Wills Eye Resident Series: A 53-year-old presents with a choroidal mass in her right eye, *p .78*

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HOW TO WIN IN THE CATARACT SURGERY ARENA

SELECT YOUR TECHNIQUE

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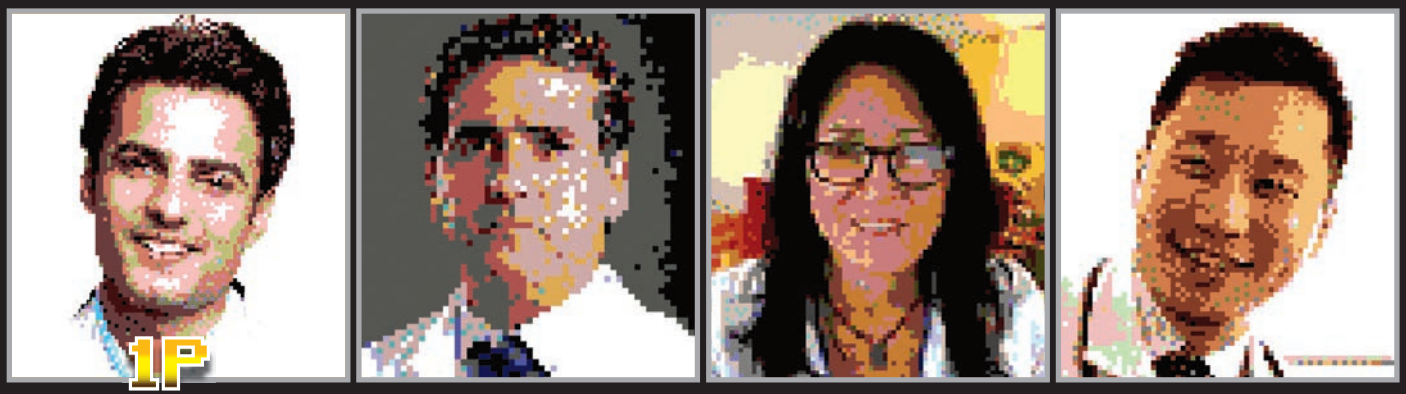

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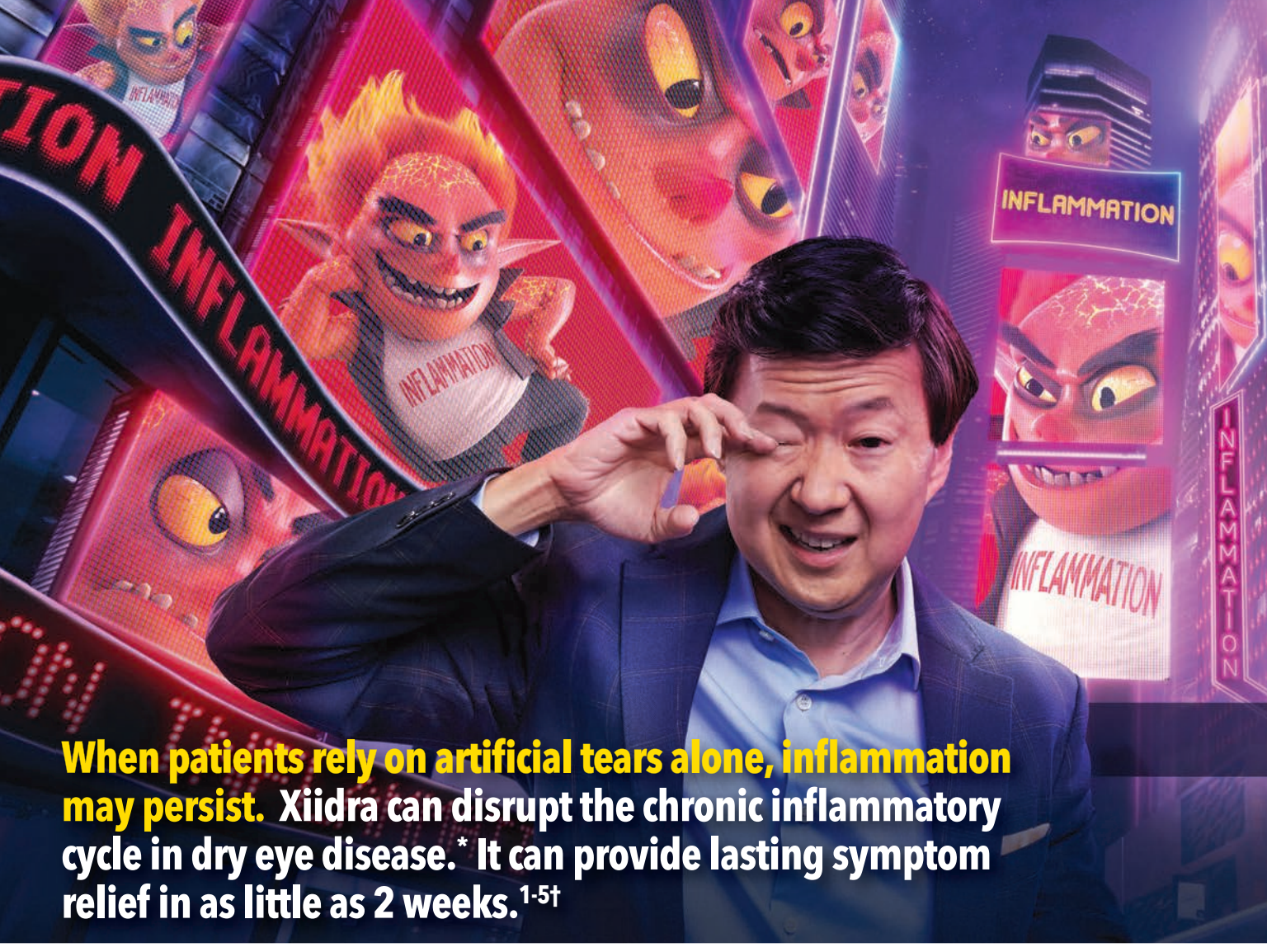

When patients rely on artificial tears alone, inflammation may persist. Xiidra can disrupt the chronic inflammatory cycle in dry eye disease.* It can provide lasting symptom relief in as little as 2 weeks.[1-5†]

*Xiidra blocks LFA-1 on T cells from binding with ICAM-1 that may be overexpressed on the ocular surface in dry eye disease and may prevent formation of an immunologic synapse which, based on in vitro studies, may inhibit T-cell activation, migration of activated T cells to the ocular surface, and reduce cytokine release. The exact mechanism of action of Xiidra in DED is not known.[1,2,5]

† The safety and efficacy of Xiidra were assessed in four 12-week, randomized, multicenter, double-masked, vehicle controlled studies (N=2133). Patients were dosed twice daily. The mean age was 59 years (range, 19-97 years). The majority of patients were female (76%). Use of artificial tears was not allowed during the studies. The study end points included assessment of signs (based on Inferior fluorescein Corneal Staining Score [ICSS] on a scale of 0 to 4) and symptoms (based on patient-reported EDS on a visual analogue scale of 0 to 100). Effects on symptoms of dry eye disease: a larger reduction in EDS favoring Xiidra was observed in all studies at day 42 and day 84. Xiidra reduced symptoms of eye dryness at 2 weeks (based on EDS) compared to vehicle in 2 out of 4 clinical trials. Effects on signs of dry eye disease: at day 84, a larger reduction in ICSS favoring Xiidra was observed in 3 out of the 4 studies.[1]

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.

NOVARTIS

Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936-1080

xiidra® (lifitegrast ophthalmic solution)5%

Dry eyes deserve a change

Important Safety Information (cont)

- 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 about XIIDRA®, please refer to the brief summary of Full Prescribing Information on adjacent page.

References: 1. Xiidra [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corp; June 2020. **2.** Bron AJ, de Paiva CS, Chauhan SK, et al. TFOS DEWS II Pathophysiology Report. *Ocul Surf*. 2017;15(3):438-510. **3.** US Food and Drug Administration. Code of Federal Regulations, Title 21, Volume 5 (21CFR349). Accessed May 25, 2021. https:/www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=349&showFR=1 **4.** Jones L, Downie LE, Korb D, et al. TFOS DEWS II Management and Therapy Report. *Ocul Surf*. 2017;15(3):575-628. **5.** Pflugfelder SC, Stern M, Zhang S, Shojaei A. LFA-1/ICAM-1 interaction as a therapeutic target in dry eye disease. *J Ocul Pharmacol Ther*. 2017;33(1):5-12.

XIIDRA® (lifitegrast ophthalmic solution), for topical ophthalmic use
Initial U.S. Approval: 2016

BRIEF SUMMARY: Please see package insert for full prescribing information.

1 INDICATIONS AND USAGE

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

4 CONTRAINDICATIONS

Xiidra is contraindicated in patients with known hypersensitivity to lifitegrast or to any of the other ingredients in the formulation *[see Adverse Reactions (6.2)]*.

6 ADVERSE REACTIONS

The following serious adverse reactions are described elsewhere in the labeling:

- Hypersensitivity *[see Contraindications (4)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in 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 five clinical trials of DED conducted with lifitegrast ophthalmic solution, 1401 patients received at least one dose of lifitegrast (1287 of which received lifitegrast 5%). The majority of patients (84%) had less than or equal to 3 months of treatment exposure. One hundred-seventy 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%-5% of the patients were blurred vision, conjunctival hyperemia, eye irritation, headache, increased lacrimation, eye discharge, eye discomfort, eye pruritus, and sinusitis.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval 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 serious cases of hypersensitivity, including anaphylactic reaction, bronchospasm, respiratory distress, pharyngeal edema, swollen tongue, urticaria, allergic conjunctivitis, dyspnea, angioedema, and allergic dermatitis have been reported. Eye swelling and rash have also been reported *[see Contraindications (4)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

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 premating 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 *[see Clinical Pharmacology (12.3) in the full prescribing information]*.

Data

Animal Data

Lifitegrast administered daily by IV injection to rats, from premating through gestation day 17, caused an increase in mean pre-implantation 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.

8.2 Lactation

Risk Summary

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 *[see Clinical Pharmacology (12.3) in the full prescribing information]*. 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.

8.4 Pediatric Use

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

8.5 Geriatric Use

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

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NEWS

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VOLUME XXIX • NO. 3

MARCH 2022

First Bispecific Antibody for Eye Disease Approved by FDA

The U.S. Food and Drug Administration recently approved faricimab, now known as Vabysmo (faricimab-svoa, Genentech/Roche), for the treatment of nAMD and DME. The Phase III nAMD trials (TENAYA and LUCERNE, n=1,329) and DME trials (YOSEMITE and RHINE, n=1,891) comparing intravitreal faricimab 6 mg to aflibercept 2 mg, all met their primary endpoints. "This drug works as well and is as safe for the two most common disease states for which we administer anti-VEGF therapy," says Wills Eye Hospital's Carl Regillo, MD, FACS, a clinical investigator for the Phase III trials for both indications and consultant for Genentech. "Its extended durability means fewer total treatments will be needed to control disease in a comparable way."

Faricimab is a bispecific antibody that simultaneously binds both angiopoietin2 and VEGF-A. By targeting two pathologic growth factors, the drug may provide a better or more durable effect, explains Dr. Regillo.

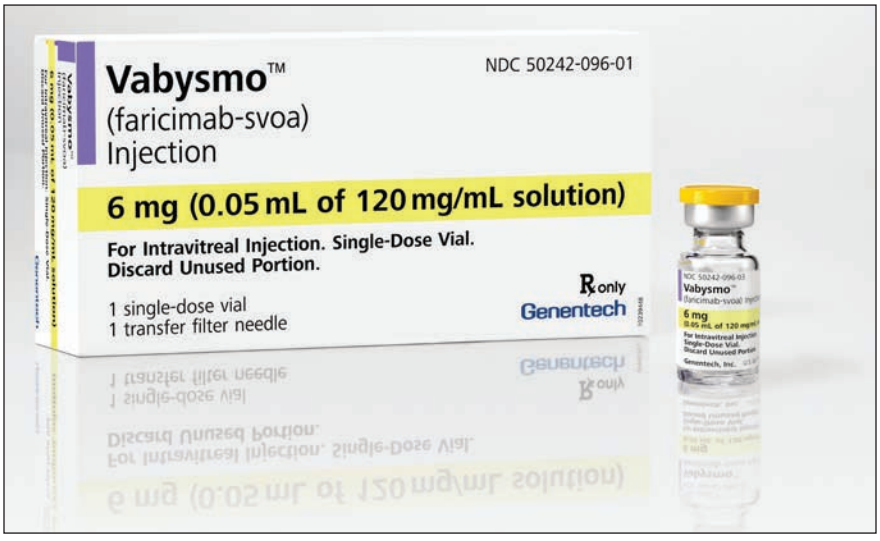
"There's a lot of pre-clinical evidence to suggest that Ang2 plays a pathologic role in disease states of the retina—both in wet AMD and DME," he says. "In disease states, Ang2 is upregulated and appears to work in conjunction with the upregulation of VEGF-A in promoting vascular instability with leakage and new blood vessel formation—the pathologic signs we see clinically in these conditions. Blocking both factors has a potential advantage over blocking only VEGF-A."

