put in," he notes. "They require a little more dexterity, and you have to adjust the tension on them. If you use four of them, you have to make four tiny punctures in the cornea. They have no effect on the outcome of the procedure, but to save time, many surgeons prefer to simply use a ring."



Richard Mackool, MD

Capsule retractors can be used to support the capsule/zonule complex during cataract surgery.

Nick Mamalis, MD, ASCRS president, professor of ophthalmology, and director of ocular pathology and co-director of the Intermountain Ocular Research Center, part of the Moran Eye Center at the University of Utah in Salt Lake City, says that if there are no iris abnormalities or zonule issues, he finds pupil rings easier to use than iris hooks. "I have the most experience with the Malyugin Ring," he says. "You insert its eyelet rings onto the iris and it gives you a nice diamond-shaped dilation that doesn't disturb the iris sphincter. It usually doesn't cause problems with bleeding, or any pupil irregularity afterward. However, I may use iris hooks to improve visualization if there are zonular insufficiencies—especially in focal areas. If you want to pull the iris back to improve visualization at one particular point, iris hooks are invaluable."

Daniel H. Chang, MD, a partner at Empire Eye and Laser Center in Bakersfield, California, prefers using a ring to manually stretching the pupil. "The nice thing about the Malyugin Ring is that it holds the iris at eight points," he says. "Stretching it manually brings a greater possibility of focal iris sphincter damage and distortion of the pupil shape, as well as the possibility of causing bleeding. The ring also stretches the pupil, of course, but the force is applied more evenly. The only case in which I had a slightly irregular pupil after using a ring was in a patient who had some preexisting scarring of the iris.

"The ring can also function as a good guide to help me center and size my rhexis," he adds. "Later, I remove it before I take the viscoelastic out."

Strategies for Pupil Dilation

Surgeons offer this advice when dealing with a small pupil:

• ***Don't use manual stretching if the patient has been using Flomax.*** "Flomax can cause the iris tissue to lose tonicity completely," notes Dr. Yeu. "In that situation, stretching it manually with iris hooks or the Beehler tool is the worst thing you can do because the iris can cheese-wire right through. Using a Malyugin ring or similar device that circumferentially holds it open is a great way to manage that pupil."

• ***If the iris is floppy, use a lower-flow fluidics setting with continuous irrigation.*** "When the pupil is small and the iris may be floppy, the latter will have a tendency to come out of your wounds because that's the path of least resistance," says Dr. Yeu. "In that situation, use a lower-flow setting with continuous irrigation to minimize bouncing of the anterior chamber and lower the risk of extrusion."

• ***In Flomax patients, dilating chemicals in the irrigation solution may prevent a mid-surgery pupil constriction.*** "Sometimes if the patient is on an alpha antagonist such as Flomax, the pupil will stay dilated initially, but during the course of the procedure it will constrict and the

iris will become floppy," Dr. Mamalis explains. "So, you want to plan ahead to avoid dilation problems in these patients. I put Omidria into the irrigating solution to keep the pupil from coming down during the surgery."

• ***If a patient isn't dilating well, try intracameral lidocaine.*** Dr. Chang says he uses intracameral 1% preservative-free lidocaine when a patient doesn't dilate well. "If the pupil is 5 mm or smaller, I also place a Malyugin Ring," he says. "I don't use intracameral anesthesia on routine cases, but I will on patients with borderline pupils, for two reasons. One, it can help with dilation. Two, if I'm going to manipulate the iris, the supplemental anesthesia inside the eye will help to maintain patient comfort.

"If it's a 6-mm pupil, or if the patient is on tamsulosin or a similar alpha-blocking medication, I try to assess the iris rigidity while I inject the lidocaine and viscoelastic," he explains. "Once you open the capsulorhexis, you have to be very careful about placing iris retractors, so I watch the iris as I inject the lidocaine and viscoelastic. If I see it flapping around as I'm injecting either, I'm more likely to insert a Malyugin Ring."

• ***Avoid touching the iris.*** "Once you touch the iris, the pupil will want to come down even further," Dr. Yeu notes.

• ***Be on the lookout for high posterior pressure.*** "This is relevant because when there's a lot of pressure posteriorly and the bag complex comes forward, the pupil usually comes down as well," Dr. Yeu explains. "So, if you have a firm eye, a shallow chamber, a small pupil and the iris wants to come out, posterior pressure may be the problem. This can happen in small eyes even without the effusion, because the scleral wall is thicker and the eye has less volume. Often, you'll notice the signs of this as soon as you enter the eye and put in viscoelastic. For smaller eyes, applying pressure to soften the eye with a Honan balloon or reducing vitreous pressure with IV mannitol can be helpful.

"If that's the case, there may be a choroidal effusion or an anterior rotation of the ciliary body," she adds. "In that situation you have to do what you can to mitigate the positive posterior pressure. Deepen very slowly with a heavy viscoelastic device, and stop if iris tissue is moving towards prolapsing out of the wound. If possible, you may need to do a tap of the vitreous cavity to release some of that pressure."

Visualization: The Cornea

"Whenever you encounter a problem with visualization, the first thing you absolutely have to do is figure out the cause of the problem," Dr. Mackool says. "Never, ever proceed until you've answered that question."

Dr. Mackool notes that a number of issues can interfere with your ability to see into the eye clearly. "First, remember that it could be something as simple as the lens at the bottom of your microscope needing to be cleaned," he says. "Sometimes saline will spray up onto it, maybe from an earlier case; the saline dries, leaving a salt deposit on the lens. Or, the eyepieces could be smudged or have condensation on them. Then, make sure there are no mucoid deposits on the cornea. Irrigate the surface to make sure it's clear of particulate matter."

Dr. Mackool points out that a dry, edematous or irregular cornea can interfere with visualization. "The technician may have taped the lids open and the corneal epithelium simply dried out," he says. "Generally, it's good to keep the cornea very moist during the procedure. If I know there's an issue with corneal dryness—whether it was allowed to dry out, or because of a pre-existing issue such as epithelial dystrophy—I coat the surface of the eye with an OVD.

"The best OVD for this purpose is hydroxymethyl cellulose, otherwise known as OcuCoat," he continues. "It has the perfect molecular weight to coat the surface very well and give you really good visibility. Sometimes it even helps with preexisting corneal irregularities—including some keratoconic eyes that have deformities. I don't use it intraocularly, but it's great on the surface of the cornea for these situations.

"If you need to deturgesce an edematous cornea to improve visualization, you should do two things," he explains. "First, put a dispersive viscoelastic in the anterior chamber to coat the endothelium, so aqueous or BSS can't pass into the cornea during the case. Second, put topical glycerin on the surface of the cornea. It's an osmotic dehydrating agent, and within 30 to 60 seconds it will remove the fluid from the epithelium. There will still be fluid in the stroma, but that tends to have less impact on vision.

"If you need to dry out the stroma as well, keep adding glycerin for about 10 minutes," he adds. "The fluid in the stroma will gradually move toward the epithelium and be removed by the glycerin. With patience, even very edematous corneas can get pretty clear."

Dr. Mamalis says that if he has a patient with significant epithelial edema, he may try to deturgesce the cornea using hyperosmolar drops. "High-molecular-weight Dextran will sometimes help," he notes. "Glycerin does the same thing. But if you can't get a good view in spite of that, as a last-ditch option you may have to scrape off the epithelium. That's a drastic step I try to avoid, because then the patient has to wear a bandage contact lens for several days while the epithelium heals."

Dr. Yeu says that if she's faced with corneal edema when coupling cataract surgery with a procedure such as an endothelial keratoplasty, she'll proceed with the surgery until she has to denude the epithelium in order to see clearly enough to continue. "Denuding the epithelium via a superficial keratectomy buys you another 10-to-15 minute window of greater clarity," she notes.

Outside of the OR

Daniel H. Chang, MD, a partner at Empire Eye and Laser Center in Bakersfield, California, offers a few suggestions that may help prevent cataract surgery obstacles from becoming even bigger problems:

- ***If you see obstacles coming, forewarn the patient.*** "It's important to tell patients if they're outside the normal range of routine surgery," says Dr. Chang. "That way, they'll have proper expectations regarding their outcome. Patients frequently have friends who talk about how perfect and easy their surgeries were, thus setting up unrealistic expectations. I tell patients who present with unusual challenges, or who may have less than perfect outcomes, that their case is different. I do stay upbeat and let them know they'll probably do fine, but I make sure they have proper expectations."
- ***Schedule tough cases towards the end of the day.*** "That way," says Dr. Chang, "if the case does run longer, it doesn't affect the rest of the schedule."
- ***Make a list of the specifics of the cases you're doing each day.*** "I create a 'battle sheet,' " says Dr. Chang. "This includes each patient's name, date of birth, operative eye, diagnosis and planned procedure. I note the cataract density, pupil dilation, IOL type and power, and any relevant comments that may be of concern in surgery. This way, at the beginning of each day I know when I'll be taking care of a routine stretch of eyes and when I'm facing a challenging case, so I'll be mentally ready for that."

—CK

Visualization: No Red Reflex

In some patients, a cloudy cataract will minimize or eliminate the red reflex that ordinarily helps the surgeon see the anterior capsule. Dr. Yeu says if there's poor visualization through the cornea or a poor red reflex, she uses VisionBlue (trypan blue, DORC) to stain the capsule. "I generally put it into the eye without air, count to 10, and then wash it out," she says.

She notes that pupil size can be an issue when using a capsule stain. "The trypan blue is only going to stain what's actually visible on the anterior capsule," she points out. "So, with a smaller pupil I'll do what I can to stretch the pupil under cohesive viscoelastic to get as much visualization of the anterior capsule as possible before staining it. You want to be sure you get the stain across all of the anterior capsule that you need to see so you'll have enough visible surface area to perform your capsulorhexis."

Dr. Yeu notes that when the red reflex is missing, the surgeon needs to proceed much more cautiously. "Use continuous irrigation with a lower flow rate," she advises. "Be aware that it may be more difficult to see the posterior capsule, and there could be positive posterior pressure as well.

"In this situation I may use a Koch spatula, held with my nondominant hand, to hold the capsule back while disassembling the nucleus," she adds. "In fact, I always use a Koch spatula with my last quadrant of lens when performing cataract surgery, but it's especially important when you lose your red reflex. Meanwhile, fill the bag with dispersive viscoelastic, move slowly, and see if you can find any clues to the contour of the bag—especially when you only have a few pieces of nucleus left to remove."

Weak or Missing Zonular Fibers

This is a problem that can often—

though not always—be detected preoperatively. "Knowing the condition of the zonules beforehand lets you be prepared for what you'll encounter during surgery," notes Dr. Yeu. "For example, if your patient has a dislocated lens, you want to know how dislocated it is, in terms of clock hours. If you notice a generalized shimmering of the lens, you might be dealing with a pseudoexfoliation patient."

Dr. Yeu adds that if the crystalline lens is grossly dislocated, you should lay the patient in a supine position preoperatively. "You want to make sure that the lens doesn't have a tendency to fall back into the vitreous cavity to a point at which you can't access it when you're in the OR," she says. "This is especially important if the patient has gross zonulopathy, such as four to six clock hours of missing zonules. If you can't visualize the lens when the patient is lying supine, a combined case with (or a referral to) a retinal surgeon will be the safest option for an anterior segment surgeon."

Dr. Yeu admits that you can't always detect zonular problems preoperatively. "If you find, for example, that you're struggling to create a large enough rhexis, and/or the capsule wrinkles during the capsulorhexis, you may not be getting the usual counterpressure from the zonules," she says.

Dr. Chang agrees, noting that a manual capsulorhexis can help to identify locations where the zonules may be focally weak. "Be cautious, because in areas where zonules are weak the lens has a tendency to pull centrally during the capsulorhexis," he says. "When you release, it moves back and you'll find that you're farther toward the periphery of the lens than you thought."

Tools for Managing Zonules

Several options can help when weak or missing zonular fibers are present:

• ***A femtosecond laser capsulotomy.*** Dr. Yeu points out that if zonular weakness is affecting your ability to make the capsulorhexis, a femtosecond laser capsulotomy could be ideal. "If the patient has decent dilation," she says, "you can center the laser on the capsule and get exactly what you need without involving the zonules."

• ***Capsule retractors.*** "Capsule retractors hook over the edge of the capsulotomy," explains Dr. Mackool, who invented the first capsule retractors about 20 years ago. "These are fundamentally different from iris retractors, which are short and not designed to stabilize a lens capsule."

Dr. Mackool says a common error is holding off using capsule retractors, thinking you might be able to get by without them. "That's not a good idea, because they can save you from a world of trouble," he notes. "The first time you think you might need them, stop and put them in. They can dramatically reduce the likelihood of complications. I've never regretted putting in capsule retractors, but I have regretted not putting them in."

Dr. Mackool offers one important tip when using capsule retractors: Don't pull them tight to retract the capsulorhexis. "That's not how they help," he explains. "The terminal part of the retractor going out into the capsular fornix provides support. Just place the retractors so they approximate the edge of the capsulorhexis margin. In areas where there are no zonular fibers, place one about every 45 degrees; in areas where the zonule is lax or weak, put one every 90 degrees.

"If you're not used to inserting them, it will take you five minutes, but once you're used to putting them in, it takes two minutes," he adds. "Be especially careful when using them after a femtosecond laser capsulorhexis, because it might not be as resistant to tearing as a manual capsulorhexis."

• ***A capsular tension ring.*** Surgeons point out that it's important to

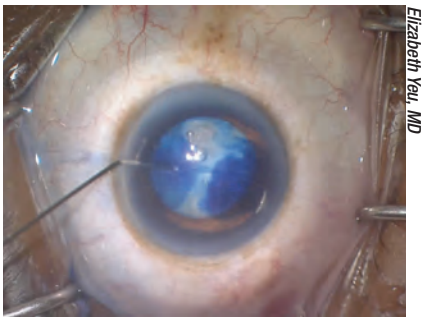
know when it makes sense to use a CTR. "A capsular tension ring will keep the capsule expanded, but it doesn't reduce zonular stress during the procedure," says Dr. Mackool. "In contrast, capsule retractors act as an artificial zonule. They take the stress off the remaining zonular fibers."

"If you're having difficulty because the lens is moving, using a capsular tension device can be helpful," notes Dr. Yeu. "However, I put it in as late as possible because once the ring is in, it makes it more difficult to do cortical removal. If you can wait until the cortex is completely removed, that will make life easier. But if you have to insert it early on—which sometimes is unavoidable—then be aware that you'll have to do extra-slow, careful viscodissection to loosen up the remaining cortical fibers."

Dr. Chang points out that sometimes when the zonules are weak, the lens has been bolstering things in place. "If that's the situation, you may take out the lens and discover that the bag is collapsing in one area," he says. "At that point, placing a capsular tension ring can be helpful."

• ***An appropriate IOL.*** "If you have just a little bit of zonulopathy, say one or two clock hours, inserting a three-piece IOL with the haptics aligned in the area of the slightly loose zonules will help to provide some tension at that location," notes Dr. Yeu. "If the eye has about three clock hours of missing zonules, or a little zonulopathy that's generalized, as you might find in a pseudoexfoliation patient, a standard capsular tension ring can be a good solution."

• ***Segments that can be sewn in place to support the capsule.*** "Once you have more than three clock hours of missing or weak zonules, or the lens is grossly dislocated, you'll have to sew in either a segment or a ring, or a combination of multiple segments," says Dr. Yeu. "How you proceed depends on your skill set and what the ultimate goal of your surgery is."



Elizabeth Yeu, MD

When a cataract is dense, the red reflex may be minimal or nonexistent. Injecting a dye such as trypan blue (shown above) helps to make the anterior capsule visible.

Dr. Mamalis says that the tool that makes the most sense depends mostly on whether the zonular disruption is focal or diffuse. "Patients who've had a trauma sometimes have disruption of the zonules in just one quadrant," he points out. "In those patients, you may want to put a capsular hook or two in that area to protect the zonules while you do the phaco. If the area of disruption is three clock hours or less, you can proceed to put a capsular tension ring into the bag, followed by the implant, and you don't have to do anything further.

"Some patients, such as those with Marfan syndrome or severe exfoliation syndrome, can have zonular weakness all the way around," he continues. "In that case, I think it's very helpful to use capsular hooks to support the lens capsule while you're removing the cataract. After that, a capsular tension ring may not be sufficient to support the capsule with the lens in it, so you may want to consider using a device that can be placed into the capsular bag and sutured to the ciliary sulcus, such as a Cionni ring or an Ahmed segment."