For both nAMD and DME, patients receive four loading doses, followed by maintenance dosing every two, three or four months for nAMD and every one to four months for DME, depending on anatomical and visual outcomes. The drug was also approved for a second DME treatment regimen consisting of six monthly loading does and maintenance treatment every two months. Monthly treatments for nAMD and DME are approved, if needed, but the studies didn't find additional efficacy at this dosing frequency.

In both the Phase II and Phase III trials, faricimab was well-tolerated and demonstrated safety comparable to ranibizumab and aflibercept. "For both nAMD and DME, faricimab dosed in a less-frequent regimen (q8, q12 or up to q16 weeks) during the maintenance phase produced noninferior vision gains compared to aflibercept dosed on-label," Dr. Regillo says.

Additionally, he says faricimab demonstrated better drying than aflibercept in DME. "That's particularly relevant in DME because studies indicate there's some correlation between better drying and better visual outcomes for some patients," he notes. "Aflibercept enjoys the reputation of being a bit more effective visually with better drying in DME, so the faricimab outcomes exceeded our expectations. Similarly, when faricimab was compared to ranibizumab in the Phase II trial, it also showed trends indicating better drying and durability."

(Continued on p. 8)



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tyrvaya™
(varenicline solution)
nasal spray 0.03 mg

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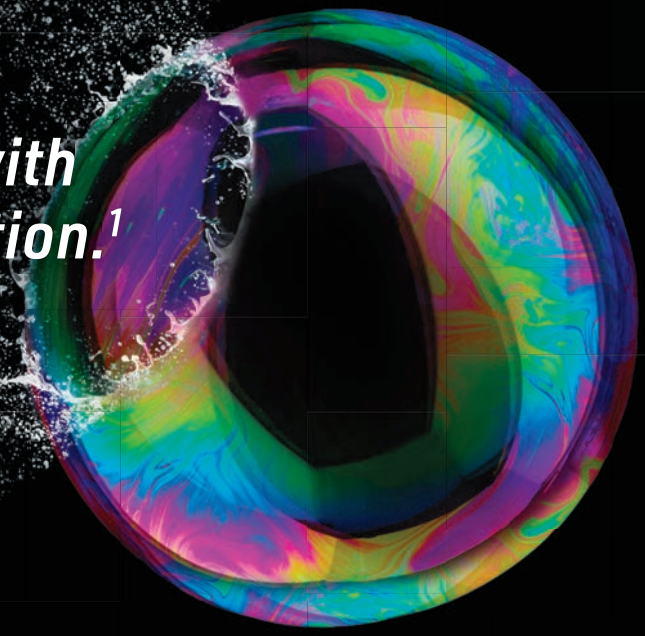

Dry eye starts with tear film disruption.[1]

Treat by activating tear film production.[2]

INTRODUCING A WHOLE NEW WAY TO TREAT DRY EYE DISEASE.[2]

Tyrvaya™, the first and only nasal spray approved to treat the signs and symptoms of dry eye, is believed to activate the trigeminal parasympathetic pathway via the nose, resulting in increased tear film production.[2] The exact mechanism of action is unknown at this time.

Watch Tyrvaya in action at Tyrvaya-pro.com.

INDICATION

Tyrvaya™ (varenicline solution) Nasal Spray is indicated for the treatment of the signs and symptoms of dry eye disease.

Please see Brief Summary of Prescribing Information on the adjacent page and the full Prescribing Information at Tyrvaya-pro.com.

IMPORTANT SAFETY INFORMATION

Adverse Reactions

The most common adverse reaction reported in 82% of patients was sneezing. Events that were reported in 5-16% of patients were cough, throat irritation, and instillation-site (nose) irritation.

References: 1. Craig JP, Nelson JD, Azar DT, et al. *Ocul Surf.* 2017;15(4):802-812. **2.** Tyrvaya. Prescribing Information. Oyster Point Pharma; 2021.

Vabysmo Approval

(Continued from p. 5)

Dr. Regillo says the rates of intraocular inflammation in all four Phase III trials were consistent and about the same as those among aflibercept-treated patients. "Faricimab rates were numerically slightly higher in both programs, but these rates were still low, in the 1- to 2-percent range. This is similar to what we've seen in clinical trials with anti-VEGF biologics over the years. We didn't see any concerning adverse events of special interest such as retinal vasculitis or inflammation-related vascular occlusion.

"For a drug to perform as well both in efficacy and safety, and to last longer, helps to decrease the treatment burden, which is a major unmet need," Dr. Regillo continues. "Our anti-VEGF biologics that we've been using for years work really well, but they must be administered frequently to get optimal long-term vision outcomes for both nAMD and DME. It's really hard to do that in practice. Real-world studies show that we're not able to sustain the vision gains we get upfront after the initial loading phase very well, because we simply can't provide the number of treatments per year that we need to in order to keep these conditions under optimal control. It's a burden on patients, who must make time to come to the office for their injections. We hope that in the long-run, more durability will translate into better maintenance of vision gains, and therefore better long-term vision outcomes.

"It's a big year to have this drug approved simultaneously for both nAMD and DME," Dr. Regillo says. "We welcome the increased durability. I think we're all expecting it to be utilized quite a bit over time."

What's Behind "Dead Bag" Syndrome?

In a case-series study, researchers recently set out to more fully describe the recently recognized phenomenon known as "dead bag" syndrome, in which the capsular bag appears to be clear for years following cataract surgery, but then becomes diaphanous, floppy and unable to support the intraocular lens that was implanted.

In the study of 10 cases that the surgeons suspected to represent a dead bag syndrome, eight IOLs and seven capsular bags were removed because of subluxation or dislocation. The researchers fixed the seven bags available for analysis in formalin and submitted them to histopathological examination

(Continued on p. 14)

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).

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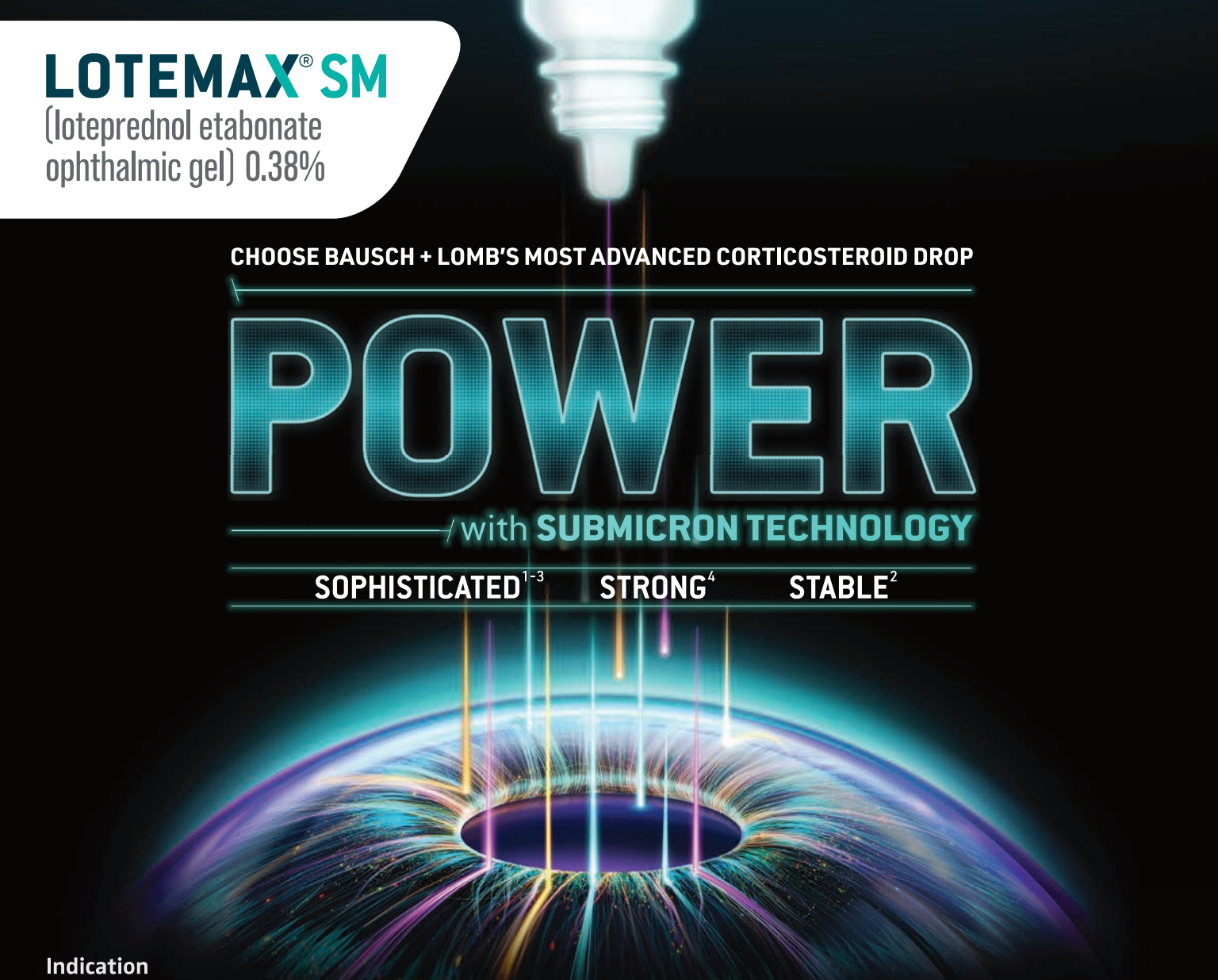
Manufactured by: Bausch & Lomb Incorporated, Tampa, FL 33637 USA
U.S. Patent Number: 10,596,107

Based on 9669601 (Folded) 9669701 (Flat) Revised: 4/2020
LSM.0032.USA.21 Issued: 2/2021

LOTEMAX® SM

(loteprednol etabonate ophthalmic gel) 0.38%



CHOOSE BAUSCH + LOMB'S MOST ADVANCED CORTICOSTEROID DROP

POWER

with SUBMICRON TECHNOLOGY

SOPHISTICATED[1-3] STRONG[4] STABLE[2]

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.

Important Safety Information

- 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, and also in mycobacterial infection of the eye and fungal diseases of ocular structures.
- 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.
- 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 full Prescribing Information on adjacent page.

References: 1. Phillips E, Coffey MJ, Shawer M. Viscoelastic and dissolution characterization of submicron loteprednol etabonate ophthalmic gel, 0.38%. Poster presented at: 2015 ARVO Annual Meeting; May 4, 2015; Denver, Colorado. **2.** Data on file. Bridgewater, NJ: Bausch & Lomb Incorporated. **3.** Cavet ME, Glogowski S, DiSalvo C, Richardson ME. Ocular pharmacokinetics of submicron loteprednol etabonate ophthalmic gel, 0.38% following topical administration in rabbits. Poster presented at: 2015 ARVO Annual Meeting; May 4, 2015; Denver, Colorado. **4.** LOTEMAX® SM [prescribing information]. Bridgewater, NJ: Bausch & Lomb Incorporated.

BAUSCH + LOMB

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Vol. 29, No. 3 • MARCH 2022

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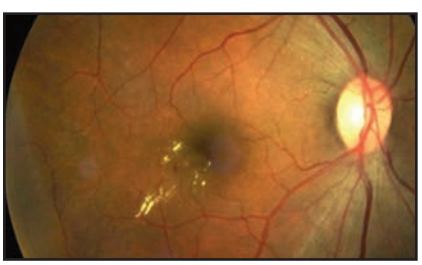

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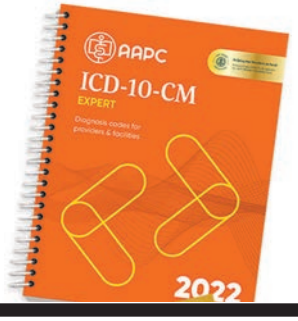

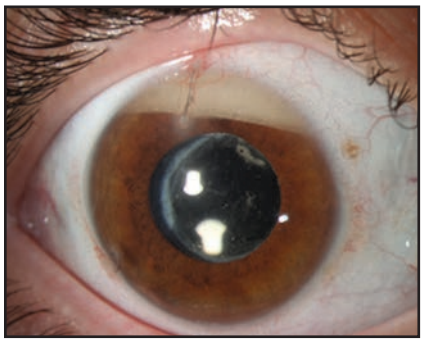

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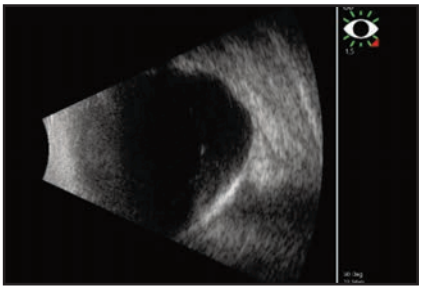

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To treat ocular inflammation and pain following ophthalmic surgery or ocular itching associated with allergic conjunctivitis.

DEXTENZA KEEPS PATIENTS COMPLIANT AND SATISFIED[1-3*]

A hands-free advancement in ophthalmic steroid treatment.[1,4]
Easy-to-insert[†] and preservative-free intracanalicular DEXTENZA offers patients a satisfying post-op experience—providing up to 30 days of sustained steroid coverage.[1-5]

INDICATIONS

DEXTENZA is a corticosteroid indicated for:

- The treatment of ocular inflammation and pain following ophthalmic surgery.
- The treatment of ocular itching associated with allergic conjunctivitis.

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

Intraocular Pressure 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. Intraocular pressure should be monitored during treatment.

Bacterial Infections - 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.

Viral Infections - 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 - 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.

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

Other Potential Corticosteroid Complications - The initial prescription and renewal of the medication order of DEXTENZA 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. If signs and symptoms fail to improve after 2 days, the patient should be re-evaluated.

ADVERSE REACTIONS

Ocular Inflammation and Pain Following Ophthalmic Surgery

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 was headache (1%).

Itching Associated with Allergic Conjunctivitis

The most common ocular adverse reactions that occurred in patients treated with DEXTENZA were: intraocular pressure increased (3%), lacrimation increased (1%), eye discharge (1%), and visual acuity reduced (1%). The most common non-ocular adverse reaction was headache (1%).

Please see adjacent Brief Summary of full Prescribing Information.

*93% (187/201) DEXTENZA patients were satisfied with the insert in the Phase 3 Study for the treatment of ocular inflammation and pain following ophthalmic surgery.[3]

†73.6% of physicians in Study 1, 76.4% in Study 2, and 79.6% in Study 3, for the treatment of ocular inflammation and pain following ophthalmic surgery, rated DEXTENZA as easy to insert.[2,5]

References: 1. DEXTENZA [package insert]. Bedford, MA: Ocular Therapeutix, Inc; 2021. **2.** Tyson SL, et al. *J Cataract Refract Surg*. 2019;45(2):204-212 [erratum in: 2019;45(6):895]. **3.** Data on File 00837. Ocular Therapeutix, Inc. **4.** Sawhney AS, Inventors, et al. Incept, LLC, Assignee. Drug Delivery Through Hydrogel Plugs. US Patent 8,409,606 B2. April 2, 2013. **5.** Walters T, et al. *J Clin Exp Ophthalmol*. 2016;7(4):1-11.

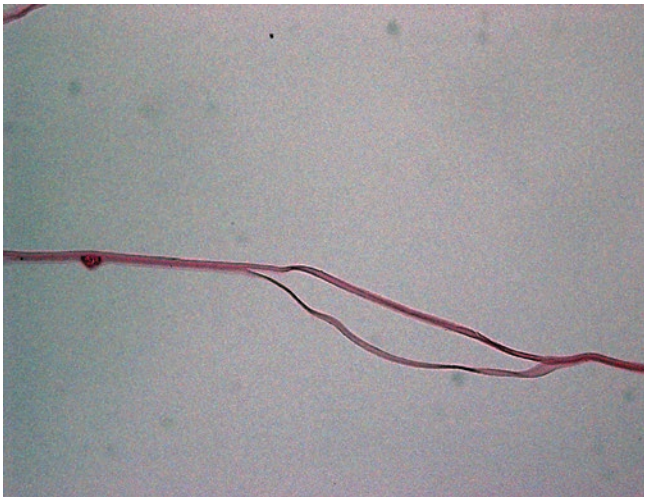
Dextenza®
(dexamethasone ophthalmic insert) 0.4 mg
for intracanalicular use

Dead-Bag Syndrome

(Continued from p. 8)

(hematoxylin-eosin and Masson trichrome stains). They also examined the explanted IOLs in five cases.

Histopathologically, the seven capsular bags showed capsular thinning and/or splitting. Lens epithelial cells were completely absent on two specimens, whereas the other five specimens had rare LECs on the inner surfaces of their capsules. Explanted IOLs were three-piece silicone IOLs or single-piece hydrophobic acrylic IOLs. One IOL optic showed a small amount of granular pigment deposition, but the optics of the other four IOLs were unremarkable, the researchers say.



Light photomicrograph of a histopathological section cut from a capsular bag from a suspected dead bag case, showing capsular splitting/delamination. *Image courtesy of Liliana Werner, MD, PhD, John A. Moran Eye Center, University of Utah.*

The authors say that, in this syndrome, there seems to be an absence of secondary proliferation of LECs and fibrotic changes. The capsule shows some signs of degradation, such as thinning and/or splitting. Weakness of zonular attachments seems to be an associated finding, with subsequent in-the-bag IOL dislocation. "Although the dead bag syndrome specimens reported in this study share characteristics with both true exfoliation and pseudoexfoliation, there are specific differences that show dead bag syndrome to be a distinct entity," the researchers say. They add that further studies will be required to pin down the etiology of the condition.

1. Culp C, Qu P, Jones J, et al. Clinical and histopathological findings in the dead bag syndrome. J Cataract Refract Surg 2022;48:2:177-184.

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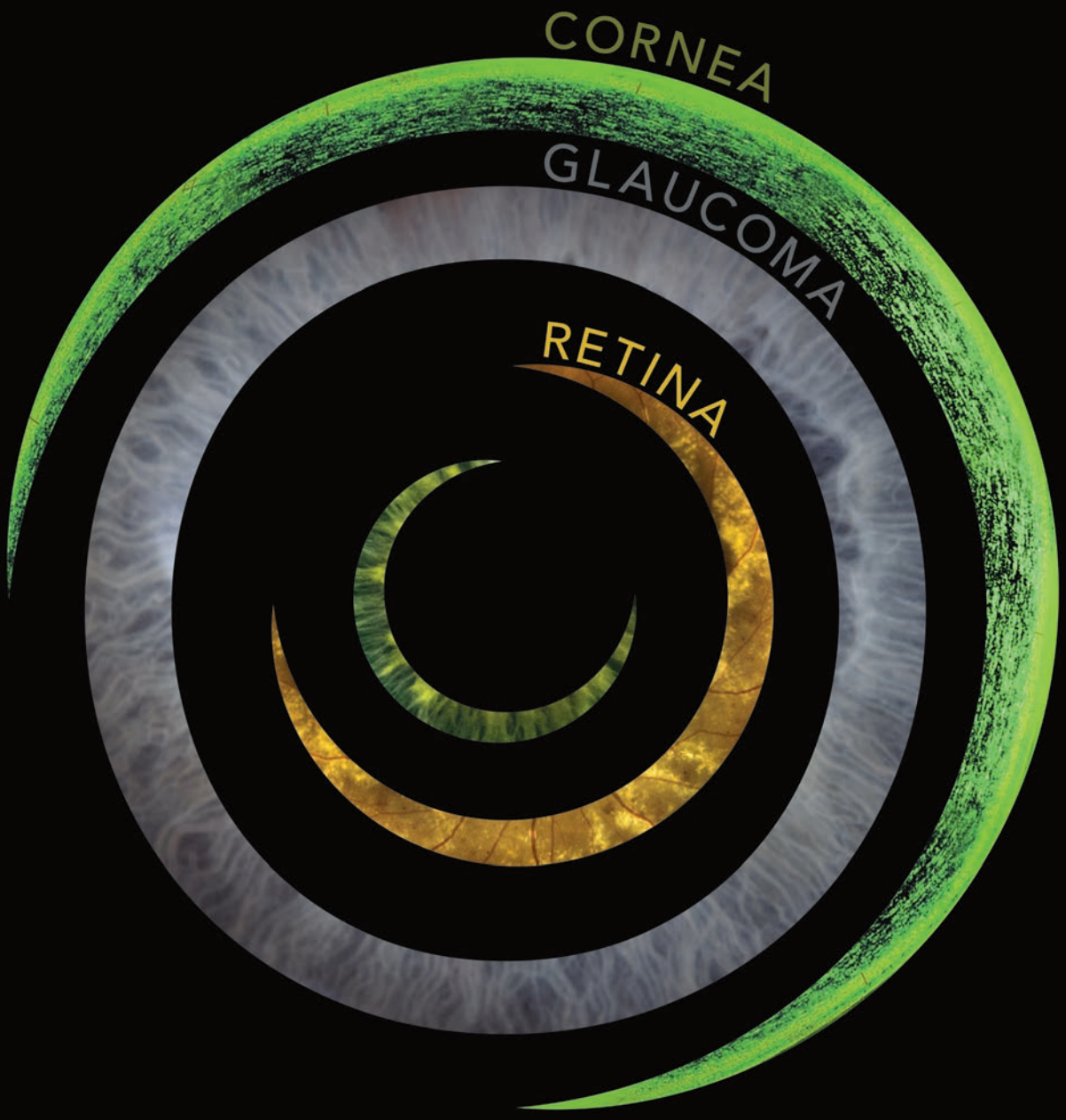

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REVIEW of OPHTHALMOLOGY

WALTER C. BETHKE, EDITOR IN CHIEF

EDITOR'S PAGE

Charting a Course to Better Cataract Surgery

A quote often attributed to President Franklin D. Roosevelt maintains, "A smooth sea never made a skilled sailor," implying that if you want to get better at your chosen profession, you'll need to face adversity and figure out a way to overcome it. Or, maybe you'll fail, in which case American journalist John Hersey assures us, "Learning starts with failure; the first failure is the beginning of education."

I'm sure cataract surgeons at the beginning of their careers, as well as seasoned veterans, not only see the wisdom in these words, but have lived them. Many of the innovative techniques highlighted in this month's features no doubt grew out of a response to tough situations in the O.R., and produced better surgeons as a result.

For instance, because of having to contend with pupil issues during cataract surgery, rather than perfectly dilated pupils every time, surgeons and manufacturers were spurred to develop the pupil expanders and chemical dilating agents we have today. Because these options were developed, surgeons were ready for such surgical setbacks as intraoperative floppy iris syndrome.

In some cases, a surgical technique or technology that's developed to facilitate one aspect of cataract surgery winds up being a valuable "utility player" that pays dividends in multiple areas. For example, bimanual cataract surgery, initially developed as a way to decrease the width of cataract wounds, and possibly get some fluidic advantages by separating the irrigation and aspiration into two different handpieces, may be a useful technique in patients with weak zonules.

"I used to just inject the CTR into the capsular bag as gently as possible," says the University of California, Irvine's Sumit (Sam) Garg MD, in the feature on complicated cataracts that begins on page 25. "Now, I've transitioned to a bimanual technique in which I use a Sinskey hook to stabilize the leading eyelet of the CTR. This allows me to place the CTR into the capsular bag even more gently."

Physicians share even more techniques in our e-survey on cataract surgery on page 37, and experts discuss how the technology they use dovetails with their particular phacoemulsification styles in the phaco technology and technique article that opens on page 45.

When you look at the diverse range of cataract surgery techniques on display in this month's features, it occurs to me we may have found a loophole in FDR's aphorism: You don't always have to face rough seas to be a better sailor—just listen well to the wisdom of the sailors who have.

— Walter Bethke
Editor in Chief


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(Continued from p. 14)

Surgeons Shaking Off COVID-19 Rust

During the pandemic, elective cataract surgery has been significantly curtailed. In an effort to investigate whether a consequent reduction of surgical skill led to higher operative complication rates, researchers recently found that following nine months of curtailed elective cataract surgery, posterior capsular rupture rates were increased across all surgeon grades, with similar risk percentage scores.[1] Cystoid macular edema rates were also increased, unrelated to the proportion of diabetics or increased PCR rates.

The researchers note that, after six months, de-skilling, particularly of fine-motor skills, is rapid and followed by a slower skill degradation with time, with the rates of deskilling varying between individuals, due to mitigating factors such as stress, anxiety and lost confidence.

This single-center study evaluated consecutive patients undergoing cataract surgery during three periods:

P1: prior to the pandemic (February 1, 2019 to January 13, 2020)

P2: after the first lockdown (June 3, 2020, to January 11, 2021

P3: during/after the second lockdown (January 25, 2021, to July 30, 2021)

A total of 2,276 operations occurred during P1, 999 during P2 and 846 during P3. During P1, the PCR rate was 1.7 percent, similar to P2 (1.3 percent) but lower than P3 (3.6 percent). There was no difference in PCR risk percentage score between routine and PCR cases during P1 (1.9 percent vs 2.0 percent), P2 (2.0 percent vs 2.2 percent) or P3 (1.9 percent vs. 2.7 percent).

During P2 and P3, there was a higher rate of CME compared with P1 (4.9 percent and 6.9 percent, respectively, vs. 1.9 percent), with no difference in proportion of diabetics or cases with CME in combination with PCR. There was no difference in surgeon grade experiencing PCR.

"With the knowledge that extensive breaks from surgery lead to skill fade, it would seem very sensible that ophthalmology attempts to investigate factors that may optimize returns after surgical breaks," the study authors concluded in their paper. "Clearly, there is a need—to improve patient safety—for more support for surgeons of all grades when they return to surgery after an extended hiatus, with the development of robust guidelines, including, perhaps, mandatory time spent on surgical simulators." ◂

1. Theodoraki K, Naderi K, Lam CFJ, et al. Impact of cessation of regular cataract surgery during the COVID pandemic on the rates of posterior capsular rupture and post-operative cystoid macular oedema. Eye (Lond). February 3, 2022. [Epub ahead of print].