More Zonule Strategies

Surgeons offer these additional tips:

• ***If you can see the edge of the capsular bag equator, use viscoelastic to prevent vitreous prolapse.*** "In this situation you have several missing zonules," Dr. Yeu points out. "That space is going to allow communication to the vitreous cavity. So it's extremely important that you tamponade that space with dispersive viscoelastic to prevent vitreous prolapse."

• ***Remember that weak zonules can lead to nuclear fragments migrating posteriorly.*** "When there are areas of zonular compromise, it's crucial to make sure you get all of the cataract out," says Dr. Chang. "Be sure you don't still have a lens fragment behind the posterior capsule. If you're not sure, dilate early postoperatively or send the patient to retina."

• ***Don't hesitate to refer.*** Dr. Chang believes there's no shame in referring a very complex case. "If a patient is missing significant zonules or if the lens is significantly dislocated, I refer those cases either to a colleague who specializes in managing that type of case or to a retina specialist," he says. "They can take the lens out from the back."

Dr. Yeu agrees. "For example, you might encounter a patient with zonulopathy and a very dense lens," she says. "That's going to be a very tough case, because disassembling that lens will require a lot of manipulation, making it likely that you'll cause more zonulopathy intraoperatively. You have to decide if this is a case that you want to do yourself. You always have the option of sending the case to someone else." REVIEW

Dr. Chang is a consultant for Zeiss. Dr. Yeu is a consultant for Omeros. Drs. Mackool and Mamalis have no financial ties to any product discussed.

Next month in Part 2: Managing anterior and posterior capsule tears, problems resulting from the patient coughing, bleeding inside the eye, wound burns and removing a very dense cataract.

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Technology Takes a Back Seat to Technique

Walter Bethke, Editor in Chief

Femto and intraop aberrometry level off, but Yamane captures surgeons' interest.

According to our most recent survey of cataract surgeons, new technology like femtosecond cataract surgery is leveling out, while new techniques like the Yamane suturing technique are taking off. Surgeons also say toric intraocular lenses are tops when tackling cylinder, topical drops still rule for postop inflammation/infection control, and quadrant division is best for nucleofractis.

This month, 1,698 surgeons of the 11,524 who received the survey opened it (14.7 percent open rate) and, of those, 89 completed the survey. Read on to see how your approach compares to theirs.

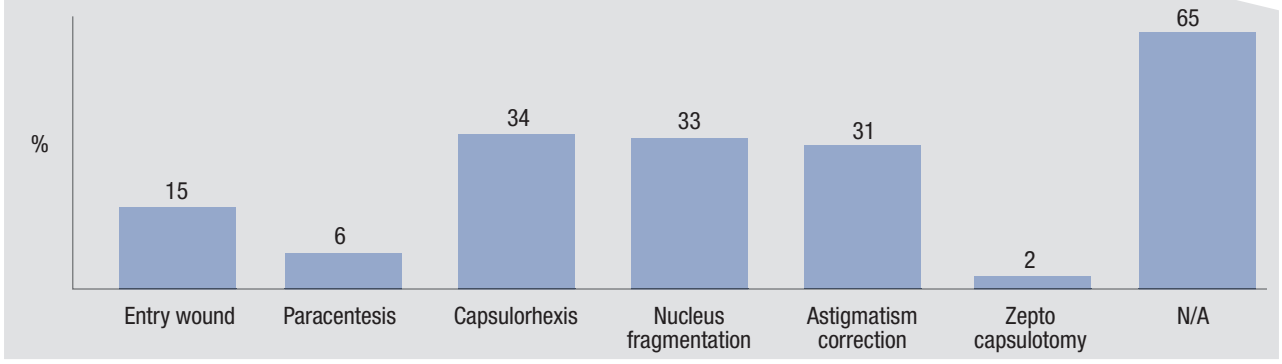
Managing Astigmatism

The surgeons say that toric IOLs are their preferred method for treating pre-existing astigmatism in their cataract patients, with this option chosen by 56 percent of the respondents. The next most popular option is a toric lens combined with placing the entry wound on the steep axis (15 percent). Manual limbal relaxing incisions were chosen by 8 percent. The remaining options were chosen by less than 8 percent of surgeons.

"[Toric IOLs have a] broad range of astigmatism correction and are very accurate," says ASCRS President Nick Mamalis, MD, of Salt Lake City. "It doesn't affect the cornea." Another surgeon agrees, saying that he prefers a toric lens because of "Predictability and less need for corneal manipulation."

A surgeon from Iowa says that toric

Surgeons' Use of the Femtosecond Laser or Zepto in Cataract Surgery



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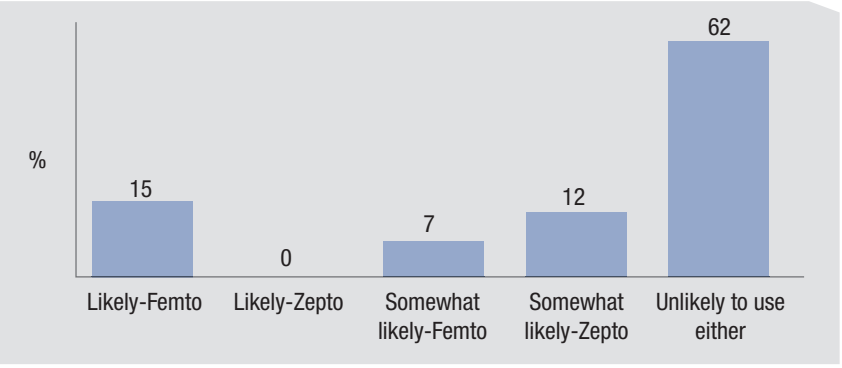
References: 1. Chan JE, Netland PA. EX-PRESS Glaucoma Filtration Device: efficacy, safety, and predictability. *Med Devices (Auckl).* 2015;8:381-388. **2.** Lee RMH, Bouremel Y, Eames I, Brocchini S, Kaw PT. The implications of an ab interno versus ab externo surgical approach on outflow resistance of a subconjunctival drainage device for intraocular pressure control. *Transl Vis Sci Technol.* 2019;8(3):58. **3.** Amoozgar B, Wei X, Lee JH, et al. A novel flexible microfluidic meshwork to reduce fibrosis in glaucoma surgery. *PLoS One.* 2017;12(3):e0172556. **4.** Agrawal P, Bradshaw SE. Systematic literature review of clinical and economic outcomes of micro-invasive glaucoma surgery (MIGS) in primary open-angle glaucoma. *Ophthalmol Ther.* 2018;7(1):49-73.

Likelihood of Using Femto or Zepto in the Coming Year



IOLs are ideal because of their "Consistently best results—a surgeon can use femtosecond or manual LRIs for smaller amounts of astigmatism not requiring a toric IOL."

Bernard Milstein, MD, of Houston, says he prefers to use a toric lens because you can "supplement it with a postop LASIK procedure; this is more predictable."

For the surgeons who prefer to both insert a toric lens and also make their entry wounds on the steep axis, they prefer that approach for similar reasons.

"This approach works best in most cases and is the least invasive technique," says George Walters, MD, of Beaumont, Texas. Charles Ahn, MD, of Lombard, Illinois, likes this technique due to the "better patient payment and comfort."

Femto Usage

For the past several years of our survey, surgeons who use either a femtosecond laser or the Zepto capsulorhexis device have hovered in the 33 to 36 percent range, and this year is no different, with 36 percent of the surgeons using one of them. The most popular usage for the femtosecond is capsulorhexis creation (34 percent), though nuclear fragmentation and femto AK incisions are close behind at 33 and 31 percent, respectively (2 percent say they use a Zepto to make the capsulorhexis). The next most popular applications for femto are the creation of the entry wound, at 15 percent, and creation of a paracentesis (6 percent). Twenty-two percent of the femto users say they'll perform more femto cataract in the coming year, 9 percent will do less and 68 percent will do the same amount.

"Femto is accurate, safe and reproducible," says Dallas surgeon Jeffrey Whitman. Another surgeon, from Minnesota, likes the Zepto technology, saying, "Zepto is ideal for mature, white cataracts; it makes them routine cases."

Most of the other respondents, however, don't appear to be sold on femto or Zepto's attributes. "I used to perform FLACS but I felt patients didn't benefit from the laser and it slowed everything down," says Richard Wieder, MD, of St. Louis. John Willer, DO, of The Dalles, Oregon says, "Femto is a solution looking for a problem. Also, I feel the push towards femto is more financial than what is in the patient's best interest … I can make my own rhexis and don't need some overpriced gadget to do it for me." A surgeon from Kentucky has no plans to use a femtosecond laser for his surgeries. "I don't like femto because it is expensive," he says. "It doesn't improve safety or refractive results and it adds a lot of time."

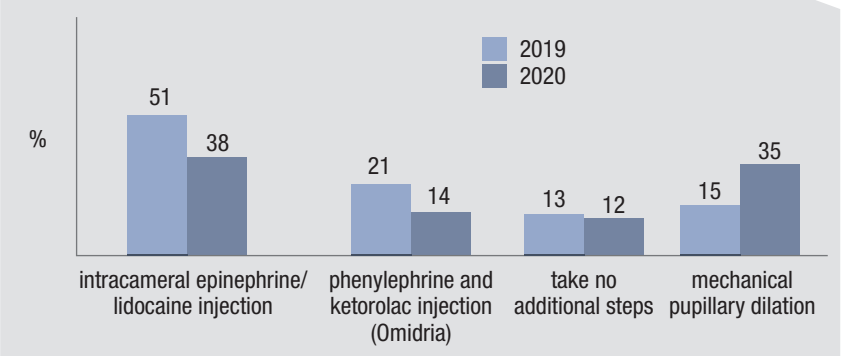
Complicated Cases

Surgeons also weighed in on how they manage some sticky situations, such as their approach to fixating IOLs in cases of compromised capsular support and how they deal with small pupils.

For a lens in an eye with no capsular support, the largest proportion of respondents, 44 percent, prefer to use an anterior-chamber IOL. The next most popular option, chosen by 31 percent of surgeons, was the Yamane technique for scleral fixation, followed by scleral fixation by some other method. Iris fixation was chosen by 5 percent.

"The Yamane technique is reliable without significant long-term complications, such as suture erosion," says a surgeon from New Jersey. A fellow New Jersey physician agrees, saying,

How Surgeons Create a Wide Pupil During Surgery



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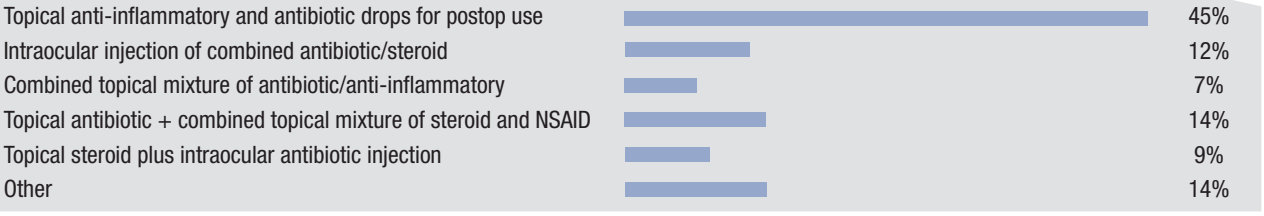
Surgeons' Preferred Method for Controlling Postop Inflammation/Preventing Infection



"It makes physiological sense."

For cases of small pupils, mechanical dilation (mostly with the Malyugin ring) made a big jump this year, going from 15 percent last year to 35 percent. "If you're thinking about using a Malyugin—use it!" states Inna Ozerov, MD, of Hollywood, Florida. The most popular option is still an intracameral injection of epinephrine and lidocaine (38 percent), followed by the use of Omidria (phenylephrine and ketorolac injection, Omeros), chosen by 14 percent. Twelve percent of the respondents say they take no additional steps in these patients.

Points of Interest

Surgeons also discussed other aspects of surgery, including:

• ***Intraocular aberrometry.*** Only 38 percent of the respondents use this technology. Of the surgeons on the survey who do use it, 40 percent rate it as good, and 18 percent say it's excellent. Twenty-two percent say it's fair, and 18 percent deem it poor. "It's great for post-refractive-surgery patients," says Jonathan Rubenstein, MD, of Chicago. A surgeon from Minnesota agrees, adding that it's ideal for "aligning the toric IOL axis and IOL power confirmation or adjustment." Matthew Kruger, MD, of Denver says that though it's good, "With newer lens formulas, the need for it is less. It takes more time than it's worth now."

Andrew F. Kolker, MD, is also less-than-enthused about the technology. "I find it useful [for post-LASIK patients]," he says. "Otherwise, I don't find it helpful and in fact confusing for toric patients, and not useful in standard cases (it's not helpful, takes longer and the machine is bulky)."

• ***Postop inflammation/infection control.*** The most popular approach to this is topical anti-inflammatory and antibiotic drops that the patient uses postop (45 percent). Fourteen percent of the surgeons give a topical antibiotic and a combined mixture of a topical steroid and an NSAID; 12 percent administer an intraocular injection of combined antibiotic/steroid. The rest of the results appear in the graph above. For surgeons who use another method (14 percent), some responses were: subconjunctival injection plus a topical anti-inflammatory; pre- and postop topical antibiotic; postop topical steroids with an antibiotic in the infusion; intraocular antibiotic injection and a sub-conjunctival Kenalog injection; and topical anti-inflammatory and intracameral moxifloxacin.

• ***Breaking up the nucleus.*** Thirty-seven percent of surgeons chose quadrant division as their preferred method for breaking up the nucleus, followed by stop-and-chop (21 percent) and horizontal phaco chop (12 percent). The rest of the options were chosen by less than 10 percent of respondents. "Quadrant division works for 90 percent of my cases and has the lowest capsular risk in my hands," says a surgeon from Minnesota. "It's safe and predictable," says Houston's Dr. Milstein.

The stop-and-chop proponents focus on efficiency and control. "It uses less energy and fluidics," says a surgeon from Arkansas. Kerry Hunt, MD, in Raleigh, North Carolina, says he likes stop-and-chop because it "facilitates the initial chop." The horizontal choppers, however, are also outspoken in their affinity for the technique. "It uses the least ultrasonic energy," says a surgeon from New York. "There's no peripheral sculpting required. It's efficient and safe when done with the proper (blunt) instrumentation." Dr. Kruger agrees, saying, "It works on everything from soft to very hard cataracts. It's very safe and the surgeon never approaches the posterior capsule."

• ***Surgical pearls.*** As they do every year, the surgeons in our cataract survey shared their best pearls:

• Spend plenty of time and effort with hydrodissection (Richard Wieder, MD, St. Louis);

• Maintain excellent visualization at all times;

• When checking the keratome incision for leakage don't forgot to check the paracentesis, as this may leak at the end of surgery (Max Walsh, MD, Royal Oak, Michigan);

• Lift the iris off the lens for an overly deep chamber;

• Relax and keep your eyes open for subtle operative field changes;

• Use a corneal marker to ensure accurate reproducible rhexis size (Stewart Galloway, MD, Crossville, Tennessee);

• When sculpting, always start less deep centrally; you can always deepen your groove if you can't crack it (Dr. Kolker); and

• When that voice in your head tells you that something isn't right, listen to it and take precautions. Don't plow ahead as usual. REVIEW

MIGS and the Arc Of Glaucoma Care

Christine Leonard, Associate Editor

Glaucoma experts weigh in on the impact of MIGS.

As a chronic disease, glaucoma marches steadily toward irreversible vision loss. Treatment focuses on preventing and slowing the development and progression of optic nerve damage with IOP-lowering measures such as topical and systemic drugs, selective laser trabeculectomy and incisional surgery.[1]

Trabeculectomy turned 50 in 2018, and today it remains the gold standard for the surgical management of glaucoma. With half a century behind it, trabeculectomy has a long record of published results and well-refined techniques that have made it one of the most effective, cheapest and simplest options for glaucoma surgeries.[2] But despite being the most used surgical method for managing glaucoma, trabeculectomy still fails and often yields inconsistent results,[2] such as postoperative IOPs that are either too low or too high, and complications such as hyphema, decompression retinopathy and choroidal detachment.[3] As a result, alternative procedures with better safety outcomes and lower risk profiles have been sought.

Most experts agree that having MIGS as an additional, less-invasive surgical option for their patients is valuable in the overall arc of glaucoma care. In the interest of increasing safety and reducing the number of surgical interventions needed to manage glaucoma, however, you may wonder if doing MIGS procedures earlier on is worth it if some patients still wind up needing additional, more invasive procedures down the road. In this article, surgeons share their thoughts on MIGS' impact on the arc of glaucoma care and the role these procedures play in staving off blindness.