INDUSTRY NEWS

Thea Acquires Select Akorn Products

Théa SAS, based in Clermont-Ferrand, France, entered into an agreement to purchase seven branded ophthalmic products from Akorn. Once the transaction with Akorn is completed, its portfolio will comprise brands including Zioptan, AcellFx, Cosopt, Cosopt PF and Azasite.

Opthea Announces OPT-302 Data in PCV

Opthea announced that findings on OPT-302 were presented at the annual Angiogenesis, Exudation, and Degeneration annual meeting, held virtually. OPT-302 combination therapy had a safety profile consistent with standard of care anti-VEGF-A monotherapy, and demonstrated greater improvements in best-corrected visual acuity and less retinal fluid compared to ranibizumab monotherapy.

EyePoint Announces Updated Interim Data from Phase I DAVIO

EyePoint Pharmaceuticals announced updated interim data from the DAVIO Phase I clinical trial of EYP-1901, a bioerodible sustained-delivery intravitreal anti-vascular endothelial growth factor treatment targeting wet age-related macular degeneration, at the Angiogenesis, Exudation, and Degeneration annual meeting. The interim eight-month follow-up data presented from the Phase 1 DAVIO clinical trial continue to show no reports of ocular or drug-related systemic serious adverse events, the company says.

Eyenovia Receives FDA Guidance on MydCombi NDA Resubmission

Eyenovia announced that the company completed a Type A meeting with the FDA related to the refiling of the NDA for MydCombi, the company's combination of tropicamide and phenylephrine for in-office pupil dilation. In 2021, Eyenovia received a complete response letter from the FDA stating that MydCombi had been reclassified as a drug-device combination product. The FDA requested the company conduct additional device testing related to the Optejet dispenser, but no additional clinical studies of MydCombi were requested.

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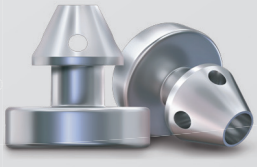

INDICATION FOR USE. The iStent *inject*® W Trabecular Micro-Bypass System Model G2-W is indicated for use in conjunction with cataract surgery for the reduction of intraocular pressure (IOP) in adult patients with mild to moderate primary open-angle glaucoma. **CONTRAINDICATIONS**. The iStent *inject* W 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* W 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* W 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 iStent *inject*® 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.

GLAUKOS

Is There a Doctor In the House?

Musings on life, ophthalmology and the practice of medicine.

MARK H. BLECHER
CHIEF MEDICAL EDITOR

So many health-care crises, so little time. And no, for once, I'm not talking about COVID. Well, maybe I am a little bit. I'm primarily referring to access to health care, specifically the staffing shortage that we were always facing but has been made acute by COVID.

Long before we cared about coronaviruses, we knew that in the years to come there would be physician shortages. I can't say I worried about it for my own health care; it was more of a conceptual thing. But now it has become very real. It's something we've all encountered, if not while trying to get to see our own doctors, but in trying to refer our patients. It's become almost impossible. Forget the issue of getting anyone on the phone; now even online access is challenging. The problem is when you have an acute issue that requires an immediate referral you often need to talk to someone quickly and get your patient an appointment within days. Good luck with that.

The AAMC, American Association of Medical Colleges, undertakes physician workforce studies on a regular basis. Its 2021 report looked at the estimated physician shortage between now and 2034. It's not a pretty number. It of course varies by specialty and by location, and there may be more shortages in primary care and in rural and inner city areas. No great surprises there. There's also no surprise as to the causes: a growing, aging population; and more physician retirements. In the next decade, 20 percent of physicians will be 65 or older. Wow.

Why is that percentage so high? There are several reasons, including a 25-year cap on the number of physicians being trained. Graduate medical education is funded by Medicare, so it controls how many doctors are being trained, and a not inconsequential number of new physicians either choose to work part-time or drop out of the workforce completely—and this group has grown tremendously due to workplace dissatisfaction, career change and choosing to be a stay-at-home parent. All of these factors are at higher numbers than ever.

There have been some attempts to counter this: Congress has increased the number of training slots by 200 per year—big whoop. Improved working conditions? Not likely. One possible solution would be to select medical students who really want to work full time as a physician. (Hint: Medicine is not a hobby.)

Yes, COVID has caused many providers to decrease their patient load, and yes, COVID has caused a few providers to retire early. However, the acute difficulties I and everyone I talk to have been experiencing, even in a major metropolitan area, seem far beyond the calculated and pandemic-induced challenges. There's clearly something else going on.

Bottom line? The world has changed in far greater ways that we could have imagined, and this is having sobering, real-world impacts on access to health care for our patients and ourselves. As physicians, we know the system and can usually get access for ourselves and our loved ones. I shudder to think, however, how everyone else negotiates securing an office visit.

Actually, I don't have to think; I see it every day. There's an excess of patients seeking care. This is usually a good thing, but it's now at a level that's straining resources and, with the employment situation being what it is, difficult to quickly address. While delays in routine care are the norm, delays in care for more emergent and serious problems are very concerning. I hope that, as COVID abates, we can address that backlog and get ahead of our communities' needs. My fear is that we won't. The need for care, the expectation of care, the ability to provide that care and, of course, the funding to make it happen are probably going to be out of sync for a long time to come.

I've only really addressed the shortage in physicians, however. Now let's talk about the lack of nurses, home health aides, nursing home staff, etc. OK, maybe another day; I need to try get a doctor's appointment—I think I'm feeling ill. ◀

This article has no commercial sponsorship.

Dr. Blecher is an attending surgeon at Wills Eye Hospital.

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Pred-Moxi®
Prednisolone acetate and moxifloxacin (1/0.5)%

Pred-Nepaf
Prednisolone acetate and nepafenac (1/0.1)%

Pred-Brom®
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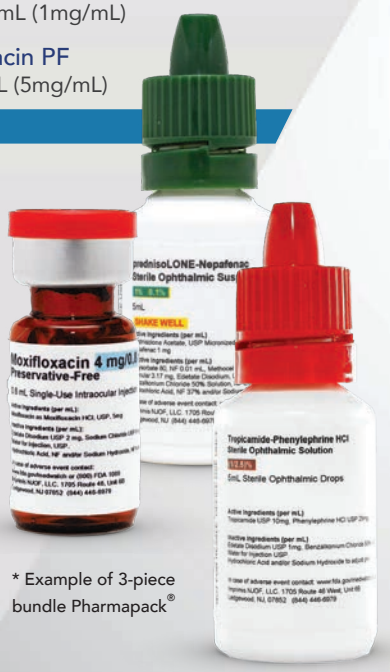

* Example of 3-piece bundle Pharmapack®

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MEDICARE Q&A

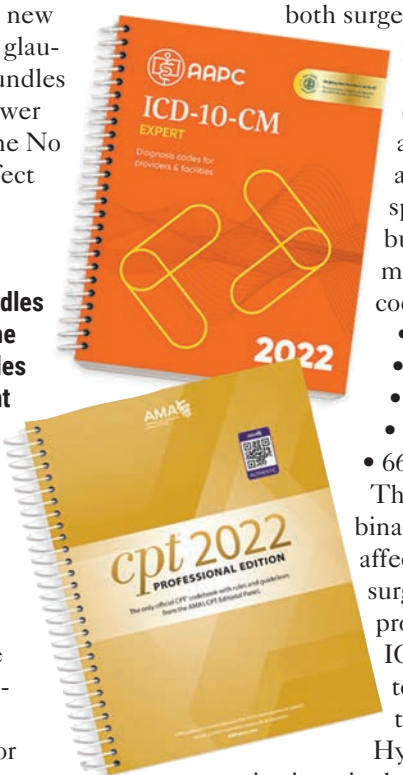
The No Surprises Act Goes Live

An update on the NSA, and how MIGS surgery is separately impacted by payer bundles.

Since the MPFS was adjusted by Congress after our most recent column, many—but not all—of the largest hits to reimbursement were lessened. Here, we discuss a few new wrinkles related to the glaucoma MIGS surgery bundles and payments, and answer questions about how the No Surprises Act might affect practices in 2022.

Q Did any new January 2022 bundles or payment edits from the new glaucoma MIGS codes affect possible treatment options?

A They did. The two new combination codes for cataract/IOL/MIGS, 66989 and 66991, received a mutually exclusive edit with the other cataract combination codes established a couple of years ago for cataract/IOL/endocyclophotocoagulation (66987 and 66988). Remember that there are two distinct codes in each of them because one of them is for "complex" cataract/IOL surgery done with the other surgery. The pairs of combination codes listed below are mutually exclusive with one another for 2022 Q1, so you can't bill both on the same eye; one of these combination codes will go unpaid for both surgeon and facility. Importantly, an ABN or financial waiver can't be used to ask the patient to accept financial responsibility for the bundled code. The mutually exclusive code pairs are:



- 66987 – 66989
- 66987 – 66991
- 66988 – 66989
- 66988 – 66991
- 66989 – 66991

This latest set of combination bundles only affects the unusual surgical combination procedure of cataract/IOL, endocyclophotocoagulation, and the concurrent Hydrus or iStent device in a single eye on the same day. That combination is sometimes abbreviated "ICE." The NCCI edits do seem to allow unbundling but, importantly, you would only do that if billing for one of each code on the same day in different eyes.

Fortunately, there are lots of alternatives surgeons can choose from in the MIGS space. As you might expect, there are some other MIGS coding considerations already in place and most didn't change even if payment might be lower now.

Q What's the purpose of the No Surprises Act?

A The Act was put into place January 1, 2022 to help prevent most types of surprise medical bills patients often run into. CMS has a Provider resource page you can access to learn more about it.[1] While the Act doesn't apply in every situation, it will apply in many, such as when a patient gets care at an in-network hospital and an out-of-network (OON) provider that the patient wouldn't have known about ahead of time delivers care. Since OON charges can be significantly larger, the surprise isn't that the patient gets a bill, but that the bill they get and the cost-sharing they incur will be much larger. If you take call at the local hospital ER, you might be that OON provider to a patient's private medical insurance, so you must accept the in-network payment provisions and can't balance-bill.

When patients have no insurance (or when they wish not to use it), there are now separate protections related to giving a cost estimate before you deliver services.

Importantly, CMS notes that the Act doesn't impact some Federal programs such as Medicare, Medicaid, Indian Health Services, Veterans Administration or TRICARE, since other regulatory protections against high medical bills already exist. When the patient has those types of coverage, items like refractions,

This article has no commercial sponsorship.

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Your glaucoma patients have seen tremendous things, and plan to see a whole lot more. That's why the Hydrus Microstent was purposefully designed for outcomes that stand the test of time. Choose the MIGS device built to enable life's biggest experiences.

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The only MIGS option proven in a pivotal trial at 5 years to deliver:

- 66% of patients medication-free[1]
- 61% reduction in risk of invasive secondary glaucoma surgeries[1]*
- A safety profile similar to cataract surgery alone[1]

upgrades on premium intraocular lenses, cosmetic surgery and screening tests don't fall under the provisions of the No Surprises Act because those services: 1) are being delivered to people with coverage under those Federal programs; and 2) there is written regulatory guidance on noncoverage that already exists for those services.

> **When the No Surprises Act applies outside of the emergency room, a good-faith estimate of your charges may need to be given to patients up front so they can consent to them.**

Of course, you want to still be transparent and inform the patient about the lack of coverage, the costs for those services and patient responsibility to pay in this situation.

Q When the Act does apply to me outside of the ER situation above, what else must I know?

A Three main things are key. The first is knowing when the Act applies and when it doesn't, as noted above.

Second, when the Act does apply, a good-faith estimate of your charges may need to be given to patients up front so they can consent to them. Since the Act allows patients to request this, it also seems clear to me that all offices should step up their pricing transparency even if the Act isn't implicated; I'll bet patients will ask more often as knowledge about their ability to do so spreads.

Third, the Act sets up a specific dispute resolution process that is more formal than one you might already have in place for arbitration. If a patient gets a bill that's more than $400 over your good-faith estimate, they can use the Act's dispute resolution process. As you might expect, you're obligated to tell them about it in your good-faith estimate. (CMS also has a webpage with information on what that means.)[2] Since the dispute will invariably involve your estimate, you should keep a copy of these documents, since the Centers for Medicare and Medicaid Services will ask for your copies of the estimate should dispute resolution begin.

The patient must exercise their rights in such cases within 120 days of receiving your bill, not the date you delivered the services. Though it's not part of the Act, it's apparent that getting your bills out promptly is now even more important than ever.

Q What if my state already has a similar No Surprise medical bill regulation? Which one takes precedence?

A Your state-specific guidelines remain in play; the No Surprises Act provides a floor for consumer protections. CMS notes "as long as a state's surprise billing law provides at least the same level of consumer protections against surprise bills and higher cost-sharing as does the No Surprises Act and its implementing regulations, the state law generally will apply ...[and] if your state has an All-payer Model Agreement or another state law that determines payment amounts to out-of-network providers and facilities for a service, the All-payer Model Agreement or other state law will generally determine your cost-sharing amount and the out-of-network payment rate."[3] ◀

1. CMS. No Surprises Act. Provider requirements and resources. https://www.cms.gov/nosurprises/policies-and-resources/provider-requirements-and-resources. Accessed February 2, 2022.

2. CMS. Providers: What to expect when a patient starts payment dispute resolution. https://www.cms.gov/nosurprises/providers-payment-resolution-with-patients. Accessed January 31, 2022.

3. CMS. Fact Sheet. No Surprises: Understand your rights against surprise medical bills. Jan 03, 2022. https://www.cms.gov/newsroom/fact-sheets/no-surprises-understand-your-rights-against-surprise-medical-bills. Accessed February 3, 2022.

CHALLENGING CATARACT CASES: SURGEON PEARLS

Surgeons offer some of their favorite strategies for dealing with less-than-ideal situations.

CHRISTOPHER KENT
SENIOR EDITOR

Although cataract surgery almost always goes smoothly, the fact that it's performed on millions of individuals every year guarantees that any cataract surgeon will encounter plenty of challenging cases over time. Here, cataract surgeons share their advice for dealing with challenging cases that they've encountered.

Patients with Corneal Pathology

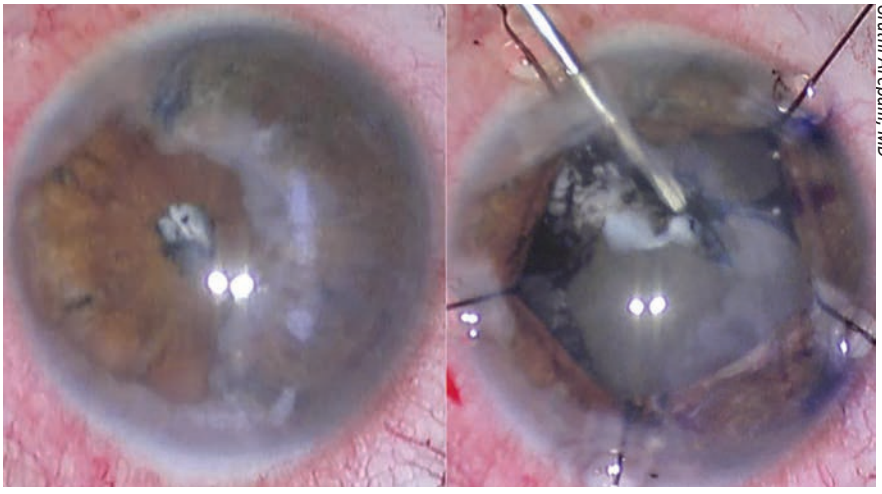
Zaina Al-Mohtaseb, MD, an associate professor of ophthalmology and associate residency program director at Baylor College of Medicine, offers these pearls:

• ***Always look for corneal pathology preoperatively.*** "It's important to diagnose co-existing corneal pathology in cataract patients because corneal diseases can affect IOL selection," she notes. "In addition, cataract surgery can contribute to the progression of co-existing corneal disease, limiting visual outcomes postoperatively. Diagnosing epithelial basement membrane disease in particular is vital, as it can lead to decreased vision, irregular astigmatism and inaccurate IOL power calculations. If your patient has this problem, perform superficial keratectomy and then await stabilization of the topography. That stabilization takes an average of at least three months after the keratectomy procedure."

• ***If the view through the cornea isn't ideal…*.** For cataracts with a difficult view through the cornea (secondary to scarring or neovascularization, for example), Dr. Al-Mohtaseb offers these tips to help ensure a safe cataract extraction:

— Optimize the ocular surface prior to the cataract surgery.

— Use the topography and IOL



Sruthi Arepalli, MD

Cataract surgery in a young man with previously uncontrolled uveitis, resulting in dense cataract, posterior synechiae and iris-cornea touch. A combination of employing iris hooks, creating space with viscoelastic between the iris and cornea, releasing synechiae and staining the anterior capsule with trypan blue allowed for careful capsulorhexis and in-the-bag placement of the lens.

This article has no commercial sponsorship.

Dr. Garg is a consultant to Johnson and Johnson Vision. **Dr. Miller** is a consultant to Johnson and Johnson Surgical Vision, Long Bridge Medical and Oculus USA. **Dr. Weinstock** is a consultant to Alcon, Johnson and Johnson Vision, Bausch + Lomb and Zeiss. **Dr. Mah** is a consultant to Alcon, Johnson and Johnson Vision and Bausch + Lomb. **Dr. Arepalli** and **Dr. Al-Mohtaseb** have no relevant financial ties to report.

WHAT COULD SHE SEE THIS YEAR?

EYLEA®
(aflibercept) Injection
For Intravitreal Injection

36 FAMILY RECIPES

Inspired by a real patient with MEfRVO.

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

- Intravitreal injections, including those with EYLEA, have been associated with endophthalmitis and retinal detachments. Proper aseptic injection technique must always be used when administering EYLEA. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay and should be managed appropriately. Intraocular inflammation has been reported with the use of EYLEA.
- Acute increases in intraocular pressure have been seen within 60 minutes of intravitreal injection, including with EYLEA. Sustained increases in intraocular pressure have also been reported after repeated intravitreal dosing with VEGF inhibitors. Intraocular pressure and the perfusion of the optic nerve head should be monitored and managed appropriately.
- There is a potential risk of arterial thromboembolic events (ATEs) following intravitreal use of VEGF inhibitors, including EYLEA. ATEs are defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause). The incidence of reported thromboembolic events in wet AMD studies during the first year was 1.8% (32 out of 1824) in the combined group of patients treated with EYLEA compared with 1.5% (9 out of 595) in patients treated with ranibizumab; through 96 weeks, the incidence was 3.3% (60 out of 1824) in the EYLEA group compared with 3.2% (19 out of 595) in the ranibizumab group. The incidence in the DME studies from baseline to week 52 was 3.3% (19 out of 578) in the combined group of patients treated with EYLEA compared with 2.8% (8 out of 287) in the control group; from baseline to week 100, the incidence was 6.4% (37 out of 578) in the combined group of patients treated with EYLEA compared with 4.2% (12 out of 287) in the control group. There were no reported thromboembolic events in the patients treated with EYLEA in the first six months of the RVO studies.

REGENERON

777 Old Saw Mill River Road, Tarrytown, NY 10591

CLINICALLY SIGNIFICANT VISION GAINS IN MEfRVO ACROSS 3 ROBUST CLINICAL TRIALS

Proportion of patients who gained ≥15 ETDRS letters (primary endpoint) and mean change in BCVA (ETDRS letters) (secondary endpoint) at Month 6 from baseline vs control[1-4,*]

VIBRANT (MEfBRVO)		COPERNICUS (MEfCRVO)		GALILEO (MEfCRVO)	
Gained ≥15 ETDRS letters	Mean change in ETDRS letters	Gained ≥15 ETDRS letters	Mean change in ETDRS letters	Gained ≥15 ETDRS letters	Mean change in ETDRS letters
EYLEA (n=91)	**EYLEA (n=91)**	**EYLEA (n=114)**	**EYLEA (n=114)**	**EYLEA (n=103)**	**EYLEA (n=103)**
53% vs 27% in the control group (n=90)	**+17.0** vs +6.9 in the control group (n=90)	**56%** vs 12% in the sham control group (n=73)	**+17.3** vs -4.0 in the sham control group (n=73)	**60%** vs 22% in the sham control group (n=68)	**+18.0** vs +3.3 in the sham control group (n=68)

P<0.01 vs control and sham control.

VIBRANT study design: Randomized, multicenter, double-masked, controlled study in which patients with MEfBRVO (N=181; age range: 42-94 years, with a mean of 65 years) were randomized to receive: 1) EYLEA 2 mg Q4 or 2) laser photocoagulation administered at baseline and subsequently as needed (control group). The primary efficacy endpoint was the proportion of patients who gained ≥15 letters in BCVA at Week 24 compared with baseline.[1]

COPERNICUS and GALILEO study designs: Randomized, multicenter, double-masked, sham-controlled studies in patients with MEfCRVO (N=358; age range: 22-89 years, with a mean of 64 years). Patients were assigned in a 3:2 ratio to either: 1) EYLEA 2 mg Q4 for the first 6 months or 2) sham injections (control) Q4 for a total of 6 injections. In both studies, the primary efficacy endpoint was the proportion of patients who gained ≥15 letters in BCVA at Week 24 compared with baseline.[1]

*Last observation carried forward; full analysis set.

SEE WHAT EYLEA COULD DO FOR YOUR PATIENTS WITH MEfRVO AT HCP.EYLEA.US

BCVA, best-corrected visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study; Q4, every 4 weeks.

ADVERSE REACTIONS

- Serious adverse reactions related to the injection procedure have occurred in <0.1% of intravitreal injections with EYLEA including endophthalmitis and retinal detachment.
- The most common adverse reactions (≥5%) reported in patients receiving EYLEA were conjunctival hemorrhage, eye pain, cataract, vitreous detachment, vitreous floaters, and intraocular pressure increased.
- Patients may experience temporary visual disturbances after an intravitreal injection with EYLEA and the associated eye examinations. Advise patients not to drive or use machinery until visual function has recovered sufficiently.

INDICATIONS

EYLEA® (aflibercept) Injection 2 mg (0.05 mL) is indicated for the treatment of patients with Neovascular (Wet) Age-related Macular Degeneration (AMD), Macular Edema following Retinal Vein Occlusion (RVO), Diabetic Macular Edema (DME), and Diabetic Retinopathy (DR).

References: 1. EYLEA® (aflibercept) Injection full U.S. Prescribing Information. Regeneron Pharmaceuticals, Inc. August 2019. **2.** Campochiaro PA, Clark WL, Boyer DS, et al. Intravitreal aflibercept for macular edema following branch retinal vein occlusion: the 24-week results of the VIBRANT study. *Ophthalmology*. 2015;122(3):538-544. doi:10.1016/j.ophtha.2014.08.031 **3.** Boyer D, Heier J, Brown DM, et al. Vascular endothelial growth factor Trap-Eye for macular edema secondary to central retinal vein occlusion: six-month results of the phase 3 COPERNICUS study. *Ophthalmology*. 2012;119(5):1024-1032. doi:10.1016/j.ophtha.2012.01.042 **4.** Holz FG, Roider J, Ogura Y, et al. VEGF Trap-Eye for macular oedema secondary to central retinal vein occlusion: 6-month results of the phase III GALILEO study. *Br J Ophthalmol*. 2013;97(3):278-284. doi:10.1136/bjophthalmol-2012-301504

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

03/2021
EYL.21.02.0050

EYLEA®
(aflibercept) Injection
For Intravitreal Injection

BRIEF SUMMARY—Please see the EYLEA full Prescribing Information available on HCP.EYLEA.US for additional product information.

1 INDICATIONS AND USAGE
EYLEA is a vascular endothelial growth factor (VEGF) inhibitor indicated for the treatment of patients with:

Neovascular (Wet) Age-Related Macular Degeneration (AMD), Macular Edema Following Retinal Vein Occlusion (RVO), Diabetic Macular Edema (DME), Diabetic Retinopathy (DR).

4 CONTRAINDICATIONS

4.1 Ocular or Periocular Infections
EYLEA is contraindicated in patients with ocular or periocular infections.

4.2 Active Intraocular Inflammation
EYLEA is contraindicated in patients with active intraocular inflammation.

4.3 Hypersensitivity
EYLEA is contraindicated in patients with known hypersensitivity to aflibercept or any of the excipients in EYLEA. Hypersensitivity reactions may manifest as rash, pruritus, urticaria, severe anaphylactic/anaphylactoid reactions, or severe intraocular inflammation.

5 WARNINGS AND PRECAUTIONS

5.1 Endophthalmitis and Retinal Detachments
Intravitreal injections, including those with EYLEA, have been associated with endophthalmitis and retinal detachments [*see Adverse Reactions (6.1)*]. Proper aseptic injection technique must always be used when administering EYLEA. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay and should be managed appropriately [*see Patient Counseling Information (17)*].

5.2 Increase in Intraocular Pressure
Acute increases in intraocular pressure have been seen within 60 minutes of intravitreal injection, including with EYLEA [*see Adverse Reactions (6.1)*]. Sustained increases in intraocular pressure have also been reported after repeated intravitreal dosing with vascular endothelial growth factor (VEGF) inhibitors. Intraocular pressure and the perfusion of the optic nerve head should be monitored and managed appropriately.

5.3 Thromboembolic Events
There is a potential risk of arterial thromboembolic events (ATEs) following intravitreal use of VEGF inhibitors, including EYLEA. ATEs are defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause). The incidence of reported thromboembolic events in wet AMD studies during the first year was 1.8% (32 out of 1824) in the combined group of patients treated with EYLEA compared with 1.5% (9 out of 595) in patients treated with ranibizumab; through 96 weeks, the incidence was 3.3% (60 out of 1824) in the EYLEA group compared with 3.2% (19 out of 595) in the ranibizumab group. The incidence in the DME studies from baseline to week 52 was 3.3% (19 out of 578) in the combined group of patients treated with EYLEA compared with 2.8% (8 out of 287) in the control group; from baseline to week 100, the incidence was 6.4% (37 out of 578) in the combined group of patients treated with EYLEA compared with 4.2% (12 out of 287) in the control group. There were no reported thromboembolic events in the patients treated with EYLEA in the first six months of the RVO studies.