What MIGS Offers

MIGS has been touted as a potential alternative to conventional incisional surgeries, as well as to medication and laser treatments, but surgeons agree that it's not a panacea. So what can you expect from MIGS? When asked whether or not MIGS obviates the need for more traditional surgery, Michele C. Lim, MD, professor, vice chair and medical director of ophthalmology at UC Davis, replied that "MIGS doesn't supplant some of the more traditional surgeries."

Rather than serve as a replacement for traditional trabeculectomy or tube shunts, most surgeons say that MIGS works best as an additional option for glaucoma treatment or as a delaying procedure. "MIGS temporarily shifts and delays the need for trabs and tubes," points out Sean Ianchulev, MD, MPH, professor of ophthalmol-

This article has no commercial sponsorship.

ogy at the New York Eye and Ear Infirmary. "Patients are given another temporizing surgical treatment alternative that fills the gap between drops and conventional glaucoma surgery." Brian Francis, MD, MS, associate professor of ophthalmology at the Doheny Eye Institute, Keck School of Medicine, USC, agrees and notes that additionally, "MIGS is a safer surgical alternative to trabs and tubes when used properly."

In an editorial published in *Ophthalmology* in 2015, Ike Ahmed, MD, notes that "MIGS devices are often used earlier in the glaucoma treatment algorithm...A common misperception of MIGS is that it needs to be compared with the gold standard of mitomycin-C trabeculectomy to show its effectiveness. This inappropriate interpretation is based on the idea that MIGS procedures are designed to replace conventional filtering surgery. In fact, MIGS devices are designed to address the treatment gap that exists between medical therapy and more aggressive traditional surgical options."[5]

Philip Bloom, MB ChB, FRCS(Ed), FRCOphth, consultant ophthalmic surgeon at Imperial College Healthcare NHS Trust in London, says that MIGS is a completely new step in the surgical paradigm. "With MIGS, a proportion of patients avoid the need for more invasive surgery, but MIGS are rarely in competition with trabeculectomy, which is, in my opinion, the best single option for when you need very low pressures and for patients with advanced disease. If we get patients early enough, we'll often do a MIGS device either to prevent their being on too many drops or to even avoid starting drops in the first place.

"It's entirely possible that, as they become more effective, MIGS may take on a role more comparable to trabeculectomy, but at the moment they're not as effective," he says. "They fit earlier into the treatment paradigm than trabs or tubes."

Comparison of Glaucoma Surgical Procedures

Outflow Pathway	Surgery	IOP Reduction	Medication Reduction
Subconjunctival	Trabeculectomy	49.5% at 5 years	1.5 at 5 years
	Aqueous Shunt	41.4% at 5 years	1.4 at 5 years
	Ex-PRESS	44% at 2 years	3.4 at 2 years
	XEN	36.4% at 1 year	1.8 at 1 year
Trabecular	iStent	20% at 1 year	1.2 at 1 year
	Hydrus*	36% at 2 years	1.5 at 2 years
	Trabectome	52% at 1 year	1.3 at 1 year

*Combined with cataract surgery
Source: Bar-David L, Blumenthal EZ. Evolution of glaucoma surgery in the last 25 years. Rambam Maimonides Med J 2018;9:3:e0024.

MIGS Has Its Place

MIGS' success depends in large part on proper patient selection, Dr. Francis says. "MIGS is particularly suited to mild-to-moderate glaucoma cases, especially in patients whose pathology is in the trabecular meshwork. This includes pseudoexfoliation glaucoma, pigmentary glaucoma and steroid-induced glaucoma. On the other hand, MIGS is unsuitable for a patient with very advanced glaucoma who needs target pressures of 10 to 12 mmHg, for example.

"The biggest advantage of MIGS in general is its enhanced safety versus traditional filtering surgery and the fact that it gives patients more options," he continues. "You're giving surgical options to patients who either wouldn't have been surgical candidates before because they had mild-to-moderate glaucoma or to those patients for whom it's unsafe to do filtration surgery."

"Recovery time after a MIGS procedure is usually shorter than after traditional surgery, depending on which MIGS you're talking about," Dr. Lim notes. "Additionally, in a MIGS surgery, you're moving less tissue in the eye." This may be especially important for older patients; because surgical procedures rely a good deal on the quality of the surgical tissue, older patients are at a higher risk for complications.[4] Dr. Lim also notes that moving less tissue in the eye will open up more options if you need to do another surgery down the road.

However, for more severe cases of glaucoma, "MIGS doesn't routinely get eye pressures into the low teens," says James C. Tsai, MD, MBA, president of the New York Eye and Ear Infirmary of Mount Sinai and system chair of ophthalmology, Mount Sinai Health System. "I think it's good we have MIGS," he says. "I think the reason I don't do MIGS is that I'm not sure how much it helps for the types of patients that I see, who tend to have moderate to severe glaucoma, such as very complicated glaucomas, normal-tension glaucomas or glaucomas where they've already been on multiple medications. In those cases, patients usually don't have very high pressures. Their pressures tend to be in the mid to high teens or maybe low 20s. Many of my patients need pressures in the low teens or high single digits for the glaucoma progression to halt. If you look at the prospective MIGS studies, eye pressures tend to end up in the mid to high teens."[6]

"You want to save the more invasive surgeries for when the glaucoma is more severe," Dr. Tsai continues. "It's not very fair to ask that MIGS have comparable IOP-lowering efficacy to

a trab or tube in a moderate-to-severe case." Most MIGS clinical trials have been restricted to mild-to-moderate cases of glaucoma, and as a result, there's little data on MIGS' efficacy for moderate-to-severe glaucoma.[1]

A 2018 literature review of MIGS outcomes found that the MIGS devices used in the analyzed studies were typically associated with higher postoperative IOPs, compared to various forms of trabeculectomy, which usually result in IOPs between 11 and 13 mmHg. The review included the outcomes of nine randomized clinical trials (seven iStents, one Hydrus and one of the now de-funct CyPass stents), seven non-randomized clinical trials (three iStents, three CyPass and one Hydrus) and 23 economic studies. The authors also found that MIGS devices may result in increased hypotony rates or bleb needling in devices placed subconjunctivally. It was unclear whether the cost of MIGS is outweighed by the cost-savings of medication reduction or less need for further intervention.[6]

MIGS and Cataracts

For most MIGS procedures to be reimbursed by insurance, they must be done in conjunction with cataract surgery. (Allergan's Xen gel stent is the only FDA-approved exception to this rule.) Dr. Tsai says this is one of MIGS' major drawbacks. "Essentially, the patient has to need/have cataract surgery for you to really consider MIGS," he says.

Furthermore, cataract surgery isn't benign, Dr. Tsai adds. "A lot of our patients are myopic, and myopia is a risk factor for glaucoma," he says. "The risk of retinal detachment in myopes is likely 3 to 5 percent over the patient's lifetime, approximately a three to five times higher risk than cataract surgery in non-myopes. Moreover, some patients' cataracts aren't severe enough to warrant cataract surgery. Making a patient pseudophakic isn't well-received by all patients, especially those who still have the ability to accommodate for near work.

"If a patient has a high risk for infection, suprachoroidal hemorrhage or has a difficult time coming back for regular follow-up visits, then maybe a cataract-MIGS procedure is a procedure that you as a glaucoma surgeon should perform," Dr. Tsai says. "If you can combine the cataract surgery with another procedure to get the pressure down another 1 to 2 mmHg more than the pressure lowering with cataract surgery alone, that might be sufficient. And maybe in this particular patient, the effect with MIGS is greater—say 3 to 4 mm more—than with cataract surgery alone. As a result, that patient might be able to get off her medications or reduce the number of medications she's on.

"However, you're already going to get a pressure reduction with cataract surgery alone," he adds. "That's been clearly demonstrated.[7] But oftentimes, it's hard to say how much of the pressure reduction was from the MIGS procedure or simply due to the patient responding very well to the IOP-lowering effects of small-incision cataract surgery. Based on what I've seen in the literature and with my own patients who've had previous MIGS procedures, the results aren't significantly better with than cataract surgery alone."[8]

With outcomes similar to cataract surgery, Dr. Francis says MIGS is sometimes overused. "I've seen some patients with intraocular hypertension have cataract surgery and a MIGS procedure. For someone who has ocular hypertension, the pressure will lower with just the cataract surgery anyway."[14]

A 2015 Cochrane review of nine randomized controlled trials compared combined surgery to cataract surgery alone in eyes with co-existing cataract and glaucoma. The nine trials reviewed included 655 participants (657 eyes) with follow-up periods ranging from 12 to 30 months. Glaucoma surgeries included three studies with trabeculectomy, three studies with iStent implants, one study with trabeculotomy and two studies with trabecular aspiration. All of the studies showed a statistically significant greater decrease in mean IOP postoperatively in the combined surgery compared to cataract alone. However, with few studies reviewed, the authors concluded that there's only low-quality evidence that combined cataract and glaucoma surgery may result in better IOP control at one year compared to cataract surgery alone.[8]

Dr. Lim points out that FDA-approved MIGS devices have shown an advantage in IOP-lowering compared to cataract surgery alone.[9-11] "The crux of FDA approval is showing superiority with the device," she says. "Those studies are designed to randomize patients to receive cataract surgery alone or combined surgery. The FDA looks at the device study endpoints, such as a 20-percent reduction from baseline IOP, and those devices that achieve a higher proportion of patients reaching that endpoint, versus cataract surgery alone, receive approval."

HORIZON Study

Recently, a large, global, prospective, randomized, controlled trial was conducted for the Hydrus Microstent to test its safety and efficacy in lowering IOP in glaucoma patients undergoing cataract surgery.[11] It should be noted that this study included only mild to moderate cases of glaucoma. The three-year results found that 73 percent of Hydrus patients remained medication-free, compared to 48 percent of cataract-only patients. Among the patients

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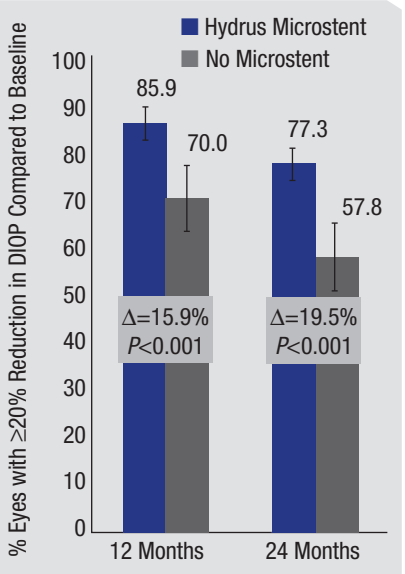
who entered the study on one medication (like about half of glaucoma patients in the United States), 81 percent remained medication-free, compared to 48 percent in the cataract-only arm.[11] The study found that the combined MIGS procedure had an overall safety profile similar to that of cataract alone, including endothelial cell density stability from year two to three and no significant changes between the Hydrus and cataract-only groups. Of note, only 0.6 percent of Hydrus patients went on to receive subsequent invasive surgery to control their glaucoma, which the company says was a first.

Though the HORIZON study demonstrated a reduction in the need for subsequent invasive surgery, some of the statistically significant findings are less impactful for cases of glaucoma that are more serious than just mild-to-moderate, further supporting many experts' view that, while MIGS is effective in some cases and a valuable option, it's not yet ready to replace trabeculectomy.

Dr. Tsai explains that "in the HORIZON study, the investigators found that cataract surgery with the Hydrus device lowered the pressure an average of 7.6 ±4.1 mmHg while the cataract surgery with no microstent lowered the pressure an average of 5.3 ±3.9 mmHg. So the difference was 2.3 mmHg (95 percent CI; $p<0.001$)," he says. "The mean number of medications was reduced from 1.7 ±0.9 at baseline to 0.3 ±0.8 at 24 months in the Hydrus group and from 1.7 ±0.9 to 0.7 ±0.9 in the no-microstent group, a difference of -0.4 medications ($p<0.001$)—about half a medication.[12] Is a 2.3-mmHg difference significant for your patient? I'd say it depends whether the IOP drop is maintained long-term. Certainly, though, a 2-mmHg difference between patients who received cataract alone and those who received the combined MIGS procedure is promising. However, we don't know the efficacy of these procedures in moderate to severe glaucoma."

The HORIZON Study: Reductions in Diurnal IOP



One of the primary endpoints of the HORIZON study was a ≥20-percent reduction in DIOP. The microstent group significantly increased the proprtion of eyes that achieved a ≥20-precent reduction in unmedicated MDIOP (n=369 in the Hydrus group; n=187 in the no-microstent group). I-bars represent 95% confidence intervals.[12]

Dr. Tsai adds that "the U.S. cohort in the HORIZON trial concluded at 24 months follow-up that the implantation of the Schlemm's canal microstent significantly reduced medications, compared to phaco-only in patients with mild to moderately severe glaucoma. The mean change in medications was -1.2 ±0.9 in the microstent group and -0.8 ±1.1 in the phaco-only group ($p<0.001$), so that's still only a 0.4-medication difference."[13]

What's After MIGS?

"Managing glaucoma therapy is a bit like being a billiards player," Dr. Lim says. "For every treatment you offer the patient, you have to think three steps into the future. You have to think: If I offer a patient a certain surgery and if it fails, I need to have another plan. What am I going to do next?"

She recommends using MIGS for cases where the need for additional surgery is highly likely. "I think MIGS can definitely fill a role in earlier stages of disease for controlling the pressures, as well as for some people who have more severe disease where you know you'll have to ramp up the type of surgery you offer them in the future," she says.

Prof. Bloom says that waiting until the glaucoma is more severe to undergo incisional surgery may increase the risk of complications and failure. "A study from 1989 on the benefit of early trabeculectomy showed that eyes which lost the most visual field were those with the least field loss at diagnosis," he says. "This paradox was attributed to a prolonged attempt at medical control in these eyes because they were thought to have a lower risk of visual field deterioration.[22] If you put off necessary surgery, patients get worse."

That's one reason why MIGS is an important addition to the surgeon's toolkit as an earlier intervention. "MIGS has very few downsides apart from the cost," Prof. Bloom notes. "Even if MIGS doesn't work out very well, you haven't lost much—you haven't lost a 'bite of the surgical cherry.' You can still proceed with a trabeculectomy or a tube later on.

"The results can be somewhat variable," he continues, "but if you do get a good response, then in that patient you might be able to avoid doing a trab. If someone has an average or suboptimal response, you can still go on to a trabeculectomy, and the fact that you've previously done MIGS hasn't lost you anything. As long as you haven't lost too much time trying to assess whether it works or not, then MIGS is a very low-risk option, really."

While MIGS procedures are sometimes followed by a trab or tube, Prof. Bloom cautions that there are still risks with having prior conjunctival-incisional glaucoma surgeries. "The risk is scarring," he says. "The efficacy of trabeculectomy relies on relative lack of scarring because the aqueous comes out of a biological valve that's formed on the surface of the eye by the operation. The more operations you do that involve the conjunctiva, the greater the risk of failure. So for example, if someone's had a Xen implant or a PreserFlo (formerly known as the InnFocus Microshunt) that impinges upon the conjunctiva, the chances of a trabeculectomy working after one of those procedures may be reduced. However, if patients have an iStent or a Hydrus or one of those other devices that don't touch the conjunctiva, then theoretically the chance of a trabeculectomy working after a procedure like that is every bit as high as if they hadn't had it. MIGS procedures don't compromise future conjunctival surgery in the way that other conjunctival surgeries do."

Limited Lifetime

"If we follow the outcome of MIGS surgeries long enough, we may see MIGS' effects wearing off and patients needing to go back on medications and/or have additional operations," Dr. Tsai says. "Many of the prospective studies for MIGS look promising, but after a longer period of follow up, we might start to see the eye pressures beginning to creep back up. That's why a robust follow-up period is needed to assess the impact and efficacy of MIGS. In my opinion, 24 months is the minimum needed. Anything shorter won't be conclusive enough. That said, the HORIZON trial was helpful since it reported both 24-month and three-year data."

A study evaluating the long-term efficacy and safety of combined MIGS and cataract surgery with the iStent implant for coexistent cataract and glaucoma found that combined surgery seems to be an effective and safe avenue for treatment.[15] The mean follow-up period was 53.68 ±9.26 months and the data showed a 16.33-percent decrease in IOP (19.42 ±1.89 mmHg to 16.26 ±4.23 mmHg [p=0.002] at the end of follow-up). One author of the study is a consultant for Glaukos.