6 ADVERSE REACTIONS
The following potentially serious adverse reactions are described elsewhere in the labeling:
- Hypersensitivity [*see Contraindications (4.3)*]
- Endophthalmitis and retinal detachments [*see Warnings and Precautions (5.1)*]
- Increase in intraocular pressure [*see Warnings and Precautions (5.2)*]
- Thromboembolic events [*see Warnings and Precautions (5.3)*]

6.1 Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in other clinical trials of the same or another drug and may not reflect the rates observed in practice.
A total of 2980 patients treated with EYLEA constituted the safety population in eight phase 3 studies. Among those, 2379 patients were treated with the recommended dose of 2 mg. Serious adverse reactions related to the injection procedure have occurred in <0.1% of intravitreal injections with EYLEA including endophthalmitis and retinal detachment. The most common adverse reactions (≥5%) reported in patients receiving EYLEA were conjunctival hemorrhage, eye pain, cataract, vitreous detachment, vitreous floaters, and intraocular pressure increased.

Neovascular (Wet) Age-Related Macular Degeneration (AMD). The data described below reflect exposure to EYLEA in 1824 patients with wet AMD, including 1223 patients treated with the 2-mg dose, in 2 double-masked, controlled clinical studies (VIEW1 and VIEW2) for 24 months (with active control in year 1).
Safety data observed in the EYLEA group in a 52-week, double-masked, Phase 2 study were consistent with these results.

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

	Baseline to Week 52		Baseline to Week 96	
Adverse Reactions	EYLEA (N=1824)	Active Control (ranibizumab) (N=595)	EYLEA (N=1824)	Control (ranibizumab) (N=595)
Conjunctival hemorrhage	25%	28%	27%	30%
Eye pain	9%	9%	10%	10%
Cataract	7%	7%	13%	10%
Vitreous detachment	6%	6%	8%	8%
Vitreous floaters	6%	7%	8%	10%
Intraocular pressure increased	5%	7%	7%	11%
Ocular hyperemia	4%	8%	5%	10%
Corneal epithelium defect	4%	5%	5%	6%
Detachment of the retinal pigment epithelium	3%	3%	5%	5%
Injection site pain	3%	3%	3%	4%
Foreign body sensation in eyes	3%	4%	4%	4%
Lacrimation increased	3%	1%	4%	2%
Vision blurred	2%	2%	4%	3%
Intraocular inflammation	2%	3%	3%	4%
Retinal pigment epithelium tear	2%	1%	2%	2%
Injection site hemorrhage	1%	2%	2%	2%
Eyelid edema	1%	2%	2%	3%
Corneal edema	1%	1%	1%	1%
Retinal detachment	<1%	<1%	1%	1%

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

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

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

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

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

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

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

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

Less common adverse reactions reported in <1% of the patients treated with EYLEA were hypersensitivity, retinal detachment, retinal tear, corneal edema, and injection site hemorrhage.
Safety data observed in 269 patients with nonproliferative diabetic retinopathy (NPDR) through week 52 in the PANORAMA trial were consistent with those seen in the phase 3 VIVID and VISTA trials (see Table 3 above).

6.2 Immunogenicity
As with all therapeutic proteins, there is a potential for an immune response in patients treated with EYLEA. The immunogenicity of EYLEA was evaluated in serum samples. The immunogenicity data reflect the percentage of patients whose test results were considered positive for antibodies to EYLEA in immunoassays. The detection of an immune response is highly dependent on the sensitivity and specificity of the assays used, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to EYLEA with the incidence of antibodies to other products may be misleading.
In the wet AMD, RVO, and DME studies, the pre-treatment incidence of immunoreactivity to EYLEA was approximately 1% to 3% across treatment groups. After dosing with EYLEA for 24-100 weeks, antibodies to EYLEA were detected in a similar percentage range of patients. There were no differences in efficacy or safety between patients with or without immunoreactivity.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy
Risk Summary
Adequate and well-controlled studies with EYLEA have not been conducted in pregnant women. Aflibercept produced adverse embryofetal effects in rabbits, including external, visceral, and skeletal malformations. A fetal No Observed Adverse Effect Level (NOAEL) was not identified. At the lowest dose shown to produce adverse embryofetal effects, systemic exposures (based on AUC for free aflibercept) were approximately 6 times higher than AUC values observed in humans after a single intravitreal treatment at the recommended clinical dose [*see Animal Data*].
Animal reproduction studies are not always predictive of human response, and it is not known whether EYLEA can cause fetal harm when administered to a pregnant woman. Based on the anti-VEGF mechanism of action for aflibercept, treatment with EYLEA may pose a risk to human embryofetal development. EYLEA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. The background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data
Animal Data
In two embryofetal development studies, aflibercept produced adverse embryofetal effects when administered every three days during organogenesis to pregnant rabbits at intravenous doses ≥3 mg per kg, or every six days during organogenesis at subcutaneous doses ≥0.1 mg per kg.
Adverse embryofetal effects included increased incidences of postimplantation loss and fetal malformations, including anasarca, umbilical hernia, diaphragmatic hernia, gastroschisis, cleft palate, ectrodactyly, intestinal atresia, spina bifida, encephalomeningocele, heart and major vessel defects, and skeletal malformations (fused vertebrae, sternebrae, and ribs; supernumerary vertebral arches and ribs; and incomplete ossification). The maternal No Observed Adverse Effect Level (NOAEL) in these studies was 3 mg per kg. Aflibercept produced fetal malformations at all doses assessed in rabbits and the fetal NOAEL was not identified. At the lowest dose shown to produce adverse embryofetal effects in rabbits (0.1 mg per kg), systemic exposure (AUC) of free aflibercept was approximately 6 times higher than systemic exposure (AUC) observed in humans after a single intravitreal dose of 2 mg.

8.2 Lactation
Risk Summary
There is no information regarding the presence of aflibercept in human milk, the effects of the drug on the breastfed infant, or the effects of the drug on milk production/excretion. Because many drugs are excreted in human milk, and because the potential for absorption and harm to infant growth and development exists, EYLEA is not recommended during breastfeeding.
The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for EYLEA and any potential adverse effects on the breastfed child from EYLEA.

8.3 Females and Males of Reproductive Potential
Contraception
Females of reproductive potential are advised to use effective contraception prior to the initial dose, during treatment, and for at least 3 months after the last intravitreal injection of EYLEA.

Infertility
There are no data regarding the effects of EYLEA on human fertility. Aflibercept adversely affected female and male reproductive systems in cynomolgus monkeys when administered by intravenous injection at a dose approximately 1500 times higher than the systemic level observed humans with an intravitreal dose of 2 mg. A No Observed Adverse Effect Level (NOAEL) was not identified. These findings were reversible within 20 weeks after cessation of treatment.

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

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

17 PATIENT COUNSELING INFORMATION
In the days following EYLEA administration, patients are at risk of developing endophthalmitis or retinal detachment. If the eye becomes red, sensitive to light, painful, or develops a change in vision, advise patients to seek immediate care from an ophthalmologist [*see Warnings and Precautions (5.1)*].
Patients may experience temporary visual disturbances after an intravitreal injection with EYLEA and the associated eye examinations [*see Adverse Reactions (6)*]. Advise patients not to drive or use machinery until visual function has recovered sufficiently.

REGENERON

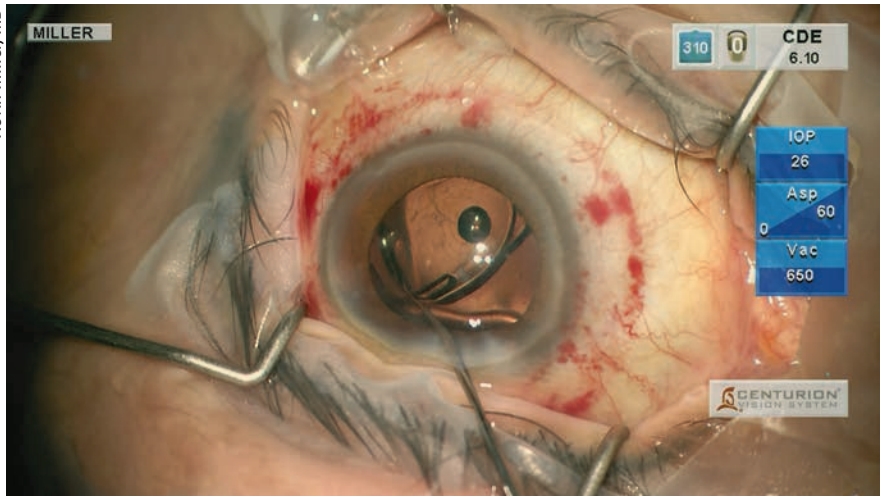
Manufactured by:
Regeneron Pharmaceuticals, Inc.
777 Old Saw Mill River Road
Tarrytown, NY 10591

Issue Date: 08/2019
Initial U.S. Approval: 2011

Based on the August 2019
EYLEA® (aflibercept) Injection full
Prescribing Information.

EYL.20.09.0052

Kevin Miller, MD



It's always important to manipulate an IOL by grabbing it at the edge or at the optic-haptic junction, surgeons say. Above: A surgeon rotates an extended-depth-of-focus, single-piece acrylic posterior chamber IOL within the capsular bag using a Kuglen hook, engaging the lens at the optic-haptic junction.

power calculations or the average K from the other eye.

— Be sure to achieve good pupil dilation.

— Use trypan blue to enhance visualization.

— Adjust the illumination to low or medium lighting, because too much co-axial lighting can cause backscatter.

— Consider using a light pipe (from a vitrectomy machine or photon laser light) to aid visualization during the case.

— If the cornea is scarred, start the capsulorhexis in a transparent area.

• ***Be cautious if the patient has Fuchs endothelial dystrophy.*** Sumit (Sam) Garg MD, vice chair of clinical ophthalmology, medical director and professor of cataract, corneal & refractive surgery at the Gavin Herbert Eye Institute at the University of California, Irvine, offers three pearls for managing these patients:

— Consider using a femtosecond laser to assist in removing the cataract. "The laser allows me to pre-soften the nucleus, which then allows for the use of less phacoemulsification energy," he explains.

— Use ample dispersive OVD in these cases. "This will protect the fragile endothelium," he says.

— Consider implanting a three-piece IOL. "I generally favor three-piece IOLs in these patients if I feel that a DMEK may be necessary in the not-too-distant future," Dr. Garg explains.

• ***Don't place your wound too far posteriorly.*** "Some corneal peripheral abnormalities such as arcus and pannus can make it challenging to know where to make the corneal wound," notes Robert Weinstock, MD, director of cataract and refractive surgery at the Eye Institute of West Florida in Largo, Florida, and an assistant clinical professor in the Department of Ophthalmology at the University of South Florida.

"The best way to avoid placing the wounds too posteriorly is to be very conscientious in wound creation," he says. "Err on the side of caution and place the wound slightly anterior to the limbus. A good rule of thumb is to place the corneal wound just at the beginning of clear corneal tissue."

Dr. Weinstock adds that surgeons in training often make their wounds too posteriorly, causing subconjunctival chemosis. "In these cases the conjunctiva is cut at the posterior edge of the wound," he explains. "During cataract surgery, fluid finds its way under the conjunctiva and balloons it up, 360 degrees. This can make for a very challenging view of the eye. It also makes it difficult to close the eye postoperatively."

If the Patient has a Cough …

Tape the patient's head to the gurney. "I actually do this for every case," says Kevin M. Miller, MD, chief of the Cataract and Refractive Surgery Division and a professor of clinical ophthalmology at the David Geffen School of Medicine at UCLA. "You never know when someone will cough, sneeze, begin snoring, or suddenly awake from sleep and shake their head."

With Highly Myopic Eyes

Pressurize the eye slowly when turning irrigation flow on. "Although this is good advice for any cataract surgery, it's especially important for large, myopic eyes," says Dr. Miller. "Slow pressurization can be achieved using the machine settings for 'IOP Ramp' if you're using the Centurion phaco unit, or by slowly raising the bottle on gravity-fed phaco machines."

If the Patient has Uveitis

"Uveitis-related cataracts are typically not straightforward, so expect surprises," says Sruthi R. Arepalli, MD, a uveitis and vitreoretinal surgeon at Tennessee Retina in Nashville. She offers these suggestions:

• ***Get inflammation under control before the surgery.*** "Peri-operative control of inflammation is necessary for better outcomes," she notes. "Generally, this means keeping the eye quiet with the help of uveitis colleagues and rheumatologists for at least three months prior to surgery.

"Of course, there are rare exceptions to this," she continues. "While I prefer to wait three months with the disease quiescent before doing cataract surgery, there are some situations in which waiting that long isn't possible. Sometimes, the patient depends on this eye for functional vision. Sometimes the patient

Robert Weinstock MD

Experts say that performing bimanual surgery can be a big help when dealing with a floppy iris, and can also allow very gentle insertion of a capsular tension ring if that's necessary. Above: Robert Weinstock, MD, observes fellow Kirk Castellano, MD, doing bimanual surgery using the Beyeonics One virtual reality headset.

is young and at risk of developing amblyopia in that eye if we wait three months for surgery. In those cases, I'll add additional oral or periocular steroids to quiet the eye if I plan on entering the eye before the three-month period is up."