Since glaucoma is a chronic, incurable set of diseases, effectiveness over time is an important variable to consider when selecting treatments, experts say. "You should try to delay the more aggressive surgeries until you really need them," advises Dr. Francis. "A patient controlled for five years with a MIGS procedure who then goes on to receive a trabeculectomy can probably get through her lifetime without significant vision loss. Whereas, if you do the trabeculectomy right off the bat and it fails after five years, your options are more limited at that point. Of course sometimes

patients require a more aggressive surgery early on, and if they need it, they need it."

Using MIGS to delay a potential need for more invasive surgery is a good method for prolonging the effectiveness of glaucoma treatments. Lifetime efficacy is one goal of treatment, though the meaning of "lifetime" has shifted over the years as average life expectancy increases. Between 1959 and 2016, the U.S. life expectancy increased from 69.9 years to 78.9 years.[20] Though overall U.S. life expectancy has declined since 2014 due to midlife mortality caused by drug overdoses, alcohol abuse, suicide and various organ system diseases[20] (78.84 years in 2014 to 78.69 years today),[21] glaucoma patients diagnosed in their late 60s and early 70s can still expect to live for at least another decade. In the United States, the life expectancy for men and women at age 71, respectively, is 13.72 years and 15.82 years.[18]

On presentation, the average age was 71.1 years in a 2007 mortality study conducted in the United Kingdom that followed 57 patients diagnosed with chronic open-angle glaucoma. The study found that, after 10 years, two-thirds of the patients survived, and that for most older, white patients, preventing a visual handicap is achievable 10 years after diagnosis.[16] At the 15-year follow-up period for the same cohort, the researchers found that 44 percent of the patients had died.[17] Medium-term results over five-year periods demonstrate a continuing lowering in IOP and medications,[19] but "with longer follow-up we would no doubt observe increasing surgical failure," Leon Au, MD, says in a debate piece originally presented at the Royal College of Ophthalmologists Congress in 2017.[19] "But the benefit these procedures offer in that all-important five-to-seven-year period for this group of elderly patients is invaluable," he concludes.

Future Developments

The consensus among experts seems to point to MIGS as a valuable addition to the glaucoma treatment arc, but not a cure-all, and certainly not a replacement for traditional filtering surgery in severe cases of glaucoma. Currently, glaucoma treatments' safety and efficacy profiles are at odds with each other. "MIGS offers the patient a pressure lowering treatment with a high safety profile," Dr. Lim says. "But with a high safety profile, comes MIGS' limited efficacy." Trabeculectomy and tube shunts have more efficacy, but at the expense of safety.

Prof. Bloom says future iterations of MIGS designs will likely provide an equal safety profile with greater efficacy than current models. "We're still very early in the development cycle," he says. "We're faced with first-, second- and third-generation devices, whereas, for example, intraocular implants are perhaps on their fifteenth or twentieth generation and becoming ever more refined. When MIGS become more effective, but maintain their high safety profile, then at that point they may start to challenge traditional surgeries in terms of efficacy, whilst beating them hands down in terms of safety."

Dr. Ianchulev says he envisions a positive future for MIGS. "It's bright and glorious," he says. "It's opening up a new category which will be here to stay." REVIEW

Dr. Tsai is a consultant for Eyenovia, ReNetX and Smartlens. Dr. Francis discloses relationships with Neomedix, MST, BVI, Endo Optiks, Glaukos, Allergan and New World Medical. Dr. Lim is an investigator for Santen and a speaker for Alcon. Dr. Ianchulev discloses financial relationships with Eyenovia. Prof. Bloom has no paid consultancy relationships to disclose, but notes that he has previously been paid to participate in advisory boards for Glaukos and to lecture for EndoOptiks.

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New Anti-VEGFs: Where Will They Fit?

Michelle Stephenson, Contributing Editor

New agents are touting longer durability and better drying effects.

Many new anti-VEGF agents are in various stages of development, and the hope is that these new drugs will provide better durability and have better drying effects than the currently available options. Current anti-VEGF monotherapies for wet age-related macular degeneration are burdensome because they require frequent office visits for eye injections.

"Unfortunately, the benefits of new agents don't seem to translate directly into better vision. Durability of a drug is critical, but it's still too early to know how it's going to be translated into real-life use," says Karl Csaky, MD, PhD, who is in practice in Dallas.

In this article, experts discuss how a new addition to their armamentarium, as well as some agents in the pipeline, may fit into their therapeutic strategy.

Beovu

The Food and Drug Administration recently approved Beovu (brolucizumab, Novartis) injection for the treatment of wet AMD.[1] The approval was based on findings from the Phase III HAWK and HARRIER clinical trials, in which Beovu demonstrated non-inferiority versus aflibercept in mean change in best-corrected visual acuity (BCVA) at one year, but with a potentially less-frequent treatment schedule.

HAWK and HARRIER were similar in design (double-masked, multicenter, active-controlled, randomized).[2] They included 1,817 patients with untreated, active choroidal neovascularization due to AMD in the study eye. Patients were randomized to receive intravitreal brolucizumab 3 mg (HAWK only), brolucizumab 6 mg, or aflibercept 2 mg. After loading with three monthly injections, brolucizumab-treated eyes received an injection every 12 weeks and were interval-adjusted to every eight weeks if disease activity was present. Eyes in the aflibercept group received treatment every eight weeks.

At week 48, both brolucizumab groups demonstrated noninferiority to aflibercept in BCVA change from baseline. In the HAWK study, patients receiving 3 mg of brolucizumab gained 6.1 letters, those receiving 6 mg of brolucizumab gained 6.6 letters, and those receiving aflibercept gained 6.8 letters. In the HARRIER study, those receiving 6 mg of brolucizumab gained 6.9 letters and those receiving aflibercept gained 7.6 letters. More than half of the eyes treated with 6 mg of brolucizumab were maintained on 12-week dosing through Week 48 (56 percent in the HAWK study and

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51 percent in the HARRIER study). At week 16, after identical treatment exposure, fewer eyes treated with 6 mg of brolucizumab had disease activity compared to eyes treated with aflibercept in both studies (24 percent vs 34.5 percent in HAWK and 22.7 percent vs 32.2 percent in HARRIER).

"I now have patients just starting to come back a month after their second injection, and the hope is that Beovu will be a longer-lasting injection," says New York ophthalmologist K. Bailey Freund, MD. "It's a smaller molecule that has high affinity for VEGF so the molar concentration of the drug in the syringe with the same volume is considerably higher than the other three agents that are commonly used. It is expected that some patients will be able to be dosed less frequently."

According to Wills Eye Hospital's Carl Regillo, MD, ophthalmologists are excited about the availability of Beovu. "It just got its J-code, so that's going to pave the way for increasing utilization in practice," he says. "But, time will tell. The TALON study, which is a Phase IIIb study that has been launched in Europe, is going to give us a good idea of how well it performs in terms of durability compared to Eylea because the drugs are head-to-head and dosed in a treat-and-extend fashion that is identical in both arms. We won't know the answer for a couple of years, but at least it's in testing."

Dr. Freund notes that physicians are trying to strike a balance between safety and efficacy with these drugs. "Obviously, there is a benefit to less frequent injections in terms of treatment burden and cost, but there isn't the long-term safety data that the others have," he says. "One issue is that the FDA label for Beovu specifies that this drug is to be used monthly for three doses and then every eight to 12 weeks thereafter. The label reflects the protocol, so the expectation is that the payers might not allow for more frequent dosing than every eight weeks after the first three doses. If an eye can't be kept dry enough and stable with eight-week dosing, this would be a problem as far as reimbursement. You might have to switch the patient back to one of the other agents with which you can treat every month. My understanding is that Novartis is currently doing studies that would show that there are certain cases where monthly dosing is beneficial and safe, and there would eventually be a label change. But at the present time, that option doesn't exist."

At press time, the American Society of Retina Specialists issued a statement that could impact Beovu's usage. The ASRS stated that, in addition to reports of mild-moderate intraocular inflammation following the administration of Beovu, it's received reports of 14 cases of vasculitis, "of which 11 were designated as occlusive retinal vasculitis by the reporting provider." It adds that the etiology of the events is unclear, and long-term outcomes and treatment strategies remains undefined. It does recommend deferring anti-VEGF injection in patients that have any signs of intraocular inflammation.

In response, Novartis issued a statement, part of which notes, "Novartis' review of this information is ongoing and classification of these ASRS-reported cases by Novartis has not been established, but we are aware of recently reported adverse events following treatment with Beovu. Novartis stands behind the safety and efficacy of Beovu. In addition to our own internal assessment, we have engaged an external safety review committee to further evaluate these post-marketing cases."

Abicipar

Allergan's Abicipar is currently being studied in patients with wet AMD. Two-year data from the CEDAR and SEQUOIA clinical studies have shown that four injections of abicipar resulted in the maintenance of visual gains comparable to monthly ranibizumab.[3]

CEDAR and SEQUOIA are identical global Phase III studies designed to assess the efficacy and safety of abicipar eight-week and 12-week treatment regimens compared with monthly ranibizumab in treatment-naïve patients with wet AMD. Through week 104, patients received abicipar 2 mg every eight or 12 weeks or ranibizumab 0.5 mg every four weeks. At week 104 in the pooled Phase III data, 93 percent of patients in the eight-week abicipar group, 90 percent of patients in the 12-week abicipar group and 94 percent of patients in the four-week ranibizumab group achieved stable vision.

Mean changes in BCVA during year two were similar when compared to year one across all treatment arms.

The incidence of adverse events was comparable between the treatment groups at the end of year two. The rate of new cases of intraocular inflammation in year two was similar for all groups (1.9 percent for patients who received abicipar for both eight and 12 weeks and 1 percent for patients who received ranibizumab).

"Abicipar looks like it's more durable to some degree than the anti-VEGFs we have been using in practice, and it will potentially be FDA-approved sometime later this year," observes Dr. Regillo. "There were some issues in Phase III testing with relatively high rates of intraocular inflammation with abicipar, but there's since been some reformulation, and a recent Phase IIb (MAPLE) study shows lower rates of intraocular inflammation with the latest formulation."

Faricimab

Genentech's faricimab is a bispecific antibody designed for the treatment of retinal conditions, simultaneously binding to and neutralizing Angiopoietin-2 (Ang-2) and VEGF-A which, its maker says, may lead to improved and sustained efficacy at longer treatment intervals.

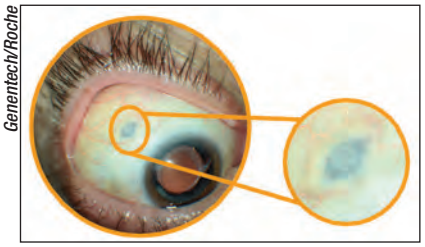
In late 2018, Genentech reported positive results from the Phase II STAIRWAY study for drug faricimab, which evaluated the extended durability of the agent in the treatment of wet AMD.[4] At 52 weeks, faricimab patients dosed either every 16 weeks or every 12 weeks demonstrated sustained vision outcomes comparable to ranibizumab dosed every four weeks. Additionally, the company has now completed patient enrollment in the Phase III YOSEMITE and RHINE clinical trials.[4] The YOSEMITE and RHINE studies will assess the safety and efficacy of faricimab for the treatment of DME compared to aflibercept. The primary endpoint of each study is the change in BCVA at a year.

"Faricimab is intriguing in the sense that you're targeting both VEGF and Ang-2, and there's reason to believe that's synergistic and will provide vessel stabilization," notes Dr. Csaky. "When we use anti-VEGF agents, we are primarily changing the permeability aspects of the disease, and that's why we think we have to continue to inject for long periods of time. As the drug wears off after a time, we're not necessarily modifying the underlying abnormal blood vessels.

"Faricimab's Phase II data indicated that there was increased durability compared with an anti-VEGF alone," he note. "Approximately 70 percent of patients who were given faricimab had no sign of CNV activity at 12 weeks. It's intriguing that faricimab may induce vessel stabilization and have even more chance for durability, but that remains to be proven."

The Port Delivery System

The Port Delivery System with ranibizumab is a refillable eye implant designed to continuously release a customized formulation of ranibizumab over a period of months, with the goal of avoiding repeat visits for multiple injections over time. Genentech/Roche have completed patient enrollment in the Phase III Archway clinical trial investigating the PDS in wet AMD.


Genentech/Roche

Observers say that Genentech/Roche's port delivery system with ranibizumab is showing good durability over time.

"It has shown tremendous durability in Phase II testing," says Dr. Regillo. "It requires a trip to the operating room to insert, and it's a device that stays in the eye wall. However, it's been shown to provide a duration of effect for over a year in most patients. It's the first long-acting delivery platform. With emerging injectable anti-VEGFs in clinical trials, we might be able to extend the durability by two to four weeks or so, but this PDS is truly long-acting—it slowly releases the drug over many months. In Phase III testing, we're automatically refilling it every six months, whether they need it or not, but its potential is really quite a bit longer than that."

Conbercept

Dr. Freund says conbercept (Chengdu Kanghong Biotech) is a molecule very similar to aflibercept. "It was developed in China and, like aflibercept, is a recombinant fusion protein that binds to VEGF-A, VEGF-B, and placental growth factor," he notes. It's approved in China.

A study found that conbercept dosing of three initial monthly administrations followed by quarterly treatments was effective in AMD.[5]

In this prospective, double-masked, multicenter, sham-controlled, Phase III randomized trial, patients with choroidal neovascularization secondary to AMD were enrolled and randomized to the conbercept group or the sham control group. The treatment group received intravitreal injections of conbercept 0.5 mg monthly for the first three months, then quarterly until month 12. The sham group received three monthly sham injections and then three monthly injections of conbercept 0.5 mg, followed by quarterly administrations until month 12.

A total of 114 patients from nine sites in China completed the 12-month study. At the three-month primary endpoint, the mean changes in BCVA from baseline were +9.20 letters in the conbercept group and +2.02 letters in the sham group, respectively. At 12 months, the mean changes from baseline in BCVA letter score were +9.98 letters in the conbercept group and +8.81 letters in the sham group. The most common ocular adverse events were associated with intravitreal injections, such as conjunctival hemorrhage and increased IOP. REVIEW

Dr. Csaky has a financial interest in Allergan, Applied Genetic Technologies Corporation, Gyroscope, Novartis, Ocular Therapeutix, Ribomics and Roche/Genentech.

Dr. Freund has a financial interest in Novartis, Allergan, Bayer and Genentech/Roche.

Dr. Regillo receives research grant support from Allergan, Chengdu Kanghong, Genentech, Novartis and Regeneron, and is a consultant for Allergan, Chengdu Kanghong, Genentech and Novartis.

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Measuring Postop IOP: Don't Be Fooled

An expert describes how to get the most accurate intraocular pressure measurements after corneal surgery.

Thasarat Sutabutr Vajaranant, MD, Chicago

Today, ophthalmologists have a number of alternatives when it comes to addressing corneal disease with a transplant, ranging from the traditional full-thickness penetrating keratoplasty to partial transplants such as deep anterior lamellar keratoplasty and Descemet's stripping endothelial keratoplasty, to an artificial cornea such as the Boston keratoprosthesis (aka KPro). Unfortunately, glaucoma often follows a corneal transplant.

The prevalence of glaucoma after a corneal transplant varies depending on the type of transplant that was done, as well as other factors such as the presence or absence of pathology in the anterior segment. For example, greater prevalence and severity of glaucoma are seen in PK and KPro transplants because of the anatomic changes associated with the surgery. These changes lead to an increased likelihood of postoperative pathology in the anterior chamber angle, leading to more frequent ocular hypertension or glaucoma. If associated preoperative corneal or anterior segment pathologies remain after the surgery, the likelihood of glaucoma is even greater.

On the other hand, the prevalence of glaucoma following transplants such as DALK and DSEK is primarily affected by the nature of the pathology that led to the transplant. For example, the incidence of glaucoma following DSEK is lowest when the transplant was necessitated by Fuchs' dystrophy, because there's not too much pathology in the anterior chamber. The same is true for PK necessitated by keratoconus. These eyes have better outcomes in terms of postoperative glaucoma.

Of course, one factor that's especially likely to increase the prevalence of glaucoma following corneal surgery is that the patient may need to use steroid drops to help with the postoperative healing. It's no secret that patients can have a steroid response—ocular hypertension—which can lead to glaucoma over the long term. I actually consider any patient with a corneal transplant to be a glaucoma suspect—especially those on steroids.

The reality that these patients need to be monitored for ocular hypertension and glaucoma raises an interesting question: Does the presence of corneal pathology and/or having undergone a corneal transplant impact our ability to accurately measure intraocular pressure? Here, I'd like to discuss this question in two parts: First, we'll talk about how corneal morphology and surgery can affect IOP measurement. Then, I'll review the commonly used tonometers and discuss how best to use them in patients with corneal transplants and pathologies.

When Does Thickness Matter?

When measuring IOP, usually the first thing we consider is the corneal thickness. Thanks to the Ocular Hypertension Treatment Study, we know that patients with healthy, thin corneas (less than 550 µm) have falsely low pressure readings when measured with Goldmann tonometry. Likewise, patients with thicker-than-average corneas have falsely high pressure readings. It turns out, however, that once pathology and/or surgery become involved, that relationship becomes far less consistent.

Of course, both pathology and surgery can affect corneal thickness.

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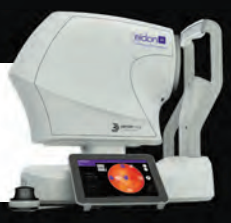


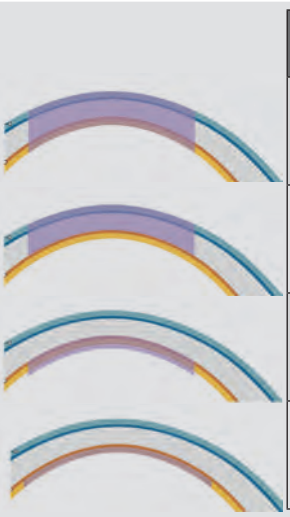
For example, both keratoconus and LASIK surgery will leave the eye with a thinner cornea, and either circumstance can result in falsely low IOP measurements. However, the reverse isn't always true. If the cornea has been made thicker, whether by pathology or surgery, the result may not always be a falsely high reading, as you would expect with a thick, healthy cornea. For example, if corneal edema is present, the pressure reading taken through the thicker cornea may be falsely low rather than high.

In 2008 our group published a study involving DSEK that compared pressure readings using different tonometers.[1] We checked the pressure in 50 eyes of 38 patients who'd undergone successful DSEK (meaning they didn't have corneal edema), using a Goldmann tonometer, a Pneumatonometer and a Dynamic Contour Tonometer. We found that the readings were highly positively correlated. When one went up, the other went up, and vice versa. However, they were not interchangeable; the measurements were different from one device to the next.

Because DSEK leaves the cornea thicker as a result of adding tissue to the posterior surface, we wondered whether the increased thickness would cause falsely high pressure readings. Although the post-DSEK corneas were thicker, the Goldmann tonometer pressure readings were not falsely high. At the practical level, this means that if you get a high IOP reading in a post-DSEK eye using Goldmann tonometry, you should have a high index of suspicion that the IOP really is elevated.

The point is that once the cornea has been altered by pathology or surgery, the OHTS findings relating to corneal thickness and IOP measurement may not apply. It appears that if the cornea is thinner for either reason, you may get a falsely low reading, as you would with a healthy thin cornea. But if pathology such as edema or a surgical procedure has left the cornea thicker, the pressure reading (by Goldmann tonometry, at least) may actually be falsely low rather than high.

How Corneal Procedures Affect Biomechanics



TYPE	SUTURE/ ASTIGMATISM	THICKNESS	EDEMA	SCAR
PK	Maybe		Maybe	Maybe
DALK	Maybe		Maybe	Maybe
DSAEK		INCREASED	Maybe	
DMEK			Maybe	

Illustrations by Lauren Kalinoski

Changes in corneal structure and biomechanics that follow surgery can affect the accuracy of our IOP measurements—and not always in the way we might expect. Increased corneal thickness due to edema, for example, can produce falsely low readings rather than high.

Structure and Biomechanics

The structural and biomechanical properties of the cornea—including ectasia, hydration, scarring, curvature, astigmatism and hysteresis (a corneal property that isn't fully understood)—can all impact the accuracy of our pressure readings. Scar tissue, for example, can cause a falsely high reading. The complexity and variability of some of these factors—as well as how we take the measurement and which instrument we use—make it challenging to predict whether or not they'll alter our IOP measurements.

The table above summarizes how different surgeries can affect the biomechanics of the cornea, in turn potentially altering the accuracy or our pressure readings. For example, all corneal transplants are prone to causing edema, which may affect our IOP readings. Likewise, sutures and corneal scars, more commonly seen after PK and DALK, can influence the IOP reading. In addition, these surgeries may be altering the biomechanical properties of the cornea in other ways we don't yet understand.

The bottom line is that when any corneal parameters have been altered by pathology or surgery, we can't assume that our IOP measurements will be unaffected—or that we can always predict in which direction the readings will be altered.

Tonometer Technology

Clearly, when an eye has undergone corneal surgery or has pathology, the type of technology and specific instrument we use to measure IOP will affect the accuracy and consistency of the measurement. Fortunately, today we have several options for making that measurement. (Tactile estimation of IOP can also be useful, especially in patients who've had keratoprosthesis. Although this approach isn't helpful for measuring subtle abnormalities of IOP, it is useful for identifying patients

with very high or low IOPs.[2,3])

Most tonometer technology today is based on one of three principles: applanation (flattening); contour matching; or rebound measurement. Most tonometers used in the clinic fall into the first category—they use corneal flattening or applanation. These include: the Goldmann tonometer, the Pneumatonometer, the Tonopen and the Ocular Response Analyzer, which uses bidirectional non-contact applanation.

A second technology that can be used to measure IOP is contour matching, used in the Dynamic Contour Tonometer. The interface resembles a little cup. Once you match the curvature of the cup to the curvature of the cornea, the device reads the pressure inside the eye. This technology appears to be less affected by corneal properties; as a result, it may give a reading that's closer to the actual pressure inside the eye (in both healthy and post-surgical eyes).

The last category is rebound tonometry. Devices using this technology have a small tip that pushes gently but rapidly against the cornea. The device detects the deceleration of the tip—how quickly it stops. Devices in this category include the Icare tonometer, which measures through the cornea, and the Diaton device, which measures through the eyelid. (The latter is not commonly used in the clinic at present.)

Next, let's consider the pros and cons of the most common tonometers.

Goldmann Tonometer

The Goldmann tonometer is still the gold standard for use in the clinic; it measures IOP using the Imbert-Fick principle. (This principle states that the pressure inside a thin-walled sphere can be determined by measuring the force necessary to flatten the surface, divided by the area of flattening.) It has an applanation diameter of 3.06 mm.

The biggest advantage of the Goldmann tonometer is that it's readily available in the clinic today. However, it's an imperfect technology. First of all, the device was calibrated to a corneal thickness of 520 µm and it assumes that the cornea is a perfect sphere. Second, its measurements can be affected by changes in corneal thickness, curvature, edema and surface alterations. (In addition, research has shown that its measurements are consistently lower than manometric pressure measurements made inside the eye.) So although it's still the gold standard in the clinic, it may not be the best choice for measuring IOP when a cornea has been altered by pathology or surgery.

Corneal changes can affect any tonometry measurement.

If you do use a Goldmann tonometer to measure an eye after corneal surgery, remember that the formula used to adjust readings based on corneal thickness may not apply. As noted earlier, thinner corneas in these eyes may produce falsely low readings, but the reverse isn't necessarily true if a cornea is thicker as a result of surgery or pathology. For that reason, we don't recommend using a formula to adjust the measurement based on the corneal thickness.

Pneumatonometer

This instrument (like the Tonopen, discussed below) has a tubular handpiece; the 0.5-mm tip has a fenestrated membrane consisting of a footplate with a microplunger in the center. The IOP equals the pressure required to keep the microplunger flush with the footplate when the tip is in contact with the cornea. (We have a pneumatonometer in our cornea service here at Illinois Eye and Ear Infirmary, which is used to check the IOP after a corneal transplant or in eyes with corneal disease.) This instrument can be used to measure IOP with the patient upright or supine, and it's not affected by corneal thickness or surface pathology.

One unique thing about this technology is that you can measure the IOP through the sclera. This is an obvious advantage in eyes where you can't measure the pressure through the cornea, such as eyes with a KPro, a lot of corneal scar tissue or in which the lens and cornea are touching, which can minimize the anterior chamber and make IOP measurements through the cornea inaccurate.

To find out more about this approach, we did a study comparing pneumatonometry readings done through the sclera and in the center of the cornea in normal eyes.[4] We found that the scleral and corneal readings were highly positively correlated. However, scleral measurements were consistently higher than corneal readings. We also found that the scleral pressure is less accurate when the IOP is high. At the practical level that means that if you have a patient with a KPro, a low pneumatonometer reading is good for confirming a palpation measurement that suggests IOP is in the normal range.

Tonopen

Some corneal surgeons like the Tonopen because it's a smaller, handheld device that uses a disposable sleeve and only touches a small area of the eye. However, it only has good reproducibility when IOP is in the normal range, from about 10 to 20 mmHg. It underestimates the pressure when it's higher than that

and underestimates it when it's lower.

If you're using this device to measure IOP in eyes that aren't normal, try to stay as close to the center of the cornea as possible. (The cornea is thicker at the periphery, and the Tonopen's accuracy is affected by corneal thickness—although it's less affected by corneal edema than some tonometers.) Try to avoid any corneal area that has pathology or a scar. The Tonopen has good reproducibility in the normal range, so a normal reading should be reassuring.

Ocular Response Analyzer

The ORA is a modified air-puff tonometer. It uses an electro-optical sensor to measure the IOP twice, when the cornea is applanated at two different levels, referred to as "bi-directional applanation." The difference between the two readings is called corneal hysteresis, a measure of viscous damping, which reflects the cornea's biomechanical properties. (A low hysteresis reading is associated with glaucoma.) The device also measures a "corneal resistance factor" (the cornea's elastic response), and produces two IOP measures: a Goldmann equivalent and a "cornea-compensated" IOP. Currently, there's a lot of research going on to expand our understanding of the clinical utility of these measurements.

The advantages of this instrument include that it's noncontact, and that it measures multiple factors (not all of which we fully understand). Disadvantages include that it's not available in many practices; it takes two to three seconds to perform a measurement; and multiple measurements are recommended, because they're affected by the ocular pulse.

Dynamic Contour Tonometer

This instrument's tip has a concave, 2.5-mm contact surface with a Mylar membrane, a silicone-filled cavity and a piezo-electric transducer. Once the patient's cornea matches the curve of the tip, the sensor determines the IOP. The device can be connected to a standard slit lamp.

The DCT is thought to produce readings close to the manometric pressure, and in theory, it's the IOP-measuring device that's least affected by corneal properties. It also measures ocular pulse amplitude—the difference between systolic and diastolic pressure, which can be useful information—and provides a reliability score for each measurement. Disadvantages include that it takes a little time to get accustomed to using it. Second, the patient has to be very cooperative, because you have to take a number of readings to make sure the measurement is accurate. Third, it's not readily available in most clinics, so not everyone has access to it.

The Icare Tonometer

This device is a handheld rebound tonometer; its disposable probe accelerates onto the cornea at a fixed speed and a sensor determines how quickly the probe decelerates. (Higher IOP causes a quicker deceleration.) It tends to produce a higher IOP reading than Goldmann tonometry.

Advantages of the Icare include that it's easy to use; it doesn't require an anesthetic; it's well tolerated by children; and it can be used as a home tonometer. It isn't affected much by corneal edema. Disadvantages include that it may be affected by other corneal biomechanical properties, including corneal thickness, and it tends to be less accurate when the IOP is outside of the normal range.

If using the Icare on a diseased cornea, my recommendation is to avoid areas with pathology but try to stay near the center of the cornea. If band keratopathy is present in the center, it's better to measure away from the rigid calcified area.

The Big Picture

There are three main things to keep in mind in this situation:

1. Corneal changes can affect any tonometry measurement, although the amount of impact is different from one device to the next. Goldmann tonometry is most affected by corneal changes; the Dynamic Contour Tonometer is least affected. Also, accuracy is often highest when the IOP is in the normal range.

2. If you know the cornea you're measuring isn't normal, you might want to use an alternative to Goldmann, such as the Pneumatonometer, which can measure through the sclera, or the ICare or Tonopen. (Both of these produce more accurate readings near the center of the cornea and away from pathology.)

3. Don't switch between instruments when monitoring a given patient over time. Measurements from one device to the next don't usually match. REVIEW

Dr. Vajaranant is an associate professor of ophthalmology at the University of Illinois College of Medicine at Chicago and director of the Glaucoma Service at the Illinois Eye and Ear Infirmary. She has no financial interest in any of the products mentioned.

For more information, check out: Desai M. Intraocular Pressure Measurement. In: Edward DP, Vajaranant, TS, eds. Glaucoma. Oxford American Ophthalmology Library. Oxford University Press 2013:1-14.

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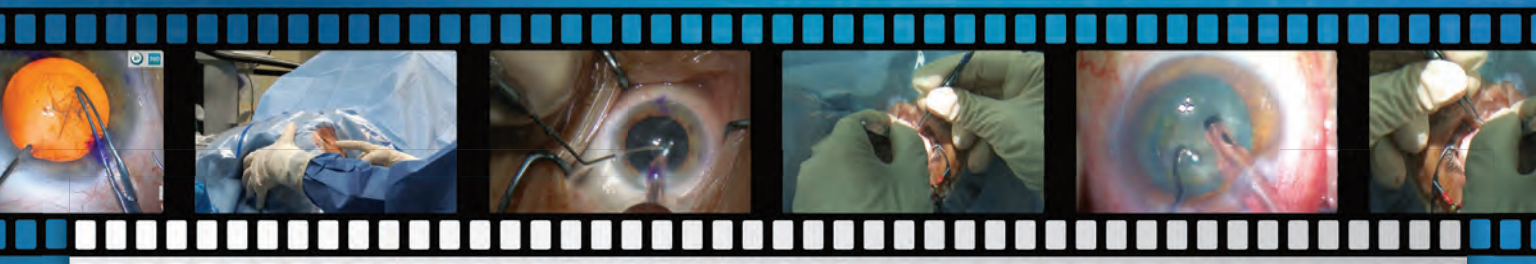

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Richard Mackool, MD, a world renowned anterior segment ophthalmic microsurgeon, has assembled a web-based video collection of surgical cases that encompass both routine and challenging cases, demonstrating both familiar and potentially unfamiliar surgical 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 Objective:

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

- discuss the features of a diffractive trifocal/toric IOL.

Satisfactory Completion - Learners must pass a post-test and complete an evaluation form to receive a certificate of completion. You must listen to/view the entire video as partial credit is not available. If you are seeking continuing education credit for a specialty not listed below, it is your responsibility to contact your licensing/certification board to determine course eligibility for your licensing/certification requirement.

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Analyzing Glaucoma Test Variability

Researchers from Duke University warn that algorithms for standard automated perimetry and spectral-domain optical coherence tomography may overestimate glaucoma progression over time.

The study included a total of 43 eyes of 43 glaucoma subjects. The patients had a mean of 4.5 ±0.8 SAP and OCT tests for short-term variability assessment. For long-term variability, the same number of tests were performed; results were collected annually over an average of 4 ±0.8 years.

Ordinary least-squares linear regression of SAP mean deviation and SD-OCT global retinal nerve fiber layer thickness were fitted over time for sequential tests conducted within five weeks (short-term testing) and annually (long-term testing). Residuals were obtained by subtracting the predicted and observed values, and each patient's standard deviation of the residuals was used as a measure of variability. The Wilcoxon signed-rank test was performed to test the hypothesis of equality between short- and long-term variability.

The average standard deviation of the residuals was significantly higher in the long-term than in the short-term period for both tests: 1.05 ±0.70 dB vs. 0.61 ±0.34 dB, respectively ($p<0.001$) for SAP MD and 1.95 ±1.86 µm vs. 0.81 ±0.56 µm, respectively ($p<0.001$) for SD-OCT RNFL thickness. The researchers remark that this may have significant implications when determining whether or not true progression has occurred when using event-based algorithms to assess progression. They theorize that the factors explaining differences between long- and short-term variability according to levels of damage are likely to be related to the precision of the instruments at different levels of disease and the dynamic range of the tests. They also suggest that subjects followed over the long term may be less motivated and will likely be tested under different conditions each time.

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Wubben TJ and Johnson MW. For the Anti-VEGF Treatment Interruption Study Group.

The Great Outdoors vs. Myopia

After implementing a new initiative to promote increased time outdoors to stave off myopia progression, researchers in Taiwan found that the policy was successful in reversing the long-term trend of increased low visual acuity in the country's schoolchildren.