• ***Avoid topical anesthesia in these patients.*** "In order to limit unnecessary variables, I stay away from topical anesthesia in cataract patients with uveitis," Dr. Arepalli says. "I often have patients receive either a retrobulbar or peribulbar block. In certain cases, such as pediatric patients or cases that may be more complicated where I anticipate a longer surgical time, I'll plan for general anesthesia."

• ***Have extra surgical tools at the ready.*** "In addition to the typical surgical set up for a phacoemulsification, I request trypan blue and iris hooks, at a minimum," notes Dr. Arepalli. "It's always good to have capsular tension rings as well, and an anterior vitrectomy set up if necessary."

• ***Placing a three-piece lens is preferable.*** "Placing a three-piece lens in a uveitic patient gives me more flexibility down the road if I need to place it in the sulcus during a later surgery, or need to rescue the lens if it falls," Dr. Arepalli explains.

• ***You may need to leave some young uveitic patients aphakic.*** "I'll leave a young patient aphakic if I anticipate that their postoperative period will have a lot of inflammation, or if I don't think I can safely place a lens during the initial surgery," Dr. Arepalli says. "I can always come back and place a lens after the eye settles down and I see how they're healing."

• ***If the uveitis is severe, increase the steroids.*** "If the disease is severe I'll give additional topical or oral steroids before and after the cataract surgery," says Dr. Arepalli. "I also taper topical steroids very slowly after the surgery and monitor the patient more frequently than other patients, in case they need further modifications to their immunosuppression."

Iris Instability

Dr. Weinstock offers these tips for managing an eye with an unstable iris:

• ***Use bimanual technique.*** "Floppy iris syndrome and iris prolapse are among the most challenging things to deal with during cataract surgery," Dr. Weinstock notes. "Using bimanual phaco and bimanual irrigation and aspiration is a great way to deal with this situation. With these techniques, the wounds are smaller and the irrigation can be kept anteriorly, pushing the iris down and away from the wounds, while the cataract is removed deeper in the eye."

• ***Avoid iris prolapse by decompressing the eye, sealing the wounds and then gently reinflating.*** "Often, at the end of the case when the eye is inflated and pressurized, an unstable iris will prolapse out of the wound," Dr. Weinstock explains. "In these situations, it's best to decompress the eye; completely soften it and then seal the wounds with stromal hydration. Then, gently reinflate the eye by injecting BSS into the anterior chamber, pushing the iris back.

"If this doesn't work," he adds, "put sutures across the wounds while the eye is soft and then gently inflate, pushing the iris down and back. Gentle fluid dynamics work in the surgeon's favor, helping to complete these cases successfully and avoid complications."

Sticky Cortex

• ***When necessary, viscodissect the cortex off the posterior capsule.*** "I often see surgeons struggle with cortical cleanup, especially in the subincisional area," says Dr. Weinstock. "Many times this leads to inadvertent tears of the capsule or zonular dehiscence because of pressure put on the posterior capsule.

"A simple way of dealing with the situation is to come out of the eye and use a viscoelastic such as Amvisc or another cohesive type to gently viscodissect the cortex off the posterior capsule and push it anteriorly up into the sulcus. Then an artificial lens can be inserted, stabilizing the capsule. The residual cortex can be removed with bimanual irrigation and aspiration once the IOL is in place."

Pseudoexfoliation/Zonular Laxity

Francis Mah, MD, who specializes in cornea, external disease and refractive surgery at Scripps Clinic in La Jolla, California, offers pearls for

We're retiring the questions that keep you guessing.

Gold standards can often mean old standards. Maestro 2 + Harmony is today's **one-touch, one-screen** solution. Unlike the others, Maestro's **user-friendly** technology empowers operators to capture images of the macula and disc with a single click. And with **device-agnostic, cloud-based** Harmony, clinicians can see a complete picture of each patient's eye health, simply and easily.

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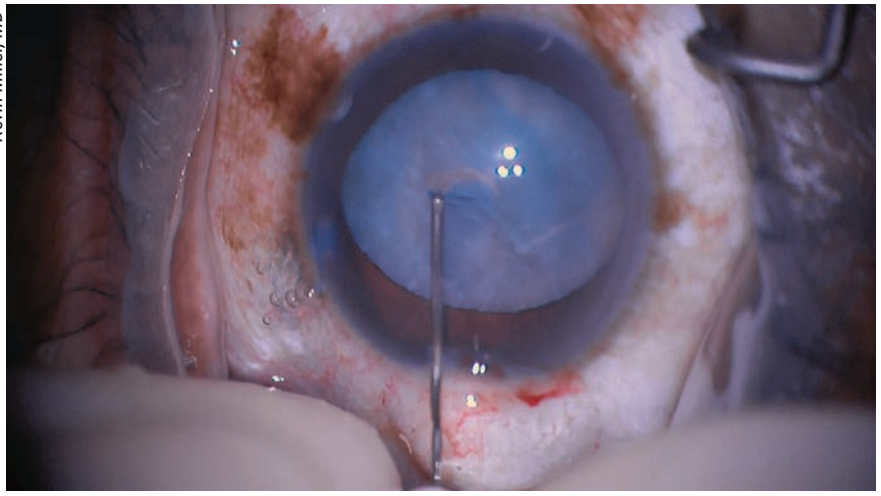
Kevin Miller, MD



When using a cystotome to create your capsulorhexis, don't start with a deep puncture; a deep puncture may dig up cortex that will later obscure your view. Above: An anterior capsule puncture is performed using a 30-gauge needle in an anterior capsule stained with trypan blue.

operating on patients with pseudoexfoliation, or in whom you have any suspicion that zonular laxity may be present:

• ***Don't overfill the anterior chamber with viscoelastic.*** "Doing so could risk causing more zonular damage," Dr. Mah points out.

• ***Create the largest capsulorhexis you can comfortably create, despite what might be a smaller pupil.*** "This will make it easier to get the cataract out, with less chance for anterior capsular phimosis and a dislocated posterior chamber IOL days, weeks or years later," Dr. Mah explains.

Should the surgeon try to enlarge the pupil in this situation?

"My general mantra in the OR is 'less is more,' so if a pupil is 5 mm or larger, I just go with it, especially in cases of pseudoexfoliation and zonular laxity," says Dr. Mah. "This is a little different than intraoperative floppy iris syndrome or Flomax cases; in those cases the pupil will most likely come down during the surgery, so use of a ring or hooks to enlarge and/or maintain pupil size is critical. In 5- or 6-mm pupils, I go right up to the pupil margin when creating the capsulorhexis. You'll find the pupil will actually be a tiny bit more dilated during the surgery and at the conclusion of the case, because removing the cataract allows more space for the pupil.

"If the pupil is between 3 and 5 mm," he continues, "I usually just stretch it with Kuglen-style hooks placed 180 degrees apart to create microtears along the pupil sphincter. Usually, you'll gain 1 to 2 mm with this maneuver. If the pupil is smaller than 3 mm, I like Greishaber-style pupil hooks. If you think you need the hooks, I'd advise making all the corneal paracentesis incisions before making the main incision, because it's easiest to make these incisions before you've done any other manipulations to the eye.

"There are various rings for enlarging the pupil, such as the Malyugin and iRing," he adds. "You might consider using a 6.25-mm Malyugin ring around a 4-mm pupil. I personally don't use these in pseudoexfoliation cases, since the pupil will stay dilated during these cases; I reserve them for IFIS cases. However, you should use whatever technology you need to feel comfortable and safely remove the cataract."

• ***Be sure to do an excellent hydrodissection.*** "You may want to devote more time to this than usual, to ensure that the cataract moves easily, so undue stress or tension on the zonules doesn't occur," Dr. Mah explains.

• ***Don't wiggle the hydrodissection cannula when you advance it out under the capsulorhexis.*** "The fluid you inject into the eye will follow the path of least resistance when it leaves the tip of the cannula," explains Dr. Miller. "If you push the cortex aside while advancing the cannula, the fluid will make a 180-degree turn when it exits the tip and come right back along the side of the cannula."

• ***Use whatever lens disassembly technique you're most comfortable with.*** "Use the technique you typically use," Dr. Mah advises. "Don't use something less familiar just because you're dealing with zonular weakness. It's good to use a technique that will allow you to avoid rotating the lens too much or pressing on it. Stop-and-chop, vertical chop, and 'V' techniques are nice if they're in your armamentarium, because they require less rotation of the lens. However, this isn't the time to try a new technique."

• ***Don't use the phaco needle to rotate a lens.*** "To avoid stressing the zonules any more than necessary, you want to maximize torque and minimize push when rotating a nucleus," notes Dr. Miller. "In other words, use a second instrument, perhaps a cyclodialysis spatula, lens manipulator or chopper, instead of the phaco needle, to engage the peripheral lens and rotate it."

• ***If implanting a CTR, considering using a bimanual approach.*** Dr. Garg says that in recent years he's changed the way that he implants a capsular tension ring when the patient has weak zonules. "I used to just inject the CTR into the capsular bag as gently as possible," he notes. "Now, I've transitioned to a bimanual technique in which I use a Sinskey hook to stabilize the leading eyelet of the CTR. This allows me to place the CTR into the capsular bag even more gently."

• ***During cortical cleanup be care-***

ful to not accidentally grab the capsule. "If you grab the capsule," Dr. Mah explains, "zonules will easily break. The capsule might become looser and the capsule will become floppier."

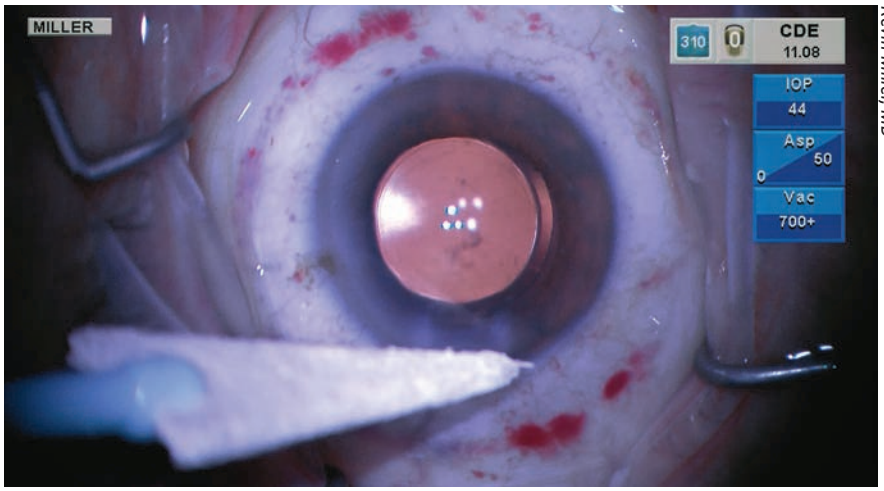
• ***Orient the lens haptic based on the location of zonular laxity.*** "If there's an area of specific zonular laxity, as opposed to general zonular laxity, try to put the haptic of the IOL in that area," Dr. Mah says. "This will ensure that the bag is fully expanded in that area."

• ***Use specifically designed anterior capsule polishers to thoroughly remove the lens epithelial cells from the entire anterior capsule.*** "The anterior capsule will be much cleaner years later, and you'll never have a lens decenter on you," adds Dr. Miller. "This will establish your reputation as a Picasso instead of a house painter! It's particularly important to polish the anterior capsule in eyes with weak zonules because aggressive contraction of the capsulorhexis postoperatively could further stress the zonules. It's also a good strategy when operating on very young eyes, because lens epithelial cells in young eyes proliferate more aggressively."

Pearls for All Occasions

Surgeons offer these tips for any cataract surgery case:

• ***Learn how to control eye position by using the corneal incisions as pivot points.*** "The experienced cataract surgeon is able to keep an eye perfectly centered under the microscope while performing complex manipulations at the tips of the instruments," says Dr. Miller. "Each instrument passes through a corneal incision, and each corneal incision can be manipulated in the axis of the incision by the instrument that passes through it. So, if the corneal incisions are 90 degrees apart, a surgeon can completely control the rotational position of the eye in three axes—back and forth, up and down, and rotationally."



Kevin Miller, MD

To reduce the risk of endophthalmitis following cataract surgery, dry the the exterior ocular surface to reduce the load of bacteria on the eye before hydrating the incisions.

• ***If employing a cystotome to create a capsulorhexis, use an appropriate technique.*** "If you're using a cystotome to create your capsulorhexis, don't start with a deep puncture," says Dr. Miller. "Instead, use the tool to barely puncture the anterior capsule. That way you won't dig up a lot of cortex that will subsequently obscure your view. Also, once the initial capsule puncture and cut are made, pull the cystitome toward you to begin the circular part of the tear. A bent needle works much better as a pulling instrument than it does as a pushing instrument."

• ***To reduce the risk of "punching through" the epinucleus and cortex at the end of a trough when sculpting, set the "Vacuum Rise" setting on an Alcon Centurion or the "Dynamic Rise" setting on an Alcon Infiniti to -2.*** "When the machine senses it's nearing vacuum limit, it will quickly dial the AFR back 50 percent to release the 'grab,' " Dr. Miller explains.