This prospective cohort study evaluated data from the Taiwan School Student Visual Acuity Screen (TSVAS), which required each school in Taiwan to measure uncorrected VA in students in grades one through six every half year in a period stretching from 2001 to 2015. An ucorrected visual acuity of 20/25 or less was considered reduced visual acuity for purposes of the evaluation.

From 2001 to 2011, the team discovered that the prevalence of reduced visual acuity in schoolchildren increased from 34.8 percent to 50 percent. After instituting a program in September 2010 that encouraged schools to take students outdoors for two hours every day for the purposes of myopia prevention, they noted that the prevalence decreased from 49.4 percent in 2012 to 46.1 percent in 2015.

Controlling by gender and grade, the investigators observed a significant constant upward trend in the mean annual change in prevalence before the intervention and a constant decrease of -2.34 percent annually afterward.

The researchers say that since the efficacy of increased time outdoors in slowing the onset of myopia has been demonstrated in randomized trials, interventions to promote increased time outdoors may be useful in other areas affected by an epidemic of myopia. REVIEW

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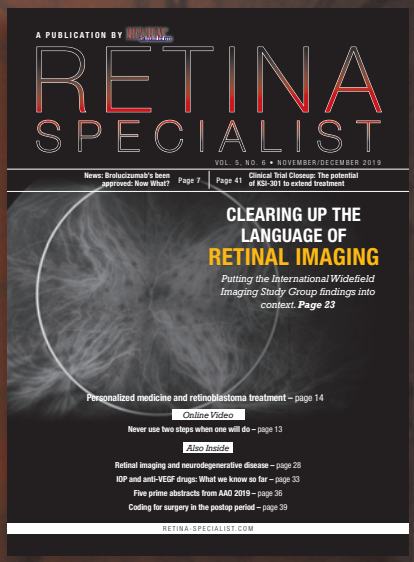

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What's Ahead for the Treatment of Dry AMD

A look at the drug therapies that may eventually bear fruit against a disease that has resisted previous attempts at treatment.

Michael Ammar, MD, and Allen Chiang, MD
Philadelphia

Age-related macular degeneration is a leading cause of blindness in patients 65 years and older.[1] Geographic atrophy (GA) is an advanced form of age-related macular degeneration characterized by loss of the retinal pigment epithelium and photoreceptors in the macula *(Figure 1)*.[2] AMD is a multifactorial disease influenced by both environmental factors such as smoking and genetic factors involving the complement system.[3] For example, Age-Related Maculopathy Susceptibility 2 (ARMS2) and Complement Factor H (CFH) are two of many genes that have been identified and associated with an increased risk of AMD.

However, despite our growing understanding of the genetics and pathophysiology of dry AMD, an effective treatment remains elusive. In contrast, the advent of anti-vascular endothelial growth factor therapy for wet AMD has enabled us to not only preserve, but in many cases, improve vision. Moreover, there are several potential treatments in the pipeline for wet AMD that may provide enhanced durability, such as the ranibizumab port delivery system, abicipar, faricimab and gene therapy. Unfortunately, there has yet to be a similar breakthrough for GA. Due to its complexity, many therapeutic approaches have been considered, including visual cycle modulation, neuroprotection, cell-based therapy, inflammation suppression and complement inhibition. In this review, we examine the past and current research into a pharmaceutical treatment for atrophic AMD.

Visual Cycle Modulation

Visual cycle modulators are oral medications that target enzymes in the visual cycle. In phototransduction, photoreceptors exert a high metabolic demand, which results in increased production of metabolic waste products. Accumulation of these byproducts may lead to increased inflammation, which is implicated in the development of GA. Modulating the visual cycle may mitigate this process and reduce inflammation and GA. A drug that can be delivered orally is especially attractive; however, a consequence of modulating the visual cycle is that dark adaptation and low-light vision are often adversely affected.

Following are the two highest-profile visual cycle modulators that have been studied.

Emixustat hydrochloride (ACU-4429) is an oral non-retinoid small molecule that inhibits the visual cycle enzyme isomerohydrolase, RPE65.[4] It was studied in the Safety and Efficacy Assessment Treatment Trials of Emixustat hydrochloride (SEATTLE) study, a large randomized clinical trial for GA by Bascom Palmer's Philip Rosenfeld, MD, and co-workers. In the study, 508 people were enrolled with GA secondary to macular degeneration. Unfortunately, the Phase IIb/III clinical trial showed that oral emixustat hydrochloride was ineffective at reducing the progression of GA.[5]

ALK-001 is a modified form of vitamin A that replaces natural vitamin A in the body. The modified vitamin A forms toxic vitamin A dimers more slowly, which is postulated to slow the accumulation of toxic end products and therefore slow the development and/or progression of AMD.[6] However, this effect may also impact the visual cycle by depleting vitamin A and causing delayed dark adaptation. It's currently being studied in a Phase

This article has no commercial sponsorship.

III clinical trial for GA.

Neuroprotection

Neuroprotection has been investigated as a possible solution for the problem of progressive cellular damage and eventual cell loss that occurs in atrophic AMD. Pharmacologic agents with cyto- and neuroprotective properties may help protect at-risk neuroretinal tissue by increasing its resilience and resistance to cellular injury, thereby providing a defense against GA progression. So far, brimonidine tartrate (Allergan) is the only agent that has shown possible neuroprotective properties that might be beneficial in GA.

Brimonidine is an alpha-2 adrenergic agonist that's an established topical ophthalmic intraocular pressure-lowering agent. However, studies in animal models with systemic administration have demonstrated that it also has neuroprotective properties, though clinical trials have yet to confirm similar efficacy in humans.[7,8] A Phase IIa clinical trial investigated intravitreal brimonidine for GA, administered by a delayed-delivery system (DDS) implant. The DDS is a biodegradable polymer drug delivery system similar to the dexamethasone implant Ozurdex (Allergan) with a 22-gauge needle attached to a proprietary applicator system. It's designed to release brimonidine over six months; patients receive a second injection at month six. The study evaluated 113 patients over a two-year period; the primary endpoint was the change in size of GA lesion area from baseline to month 12. Patients were randomized to study-eye treatment with brimonidine tartrate DDS 200 µg (n=49), 400 µg (n=41) or sham procedure (n=23). Compared with the control group, the rate of GA progression was lower in the brimonidine groups, but the difference wasn't statistically significant. A Phase IIb trial (BEACON) using the higher dose of brimonidine in a new formulation showed a reduction in GA progression, and two Phase III trials are being planned (IMAGINE and ENVISION).[9]

Cell-based Therapies

The immune-privileged environment of the subretinal space makes it a unique target for cell-based therapy, which consists of two approaches: stem cell- and non-stem cell-based therapies. The non-stem cell approach is centered on delivering cells which can produce protective factors that are deficient within the extracellular milieu. The stem cell approach involves delivering new retinal pigment epithelium cells to help maintain the health of the remaining retinal photoreceptors, which may allow damaged or dormant light-sensitive cells to return to function. Following is a look at several of the more promising cell-based therapies in development.

Janssen Pharmaceuticals evaluated a non-stem cell-based therapy with palucorcel (CNTO-2476), which uses human umbilical cord tissue-derived cells (hUTC).[10] The initial study was a Phase I/IIa, multicenter study of subretinal palucorcel in 35 patients with bilateral GA and exudative neovascular AMD, who had no other ophthalmic conditions, and were suitable candidates for ophthalmic surgery. In the first phase of the study, 29 participants received a single, subretinal dose of palucorcel of 27 µl (3.03×10^5 viable cells), 50 µl (6.03×10^4, 1.23×10^5 viable cells) or 50 µl (5.63×10^5 viable cells) via an external approach, superior to the GA lesion. The Phase IIa study was eventually suspended due to the significant risk of adverse events.

Although palucorcel was well-tolerated in the Phase I/IIa study, the *ab externo* surgical approach required to access the subretinal space with a microcatheter delivery system was associated with a high rate of retinal perforations (13/35 operated subjects) and retinal detachments (6/35 operated subjects).[11] Only 15 percent of the patients had adverse events related to palucorcel alone, and those may have been exacerbated by the surgery and delivery as well, according to the study.[12] Although patients had significant adverse events, the mean BCVA gain at one year was more than four letters, while a quarter of the patients gained three lines of vision or more. The average vision loss at one year was two letters for untreated fellow eyes.

In contrast, Ocata Therapeutics (recently acquired by Astellas Pharma) assessed a stem cell-based approach using human embryonic stem cells (hESC). The Phase I/II safety studies of hESC MA09-hRPE assessed an initial group of nine patients with AMD and nine patients with Stargardt's Disease.[13] Three dose cohorts (50,000, 100,000 and 150,000 cells) were assessed. There was no evidence of adverse proliferation, rejection or serious ocular or systemic safety issues related to the transplanted tissue. Adverse events were associated with vitreoretinal surgery and immunosuppression, including one case of endophthalmitis. After transplantation, 72 percent of patients had increased subretinal pigment at the atrophic area border and, at one year, visual function was improved in nine eyes and stable in seven. Optical coherence tomography showed reconstitution or thickening of the RPE layer in some subjects.[14] The related, Phase II PORTRAY trial of hESC-derived RPE cells in dry AMD was aimed at assessing graft rejection strategies and secondarily at change in area of GA and in visual acuity. The trial was initially suspended prior to enrollment due to changes in the study design and cell line but is now enrolling.

Another stem cell-based approach

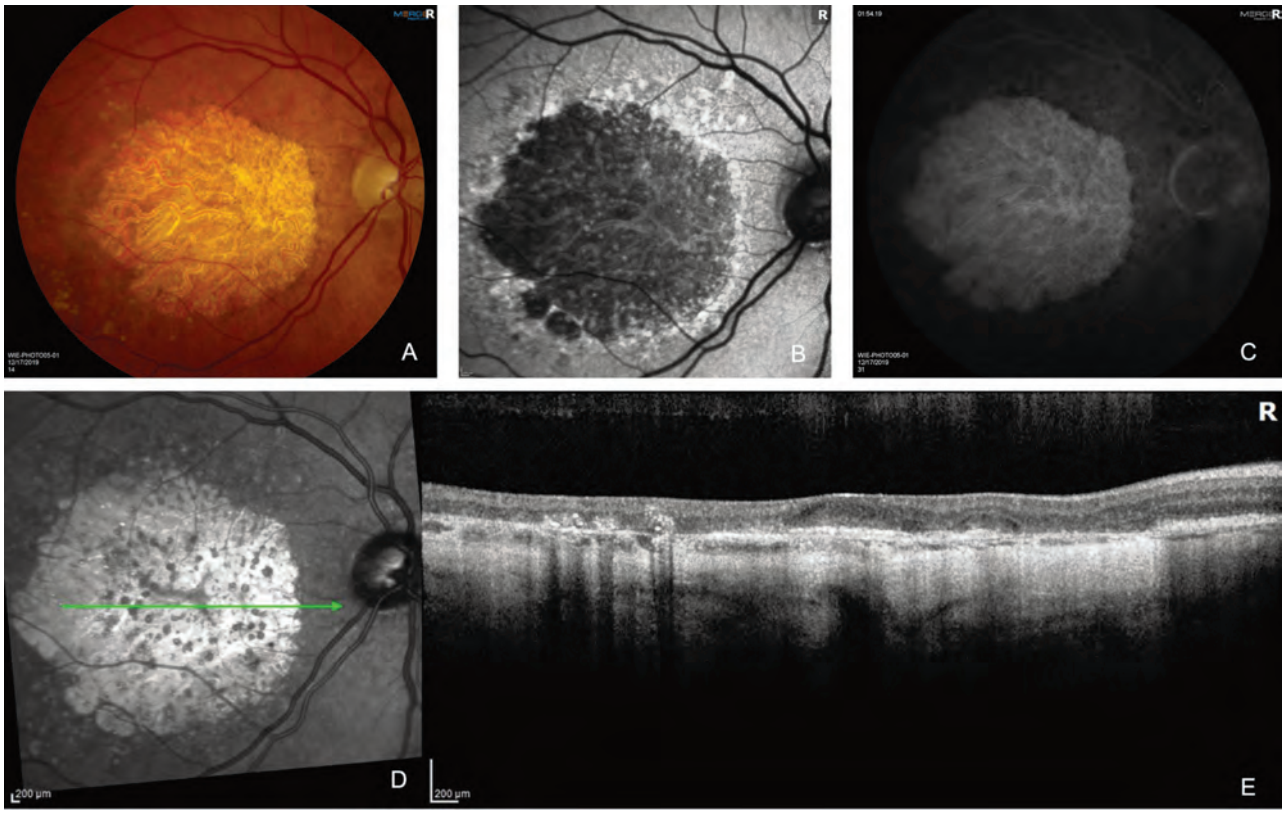

Figure 1. A: A fundus photograph demonstrating geographic atrophy of the RPE and underlying choriocapillaris, revealing the large choroidal vessels. B: Fundus autofluorescence showing hypoautofluorescence in the area of GA with a surrounding ring of hyperautofluorescence due to increased lipofuscin, an indicator of RPE dysfunction. C: Fluorescein angiography at 1:54 demonstrating a hyperfluorescent transmission window defect in the area of the GA. D: Near infrared reflectance image demonstrating mottled hyperreflectivity in the area of GA. E: Optical coherence tomography cross-section correlating with the green raster line in image D which demonstrates areas of RPE and ocular retinal atrophy within the GA.

involving a subretinal implant is being investigated by a group led by USC's Keck Eye Institute researchers Amir Kashani, MD, and Mark Humayun, MD, in a trial sponsored by the implant's maker, Regenerative Patch Technologies.[15] The composite implant, termed the California Project to Cure Blindness-Retinal Pigment Epithelium 1 (CPCB-RPE1), is a polarized monolayer of human embryonic stem cell-derived RPE (hESC-RPE) on an ultrathin, synthetic parylene substrate designed to mimic Bruch's membrane. A total of 16 patients with advanced dry AMD were enrolled in the Phase I/IIa study. Intraoperative OCT-based measurements performed before and after implant placement showed that a significant area of GA could be targeted and covered with the implant. In at least three subjects, the implant covered 100 percent of the area of GA, and in the last 14 patients, the area of GA coverage was greater than half. None of the implanted eyes showed progression of vision loss and one eye improved by 17 letters.[16] The concurrent structural and functional findings suggest that CPCB-RPE1 may improve visual function.[15,17]

Another group is working on a similar RPE patch as a part of The London Project to Cure Blindness.[18,19]

Anti-inflammatory Agents

Tetracyclines are broad-spectrum antibiotic compounds that also exhibit non-antimicrobial anti-inflammatory properties. They have been shown to reduce reactive oxygen species, inhibit matrix metalloproteinases involved in the breakdown of the barrier between the RPE and Bruch's membrane, inhibit caspase activation, prevent complement activation and inhibit cytokine production through their effects on microglia and T-cell activation.[20,21]

One example of an anti-inflammatory used in this capacity is doxycycline (Oracea, Galderma Laboratories, Fort Worth, Texas), which is being investigated in a Phase III clinical trial (TOGA) for the treatment of GA. In the study, 286 patients have been enrolled, and they'll complete a six-month observation phase followed

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by a 24-month treatment phase. Randomization occurs at month six in a 1:1 ratio, to either 40 mg of oral Oracea or placebo capsule to be taken once-daily for 24 months. The results are pending.[22]

Another treatment is the use of FHTR2163 (Genentech/Roche), a new antibody delivered by intravitreal injection that inhibits HTRA1, a serine protease gene associated with GA.[23] Recent studies have also identified HTRA1 as a major risk factor for wet AMD.[23] A Phase II clinical trial, GALLEGO, is under way to further investigate this drug. A total of 285 participants will be enrolled.[24]

Complement Inhibition

Overactivity of the complement system appears to play a pivotal role in the pathogenesis of GA.[25,26,27] The complement system, a critical component of the innate immune system, is composed of three biochemical pathways: classical; lectin; and alternative. The classical pathway is largely driven by the formation of antibody-antigen complexes, while the lectin pathway is activated by polysaccharides on microbial surfaces. In contrast, the alternative pathway is activated by surface pathogens, but doesn't rely on immune complex formation.[25,28] All three pathways converge on the cleavage of C3 (the most abundant complement protein in the blood) into activation products C3a, C3b, C5a and formation of the membrane attack complex (MAC=C5b-9) and ultimately cell death.[28] Complement factor H (CFH) and complement factor I (CFI) are negative regulators of the alternative pathway that work to inactivate C3b and interrupt the proinflammatory response.

C5 inhibitors such as eculizumab (Soliris; Alexon, Boston) were designed to inhibit the formation of C5a and the membrane attack complex (MAC=C5b-9). Eculizumab, a humanized monoclonal antibody derived from the murine anti-human C5 antibody, was evaluated in the Phase II COMPLETE Study (NCT00935883).[29] The COMPLETE study enrolled 30 patients age 50 years and older with GA and visual acuity of 20/63 or better (ETDRS). Despite decreasing systemic C5 levels to less than 1 percent of normal by week two, intravenous eculizumab didn't significantly slow GA growth rates in patients with GA at either the six-month endpoint or after an additional six months of follow-up.[29]

Another C5 inhibitor, avacincaptad pegol (Zimura, Iveric Bio, New York, New York), met its prespecified primary endpoint of reducing the rate of GA in a randomized, controlled Phase IIb clinical trial. The reduction in the mean rate of GA growth over a year was 27.38 percent (p=0.0072) for the 2-mg group compared to sham. In the 4-mg group, the percentage was 27.81 percent (p=0.0051).[30]

Lampalizumab (Genentech, San Francisco) is an antigen-binding fragment (Fab) of a humanized monoclonal antibody that acts as a selective inhibitor of complement factor D, the rate-limiting enzyme in the alternative pathway.[31] The Phase II (MAHALO) trial of lampalizumab for geographic atrophy secondary to age-related macular degeneration suggested that it could reduce the rate of GA enlargement.[32] This led to twin Phase III trials, SPECTRI and CHROMA, that were identical, double-masked, randomized trials to evaluate the efficacy and safety of 10 mg of lampalizumab administered every four or six weeks by intravitreal injection, versus sham injections.[33,34] Additionally, both trials were designed to assess whether having the CFI biomarker influences the treatment response. Together, SPECTRI and CHROMA enrolled more than 1,800 participants in more than 20 countries. However, lampalizumab didn't appear to slow lesion progression and there was no link between faster GA progression and the presence of the CFI biomarker.[33]

Pegcetacoplan (APL-2; Apellis Pharmaceuticals, Waltham, Massachusetts) is a synthetic molecule that selectively inhibits C3, effectively downregulating all three complement pathways. APL-2 was evaluated in a Phase II trial (FILLY), which enrolled 246 subjects from 43 clinical sites internationally. Subjects were randomly assigned (2:2:1:1) to four arms: 15 mg APL-2 monthly (n=86); 15 mg APL-2 every other month (EOM; n=79); sham monthly (n=41); and sham EOM (n=40). The total treatment period was 12 months followed by a six-month observation period. The 12-month primary efficacy outcome was the difference in mean change from baseline GA area based on fundus autofluorescence (FAF). Secondary endpoints included the change in BCVA and the incidence of conversion to exudative AMD, as well as other safety endpoints.

At 12 months, patients who received intravitreal APL-2 every month had a 29 percent lower rate of GA lesion growth compared with sham (p=0.008), while patients who received APL-2 EOM had a 20 percent lower rate (p=0.067). The effect was most prominent in the second six months of treatment, during which monthly and EOM APL-2 slowed GA growth by 47 percent (p<0.001) and 33 percent (p=0.01), respectively, compared with sham.[35] No differences in BCVA outcomes were observed between the groups.

Adverse events included endophthalmitis in two participants (2.3 percent) in the monthly group and one patient (1.3 percent) in the every-other-month group. There was an increased incidence of exudation in APL-2-treated eyes (20.9 percent in the monthly group and 8.9 percent in the EOM group) compared to sham-treated eyes (1.2 percent), which was

responsive to standard-of-care treatment. Among patients with a history of CNV in the fellow eye, 13 of 36 (36.1 percent) in the monthly group, five of 28 (17.9 percent) in the EOM group, and none in the sham group developed exudative AMD. For those with no history of CNV in the fellow eye, exudative AMD developed in five of 50 (10 percent) and two of 51 (3.9 percent) in the monthly and EOM groups, respectively, and in one of 52 (1.9 percent) in the sham group. Two 30-month, Phase III, multicenter, randomized, double-masked, sham-injection controlled clinical trials (DERBY and OAKS) are currently under way. The two trials will enroll 600 patients internationally across four study arms: APL-2 15 mg monthly for 24 months; APL-2 15 mg EOM for 24 months; and two respective sham groups.[36]

As the preceding review shows, unlike wet AMD, an effective pharmacologic treatment for GA secondary to dry AMD remains elusive. To date, investigational agents have failed to meet study endpoints in either Phase II or III trials. However, recent and ongoing trials have demonstrated some promise. Therefore, despite past failures there's reason to remain optimistic that a safe and effective treatment is still on the horizon. REVIEW

Dr. Ammar is a vitreoretinal surgery Fellow at the Wills Eye Hospital Retina Service. He has no financial interest in any of the products mentioned.

Dr. Chiang practices at the Wills Eye Hospital Retina Service and Mid Atlantic Retina. He's an assistant professor of ophthalmology at Thomas Jefferson University. He's received research grant support from Genentech, Regeneron and Apellis, and is a consultant for Orbit Biomedical/Gyroscope Therapeutics, Recens Medical and Apellis.

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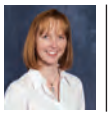

Managing Eyelid and Facial Spasms

Physicians break down the potential causes of spasms and the best way to approach their treatment.

Kalla A. Gervasio, MD, Mark L. Moster, MD
Philadelphia

Spasms of the lid and face can significantly impact a patient's quality of life, but getting to the root cause of the spasm—it can be myokymia, benign essential blepharospasm or hemifacial spasm—can be a challenge for the clinician. In this article, we'll provide advice that can help you diagnose and manage these sometimes challenging conditions.

An Overview

Within neurologic and ophthalmic practice, ranked from least to most severe, the spectrum of eyelid and facial spasms includes eyelid myokymia (involuntary, small contractions of the lid), benign essential blepharospasm (involuntary spasms that cause the eye to close partially or completely) and hemifacial spasm (spasms in the muscles controlling facial expressions) *(Table 1)*. These disorders all consist of involuntary facial movements that can be difficult for patients to deal with in daily life.

Eyelid Myokymia

The most common involuntary facial movement disorder is eyelid myokymia. Eyelid myokymia consists of involuntary, fine, continuous, undulating, non-synchronous contractions of the striated muscle fibers of the eyelid protractors. In electrophysiology, it's characterized by spontaneous asynchronous discharge of adjacent motor units in doublets or triplets at a rate of 30 to 70 Hertz with intervals of 100 to 200 ms separating individual discharges.[2,3] Eyelid myokymia is considered a benign, self-limiting process that's unilateral and intermittent, with the lower eyelid affected more than the upper lid. Episodes are transient, lasting anywhere from a few days to a few weeks or months, with spasms occurring intermittently throughout the day for up to several hours at a time.[4]

Inciting factors include stress, exhaustion, excessive caffeine intake or alcohol use, and physical exertion.[5] Elimination of these triggers is recommended as part of management. Eyelid myokymia is most commonly isolated to the orbicularis oculi muscle, but may spread to additional muscles of one or both sides of the face, in which case it is referred to as facial myokymia.[2]

Facial myokymia is caused by damage to the facial nerve nucleus in the pons from demyelinating diseases such as multiple sclerosis or compression from brainstem tumors. Rarely, persistent eyelid myokymia has been reported as a presenting sign of multiple sclerosis or a brainstem tumor.[3] If the condition is chronic, refractory to elimination of inciting factors and affects the patient's quality of life, botulinum toxin injections can be successful in treatment. The mechanism and efficacy of botulinum toxin injections is discussed extensively in the following section. Persistent eyelid myokymia refractory to the above treatments should raise suspicion for a brainstem lesion as described above and warrants analysis with magnetic resonance imaging.

Benign Essential Blepharospasm

BEB was first described in 1857 as a disorder of involuntary spasms of the eyelid protractor muscles that

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Table 1. Clinical Characteristics, Diagnosis and Management Options for Eyelid and Facial Spasms

	Eyelid Myokymia	Benign Essential Blepharospasm	Hemifacial Spasm
Laterality	Unilateral	Bilateral	Unilateral
Muscles Involved	Orbicularis oculi	Eyelid protractor muscles: orbicularis oculi, procerus, corrugator supercilii	Muscles of facial expression innervated by facial nerve: eyelid protractors, frontalis, orbicularis oris, triangularis or mentalis, platysma
Persistence During Sleep	no	no	yes
Triggers	Stress, fatigue, excessive caffeine or alcohol intake	Stress, excessive caffeine intake, driving, watching television, reading, light exposure, certain eye or head positions	Anxiety, stress, fatigue, sleep deprivation, reading, light exposure, chewing, certain head positions
Imaging	Magnetic resonance imaging of brain if refractory (to rule out multiple sclerosis and/or brainstem tumor)	None	Magnetic resonance imaging of brain
Primary Treatment	Avoidance of triggers	Botulinum toxin injections	Botulinum toxin injections
Surgical Options	None	Myectomy of one or more eyelid protractors	Microvascular decompression of facial nerve

Table 1. Eyelid and facial spasm characteristics with diagnostic modalities and management overview.

results in partial or complete eyelid closure. BEB has an incidence of 1.4 to 13.3 cases per 100,000, affects females three times more often than men, and most often occurs in the fifth to seventh decades of life.[7,8] BEB is most commonly a sporadic disorder, but 27 percent of patients have been reported to have a family member with dystonia, suggesting a possible genetic component.[1]

The pathophysiology of BEB isn't well understood. Positron emission tomography and functional magnetic resonance imaging studies have shown activation of brain regions involved in the control and regulation of the muscles responsible for blinking, including the thalamus, striatum, anterior visual cortex, primary motor cortex and superior cerebellum.[7,9]Animal studies have shown that dopamine depletion in the substantia nigra decreases inhibition of the trigeminal blink reflex leading to oversensitivity of this reflex in response to light and dryness.[10] Inciting factors for BEB include stress, excessive caffeine intake, driving, watching television, reading, bright lights, polluted air, wind, noise, and certain eye and head movements.[11,12]

The clinical presentation of BEB consists of bilateral involuntary spasms of one or more of the eyelid protractor muscles including the orbicularis oculi, procerus and corrugator muscles, with symptoms ranging from mildly increased blink rate to forceful eyelid closure that can result in functional blindness.[1] BEB symptoms don't persist during sleep and it's a progressive condition in which additional muscles become involved over time.[7] A subset of patients may experience mid or lower-facial spasms, a condition termed Meige syndrome.[1] An additional subset of patients may develop apraxia of eyelid opening in which there is a loss of co-inhibition between eyelid protractors and retractors resulting in a nonparalytic inability to open the eyelids in the absence of muscle spasm.[1]

Patients also often complain of the sensory symptom of photophobia. Proposed mechanisms for photophobia include a sympathetically maintained pain disorder, for which superior cervical ganglion blocks have provided relief in prior reports.[11] Additional management options to control photophobia include photochromatic modulation with FL-41 tinted lenses or scleral contact lenses with fluorescein in the fluid reservoir, both of which increase the intensity of light tolerated by BEB patients.[13]

The treatment of choice for BEB is botulinum toxin injections into the affected eyelid protractor muscles. Botulinum toxin inhibits the release of acetylcholine from the presynaptic terminal of the neuromuscular junction, blocking an injected muscle's ability to contract. There are seven serotypes of botulinum toxin (A through G). Types A and B are U.S. Food and Drug Administration-approved for clinical use in the United States. OnabotulinumtoxinA

(Botox) was approved by the FDA for BEB treatment in 1989 and is the most commonly used formulation, though incobotulinumtoxinA, abobotulinumtoxinA, and rimabotulinumtoxinB are also licensed for use.[14] Injections are required approximately every three to four months.[11] The FDA recommends an initial dose of 1.25 to 2.5 units injected into each affected site with a maximum dose of 15 units and three injection sites per side.[14] However, surveys have showed that oculoplastic surgeons tend to treat BEB with an average initial dose of 22.5 ±9.5 units.[14]

Typically, five to eight sites are injected around each eye, with no more than 0.1 ml of botulinum toxin injected at each site to prevent diffusion of the drug into adjacent muscles.[12] Clinicians must take care to inject medially and laterally when treating the pretarsal portion of the orbicularis oculi muscle in the upper eyelids, in order to avoid injection into the levator palpebrae superioris muscle, which can result in ptosis. Similarly, in the lower eyelid, injections are carried out centrally and laterally in order to avoid injection into the inferior oblique, which would result in diplopia. The incidence of adverse effects of botulinum toxin injections for BEB patients has been reported to be around 20 percent, including ecchymosis at the injection site, dry eye, tearing, foreign body sensation, lagophthalmos, diplopia and ptosis.[7]

Other medications that have been used in the treatment of BEB include antipsychotics, antiepileptics, anxiolytics, antidepressants, antihistamines, sedatives and stimulants, though none have been shown to have long-term efficacy.[15] In particular, dopamine agonists and dopamine uptake inhibitors have been shown to be effective in reducing eyelid spasms given the fact that dopamine deficiency has been implicated in the pathogenesis of BEB.[11] Methylphenidate, which blocks presynaptic reuptake of dopamine and norepinephrine, has been shown to decrease eyelid spasms and disability scoring.[11] BEB patients have shown partial response to gamma-aminobutyric acid agonists such as benzodiazepines, but their use is limited by the side effect of drowsiness.[11]

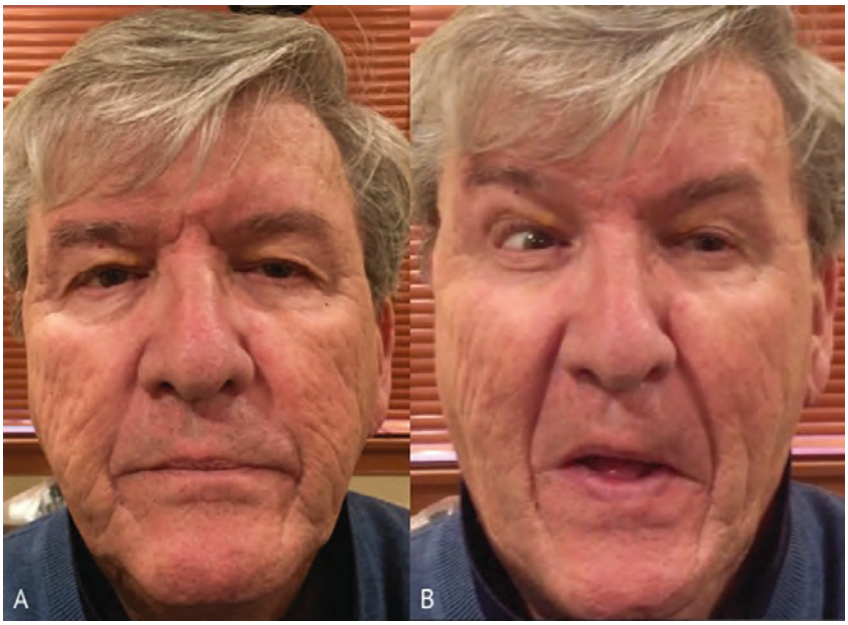

Figure 1. A: Patient with history of hemifacial spasm at rest prior to episode. B: Active left-sided hemifacial spasm with co-contraction of the frontalis and orbicularis oculi muscles, resulting in simultaneous raising of the eyebrow and partial closure of the eye.

When BEB is refractory to medical management or a patient can't tolerate botulinum toxin injections, surgical intervention with myectomy may be considered. The primary goals of this procedure are to reduce spasm severity and to increase the time interval needed between botulinum injections.[11] In surgical myectomy, one or more of the protractor muscles are resected. A limited myectomy involves resection of only part of the orbicularis oculi muscle in the upper eyelid, versus an extended myectomy in which the corrugator supercilii and protractor are additionally removed.[15]

Adverse effects of surgery include poor cosmesis and need for additional surgeries. Recurrence of symptoms after surgical myectomy has been reported to range from 30 to 50 percent of cases after six months.[12] An alternative procedure involves sectioning of the facial nerve, which effectively denervates the eyelid protractors but secondarily results in facial nerve palsy and so is rarely used.[15]

Hemifacial Spasm

Lastly, HFS is a unilateral involuntary facial movement disorder involving spasms of the muscles of facial expression innervated by the facial nerve. Estimated incidence is approximately 10 cases per 100,000, based on studies in Minnesota and Norway.[16,17] HFS tends to occur in the fourth or fifth decade of life, with females being affected two to three times more often than men, and Asian populations more commonly affected than Caucasians.[18]

Up to one-third of patients report aggravating factors for HFS, including anxiety, stress, fatigue, sleep deprivation, reading, light exposure, chewing or particular head positions.[18] HFS is often misdiagnosed as functional or psychogenic (in 38 percent of cases), tics (in 29 percent) and facial nerve palsy (in 9 percent).[19] Clinical presentation involves initial spasms of the orbicularis oculi which gradually progress or spread over time to involve other muscles on one half of the face, such as the frontalis, orbicularis oris, triangularis or mentalis, and even the platysma muscle.[7,18] Symptoms of HFS may persist during sleep, whereas those of BEB do not.

The pathophysiology of HFS involves compression of the facial nerve at its root exit zone (REZ) from the brainstem, which was first described in 1947.[20] Compression may be caused by aberrant vessels, including the anterior inferior cerebellar artery, posterior inferior cerebellar artery, basilar artery, vertebral artery; arteriovenous malformations; and very rarely by tumors such as acoustic schwannomas, meningiomas, parotid gland tumors, and pilocytic astrocytomas.[7] While diagnosis of HFS is primarily clinical, MRI should always be obtained to rule out facial nerve compression as described above. Electromyography testing may also be carried out to demonstrate a pathognomonic lateral spreading response of impulses between neighboring fibers of the facial nerve ("ephaptic transmission").[20]

The mainstay of treatment for HFS are botulinum toxin injections as described above for BEB. For HFS, five to 10 sites are injected on the affected side of the face with total doses of onabotulinumtoxinA ranging from 10 to 34 units per treatment.[20] The definitive treatment for HFS is neurosurgical microvascular decompression (MVD) to relieve facial nerve compression at its REZ. In prior studies, approximately 95 percent of patients who underwent MVD for HFS achieved good or even excellent results, with adverse effects including facial nerve palsy in 19 percent, hearing deficits in 7 percent, and lower cranial nerve palsies in 2.8 percent.[21] Given the invasiveness and risks associated with undergoing neurosurgical intervention, it's of the utmost importance to have a frank discussion with patients regarding the risks and benefits of MVD versus botulinum toxin injections, or a combination of the two, for management of HFS.

The definitive treatment for hemifacial spasm is neurosurgical microvascular decompression (MVD) to relieve facial nerve compression at its root exit zone.

In conclusion, eyelid and facial spasms represent a spectrum of involuntary facial movement disorders that can have a severe impact on patients' quality of life and psychological wellbeing. While avoidance of inciting factors is recommended in management, botulinum toxin injections have emerged as first-line treatment, particularly for BEB and HFS. Surgical therapy for BEB and HFS, however, may be pursued in refractory cases or in patients intolerant of botulinum toxin injections. Given the frequent misdiagnosis of these disorders, it's important for physicians to be familiar with the most common presenting signs and symptoms in order to connect these patients with neurologists or ophthalmologists for further evaluation and management. REVIEW

Dr. Gervasio is an ophthalmology resident at Wills Eye Hospital. Dr. Moster is an attending physician on the Neuro-Ophthalmology Service at Wills and professor of neurology and ophthalmology at Thomas Jefferson University in Philadelphia. He is chair of neuro-ophthalmology at Einstein Medical Center in Philadelphia.

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A woman with a history of headaches presents to Wills Eye Hospital with complaints of chronic double vision.

Vikram A. Shankar, MD, MPH, and Jurij R. Bilyk, MD

Presentation

A 53-year-old female presented to Wills Eye Hospital for evaluation of double vision she'd had for three months. Five months prior, she presented to her primary care physician with chronic headaches, sinus pressure and right-sided periorbital swelling. She was treated with amoxicillin/clavulanic acid and low-dose oral prednisone for presumed sinusitis, and brief improvement in her symptoms was noted. She returned for evaluation two months later with recurrence of sinus pain and headaches, as well as epistaxis and binocular diplopia, most prominent with lateral gaze. An enlarged, mobile cervical lymph node was also discovered on exam, and she was referred to an otolaryngologist for further evaluation. Transnasal endoscopic biopsy of her sinuses was performed and showed inflammatory changes consistent with chronic sinusitis, without any evidence of malignancy. She was subsequently directed to the Otolaryngology and Ophthalmology departments at Thomas Jefferson University Hospital and Wills Eye Hospital for further evaluation.

Medical History

Her past medical history included hypertension, hyperlipidemia and obstructive sleep apnea. In addition, her history was notable for several years of chronic sinusitis, for which she had undergone previous endoscopic sinus surgery with minimal relief. Her family and social histories were noncontributory. Current medications included montelukast, desloratadine, pravastatin and candesartan/hydrochlorothiazide.

Examination

Ophthalmologic examination revealed a best corrected visual acuity of 20/25 OD and 20/20 OS. Her pupils were equal, round and reactive to light with no afferent pupillary defect. Intraocular pressures were 25 mmHg OU. The patient's external exam was remarkable for mild lateral displacement of the right globe and 1 mm of proptosis of the right eye by Hertel exophthalmometry. Extraocular movements demonstrated orthophoria in primary gaze but bilateral restriction of adduction, right greater than left. Mild restriction of infraduction was also noted OU *(Figure 1)*. Her visual fields were full to confrontation and color plates were full OU. Her slit lamp exam was within normal limits except for 2+ nuclear sclerotic cataracts OU.

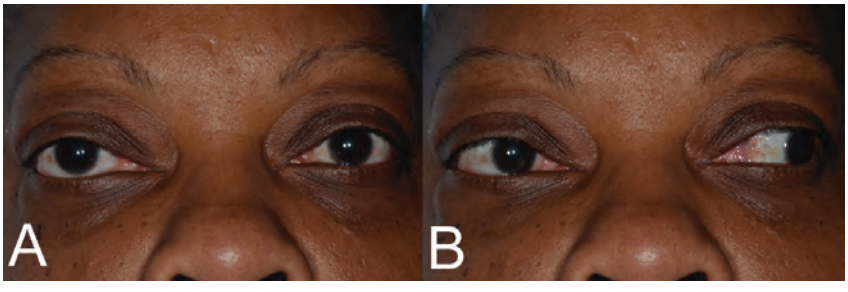

Figure 1. Clinical photographs of the patient demonstrate right-sided proptosis (A) and adduction deficit (B).

What is your diagnosis? What further workup would you pursue? The diagnosis appears on p. 73.

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Workup, Diagnosis and Treatment

The initial differential included benign and malignant neoplasms, inflammatory and autoimmune diseases, chronic infection and vascular malformations. Primary malignancies of the sinus, orbit and lacrimal sac were of greatest concern upon presentation. Manifestations of diffuse large B-cell lymphoma and mantle cell lymphoma were felt to be less likely given her absence of systemic "B symptoms." Inflammatory and autoimmune disorders such as sarcoidosis, IgG4-related disease, granulomatosis with polyangiitis (Wegener's granulomatosis), eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome) and histiocytosis were also given serious consideration. Acute bacterial infections were deemed less likely, although sino-orbital aspergillosis remained on the differential given its potential to mimic noninfectious orbital inflammation.

A CT scan of the head, orbits and maxillofacial bones, without contrast, was obtained as the first step. It showed a large soft tissue mass filling the frontal, ethmoid and maxillary sinuses bilaterally, with extension into the nasal cavities and orbits *(Figure 2 C,D)*. An extra-axial mass along the left frontal lobe with parenchymal edema was also noted, along with bilateral cervical lymphadenopathy. Initial lab studies showed a normal CBC, BMP and LFTs. ESR was found to be elevated to 97 (normal: 0 to 40). Autoimmune serologies such as ANA, ANCA panel, RF, ACE and serum IgE levels were within normal limits.

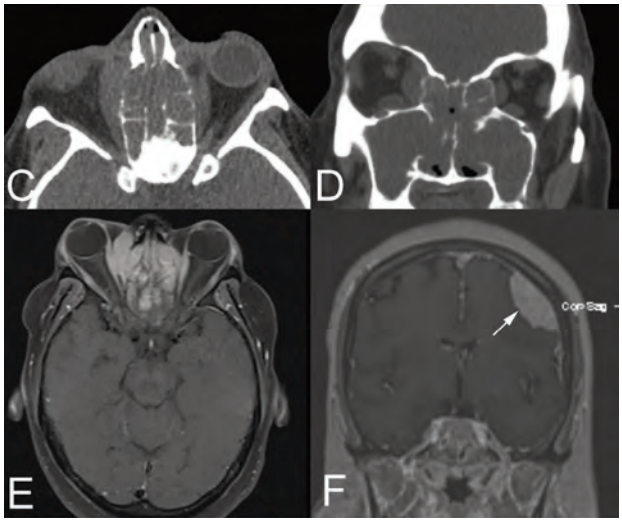

Figure 2. C and D: Axial and coronal CT, soft tissue window, demonstrated marked sinus infiltration with bone erosion and soft infiltration into the medial orbits, worse on the right.
E and F: Repeat imaging with MRI (T1-weighted, with contrast and fat-suppression) showed persistent sinus and orbital involvement. A new left parietal lesion was noted (arrow).

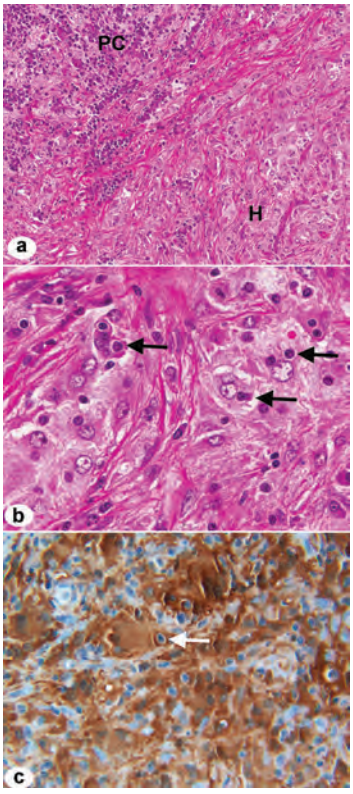

Figure 3. Pathology. A: Mixed plasmacytic and histiocytic infiltrate involves the orbital tissues. B: The histiocytic cells have round nuclei with central nucleoli and abundant eosinophilic glassy cytoplasm with intracytoplasmic vacuoles containing intact lymphocytes (arrows), a phenomenon known as emperipolesis. C: CD68 immunostain highlights the cytoplasm of histiocytes with a brown reaction product, which contrasts with the non-staining intracytoplasmic lymphocytes (arrow). [stains: (A, B) hematoxylin-eosin; (C) CD68].

Serum IgG was elevated to 2,420 (normal: 700 to 1,600) and IgG4-specific levels were elevated to 159 (normal: 2 to 96). An MRI of the brain, orbits, and sinuses was obtained with contrast, to better delineate the extent of the soft tissue mass. This confirmed CNS involvement near the left frontal lobe *(Figure 2 E,F)*. A transnasal endoscopic biopsy of the sinonasal mass was then performed in order to obtain a tissue diagnosis.

Final pathology from the nasal mass revealed fibrosis with a polymorphous infiltrate containing histiocytes and large macrophages with intracytoplasmic lymphocytes, consistent with a diagnosis of Rosai-Dorfman Disease *(Figure 3 A-C)*. The patient was started on an extended course of oral prednisone and underwent neurosurgical debulking of her left frontoparietal mass. Her prednisone was tapered and she was transitioned to sirolimus after her procedure. Several months later, she was hospitalized for bilateral pneumonia, and her sirolimus was discontinued, given concern that her infection was triggered by sirolimus-induced pneumonitis.

Without receiving any systemic treatment, over the next several months she reported worsening headaches and sinus pressure, and repeat MRI showed enlargement of the paranasal sinus mass with further infiltration of the

right orbit. Recurrence of the frontal lobe mass was also noted on imaging, with an additional focus of axial enhancement along the anterolateral right frontal lobe. At the time of this report, the patient had restarted systemic treatment with methotrexate and 6-mercaptopurine and is scheduled to follow up with pulmonology, oncology, neurosurgery and ENT over the next several months for ongoing management.

Discussion

Rosai-Dorfman Disease, also known as sinus histiocytosis with massive lymphadenopathy, is a non-malignant proliferation of histiocytes in lymph node sinuses and many other extranodal sites.[1] Clinical manifestations of RDD may include classic B symptoms of bilateral painless cervical lymphadenopathy, intermittent fevers, night sweats and weight loss.[2] Extranodal RDD occurs in approximately 43 percent of cases; it may include cutaneous, CNS, intrathoracic, retroperitoneal and osseous manifestations. Ophthalmic involvement occurs in 10 percent of cases, presenting as a mass in the orbital soft tissues, eyelids, lacrimal glands or other locations.[3] Orbital RDD has rarely been reported in isolation; it generally occurs unilaterally. CNS involvement is even rarer, occurring in less than 5 percent of cases in the literature, although the risk is greater in elderly patients.[2-4]

RDD is considered a self-limited disorder of unknown etiology, although recent studies have suggested associations with mutations in NRAS, KRAS and ARAF. These genes are involved in cell growth and development, and mutations are believed to be closely linked to tumorigenesis.[5] Diagnosis and staging of patients with RDD should include comprehensive imaging of the neck, chest, abdomen and pelvis, with consideration for PET/CT during the initial survey.[1,2,4] Patients with orbital or neurologic involvement, as described in our own case, should undergo MRI of the brain, orbits and spine, with gadolinium.[6] Although serum studies may offer some value in ruling out alternative diagnoses, definitive diagnosis is made only through tissue biopsy.[2,7] Pathologically, RDD is typified by histiocytic proliferation with infiltration of mature plasma cells and lymphocytes. A unique histologic feature of this disease is the finding of emperipolesis, whereby histiocytes phagocytize viable lymphocytes without enzymatic degradation.[2]

No uniform approach to treatment has been established for RDD, and treatment must be tailored to each patient. Initial observation is prudent in patients with only nodal or cutaneous disease, as between 20 to 50 percent of cases undergo spontaneous remission.[5] In cases with symptomatic CNS involvement or organ dysfunction secondary to compression, surgical debulking may achieve symptomatic control and restore function. Surgical excision is considered the first-line therapy for orbital masses, which tend to be more progressive and symptomatic than lesions at other sites.[1,2] Those with disseminated or multifocal disease not amenable to surgical resection are often treated with intralesional or systemic steroids, which may reduce nodal size and symptoms. Relapses are common, and durable responses to steroids alone have not been consistently achieved in the literature.[2,4,5,8]

Chemotherapy for treatment of vision-threatening compressive optic neuropathy in combination with primary surgical excision has been advocated by many authors. Combination therapy with CHOP-like regimens or methotrexate and 6-mercaptopurine have demonstrated some promise in the recent literature, although many other agents are under investigation. Low-dose salvage radiotherapy after surgical debulking has also been proposed, but guidelines for standard dosing haven't been established.[1,2,4] RDD has a variable clinical course, and several disease patterns including stable, recurrent or progressive disease have been described. Mortality from RDD approaches 7 percent and is primarily a consequence of direct renal or CNS invasion. Careful follow-up is necessary to monitor for malignant transformation and additional systemic complications.[2]

In conclusion, Rosai-Dorfman Disease is a rare disorder which presents significant diagnostic and therapeutic challenges. A high index of suspicion may facilitate diagnosis, but even early recognition and treatment may not alter the clinical course of the disease. Although classified as benign, Rosai-Dorfman Disease can have severe systemic complications, and orbital involvement necessitates timely and aggressive treatment in order to preserve a patient's sight. REVIEW

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Rx Only

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

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

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

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

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

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

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

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

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

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

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

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

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

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.

Last Modified: 01/2018 S33769

xiidra® (lifitegrast ophthalmic solution)5%

THERE'S NO SWIITCHING THIS

Xiidra is the only lymphocyte function-associated antigen-1 (LFA-1) antagonist treatment for Dry Eye Disease[1,2]

Xiidra, the first in a class of LFA-1 antagonists for Dry Eye Disease, is a prescription eye drop FDA-approved to treat both signs and symptoms of the disease.[1,3]

There's no substitute.[2,4]
Check out patient resources, insurance coverage, and more at **Xiidra-ECP.com**

References:

1. Xiidra [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; November 2019. **2.** TFOS DEWS II Research Subcommittee. Report of the Research Subcommittee of the Tear Film & Ocular Surface Society Dry Eye WorkShop II (2017). *Ocul Surf.* 2017;15(3):269-649. **3.** FDA approves new medication for dry eye disease. FDA News Release. July 2016. http://www.fda.gov/newsevents/newsroom/pressannouncements/ucm510720.htm. Accessed July 12, 2016. **4.** Food and Drug Administration. Electronic Orange Book. http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/UCM071436.pdf. Accessed June 26, 2018.

Indication

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

Important Safety Information

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

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

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

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

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

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

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