• ***Use a "last fragment setting" when removing the final piece of nucleus.*** "What that means is, dial the vacuum limit down when you're removing the last fragment," says Dr. Miller. "That way you won't get an occlusion break surge and pop a hole on the posterior capsule."

• ***Manipulate the IOL by grabbing it at the edge or at the optic-haptic junction.*** "Don't touch the surface of an optic with the I/A probe or other metallic instrument," advises Dr. Miller. "Those instruments will scratch the lens."

• ***Be sure to remove the viscoelastic behind the optic.*** "A lot of OVD can get trapped back there," Dr. Miller points out. "The best way to do this is to go behind the lens with an irrigation-aspiration probe."

• ***Always flush out the angle recesses with BSS.*** "Do this even after removing your viscoelastic," Dr. Garg advises, "especially when performing femtosecond-laser-assisted cataract surgery. You'll be surprised how much residual OVD and/or fine nuclear chips can be hiding in the angle. Flushing out the angle with BSS can help prevent retained lens fragments and postop IOP spikes."

• ***Dry the corneal incisions with a sponge before you hydrate.*** "Despite your use of povidone iodine, the fluid on the ocular surface at the end of surgery is a cesspool of bacteria and other microbes," Dr. Miller explains. "Any microbes that enter the eye during surgery will be irrigated out, but whatever gets pushed into the eye at the end of surgery when you hydrate the incision will stay in. So, be sure to soak up the contaminated fluid from the surface of the eye before you hydrate the incisions." ◀

FIRST AND ONLY
FDA-APPROVED TREATMENT FOR THYROID EYE DISEASE

In the treatment of Thyroid Eye Disease (TED),

IT'S TIME FOR A BREAKTHROUGH
IT'S TIME FOR TEPEZZA

TEPEZZA is proven to[1-4]:

- **Decrease proptosis[1]**
- **Improve diplopia[1]**
- **Reduce orbital pain, redness, and swelling[2,3]**
- **Improve functional vision and patient appearance[2,3]**

...in patients with TED, without concomitant steroids (vs placebo at Week 24).[2-4]

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.

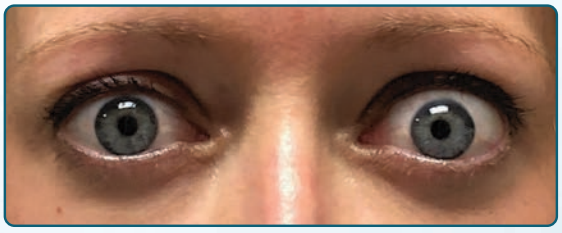
Preexisting Inflammatory Bowel Disease: TEPEZZA may cause an exacerbation of preexisting inflammatory bowel disease (IBD). Monitor patients with IBD for flare of disease. If IBD exacerbation is suspected, consider discontinuation of TEPEZZA.

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.

TEPEZZA®
teprotumumab-trbw

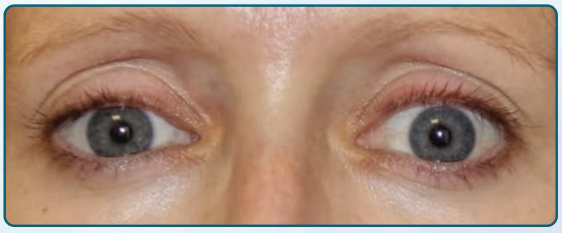
TEPEZZA significantly decreased proptosis, one of the most disfiguring symptoms of TED[1,2,5,6]

SEE THE TEPEZZA DIFFERENCE[7]*



BASELINE
Proptosis: 19 mm OD, 20.5 mm OS

OD, oculus dexter; OS, oculus sinister.



WEEK 21: ON DAY OF 8TH INFUSION
Proptosis: 17 mm OD, 18 mm OS

*Real patient treated with TEPEZZA. Individual results may vary for patients treated with TEPEZZA.

Significantly greater proptosis responder rate† (Study 2)[1,2]

TEPEZZA
83%
TEPEZZA (n=41)
P<0.001 at Week 24

vs

Placebo
10%
Placebo (n=42)

†Both the safety and efficacy of TEPEZZA were evaluated in 2 randomized, double-masked, placebo-controlled clinical trials (Studies 1 and 2) consisting of 171 patients with TED (84 were randomized to TEPEZZA and 87 to placebo). The primary endpoint in Studies 1 and 2 was proptosis responder rate, defined as having a ≥2-mm reduction from baseline in proptosis in the study eye at Week 24 without deterioration (≥2-mm increase in proptosis) in the non-study eye.[1]

» See more before and after photos

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 following page.

References: 1. TEPEZZA (teprotumumab-trbw) [prescribing information] Horizon. **2.** Douglas RS, Kahaly GJ, Patel A, et al. Teprotumumab for the treatment of active thyroid eye disease. *N Engl J Med*. 2020;382(4):341-352. **3.** Smith TJ, Kahaly GJ, Ezra DG, et al. Teprotumumab for thyroid-associated ophthalmopathy. *N Engl J Med*. 2017;376(18):1748-1761. **4.** Smith TJ, Kahaly GJ, Ezra DG, et al. Teprotumumab for thyroid-associated ophthalmopathy. *N Engl J Med*. 2017;376(18)(suppl):1748-1761. https://www.nejm.org/doi/suppl/10.1056/NEJMoa1614949/suppl_file/nejmoa1614949_appendix.pdf. **5.** Data on File. Horizon, December 2019. **6.** Bruscolini A, Sacchetti M, La Cava M, et al. Quality of life and neuropsychiatric disorders in patients with Graves' orbitopathy: current concepts. *Autoimmun Rev*. 2018;17(7):639-643. **7.** Data on File. Horizon, December 2020.

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.

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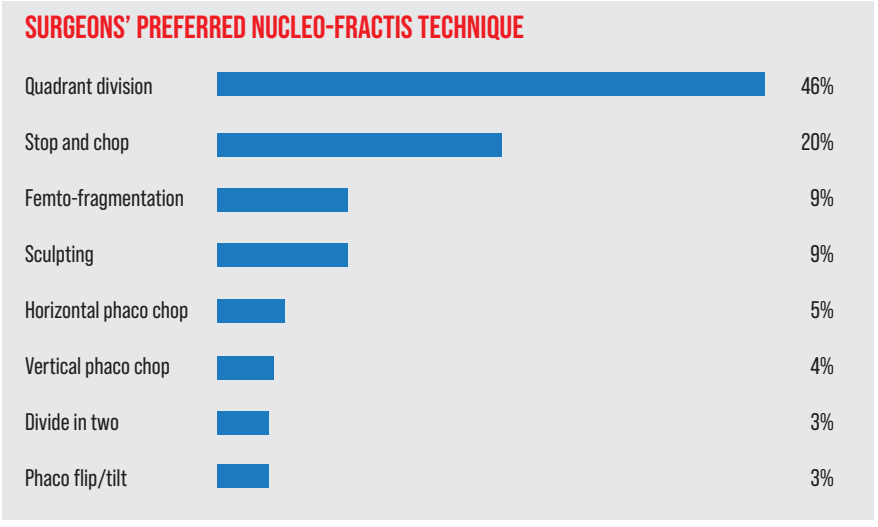
HORIZON

CATARACT SURGEONS SHARE THEIR FAVORITE TECHNIQES

Surgeons take on issues ranging from nucleo-fractis approaches and the use of femtosecond lasers to the best way to manage astigmatism and prevent postop inflammation.

WALTER BETHKE
EDITOR IN CHIEF



While it's interesting to drill down onto specific techniques in an article, it can also be very useful to pull back the camera to get a macro view of cataract surgery. Here, surgeons who responded to our 2022 cataract surgery technique survey share their thoughts on such topics as the best way to break up a nucleus, the ways they like to ensure postop inflammation and infection control, and how they manage astigmatism.

This year, 3,539 of the 11,366 surgeons receiving the survey opened it (31 percent open rate), and 95 completed the survey. To see how your techniques compare with theirs, read on.

Attacking the Nucleus

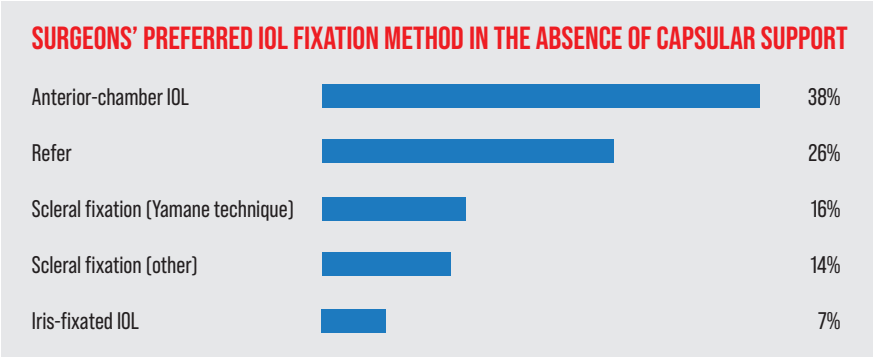
Continuing a trend from previous years, quadrant division is the most popular method for breaking up the cataract in this year's survey, with 46 percent of the surgeons choosing it. The next most popular method is stop-and-chop, selected by 20 percent of respondents. These and the other options appear in the graph above.

"[Quadrant division] is the safest," says Lawrence Shafron, MD, FACS, of Denton, Texas, "and it's easy on the corneal endothelium." David Chandler, MD, of Mechanicsville, Virginia, likes quadrant division because it's "straightforward and works most of the time, and doesn't require a lot of manipulation or zonular stress."

"It's suitable for most types of cataracts," agrees a surgeon from California.

Christopher Papp, MD, a physician in South Lyon, Michigan, echoes a sentiment expressed by several surgeons on the survey: "I was taught [quadrant division] and have become proficient in it," he says. "I adjust the technique as needed for difficult cases."

The surgeons in the stop-and-chop camp like the method's predictability and the control it affords them. "Stop-and-chop gives me good control of the nuclear halves after a single groove and cracking of the nucleus, which then allows vertical chopping," says Salt Lake City's Nick Mamalis, MD. A Maryland ophthalmologist says he



prefers the technique because it "debulks and lowers CDE compared with divide and conquer." Aric Aldridge, MD, of Dothan, Alabama, says stop-and-chop allows "controlled division with minimal risk to the bag."

Treating Astigmatism

Surgeons also commented on their preferred approaches for managing preop astigmatism in their cataract patients.

Most of the surgeons (55 percent) say they manage patients' astigmatism with a toric intraocular lens. The next most popular option is a toric IOL combined with femtosecond astigmatic keratotomy incisions (12.5 percent). In third is a toric lens with the entry wound on the steep axis (9.4 percent).

"Leave the cornea alone if possible," says a Michigan surgeon who prefers using toric lenses. "However, I also do LRIs sometimes. Also use glasses if patient doesn't want to spend the extra money for a toric." St. Louis' Bruce H. Cohen, MD, feels similarly, saying, "This is effective and far more predictable than LRI by manual or femto."

"Toric IOLs are more precise now [thanks to] the newer formulas," says a surgeon from North Carolina, "and LRIs' effects regress over time."

The surgeons who like IOLs combined with femtosecond cuts believe they've got the best of both worlds.

"Using AK for lower cylinder and a toric lens for higher cylinder is the most reproducible and consistent approach," says Asim Piracha, MD, of Louisville, Kentucky. A surgeon from Georgia agrees, saying, "This gives the most accurate results."

"It gives more repeatable outcomes," says Dee Stephenson, MD, of Venice, Florida.

Alternative IOL Fixation

When an eye's capsular support is lacking, surgeons have various methods they turn to in order to fixate the IOL securely and close the case. On this year's survey, the most popular option is to implant an anterior-chamber IOL (38 percent). A close second is a sclerally-fixated lens (with or without using the Yamane technique) at 30 percent (16 percent of these surgeons say they prefer to use the Yamane). Twenty-six percent of surgeons say they'll refer such a patient.

[An anterior-chamber fixated IOL] is quicker and easier," says a surgeon from Texas.

"If there's no glaucoma, an AC-IOL works well," avers Jonathan Adler, MD, of Bradenton, Florida. "If a patient has glaucoma, then I'll go with Yamane scleral fixation."

Several surgeons say they're simply more comfortable with an AC-IOL because of their training and background. "I'm not skilled in the other methods," says Michael Loeffler, MD, of Lighthouse Point, Florida. A surgeon from Virginia feels the same, saying, "I've got insufficient experience in suturing them."

"An AC-IOL is less prone to complications when done correctly," a surgeon from California says.

Several surgeons, however, prefer the Yamane technique. "I like the aesthetics of it," says Lancaster, Pennsylvania, surgeon Spage Yee, MD.

"It has the least pseudophakodonesis away from uveal tissue (hence a quieter eye)," says a surgeon from Florida.

"I prefer to use a modified Yamane using 27G ports ..." says another scleral suture fan. "An anterior chamber intraocular lens in older patients is also perfectly good solution."

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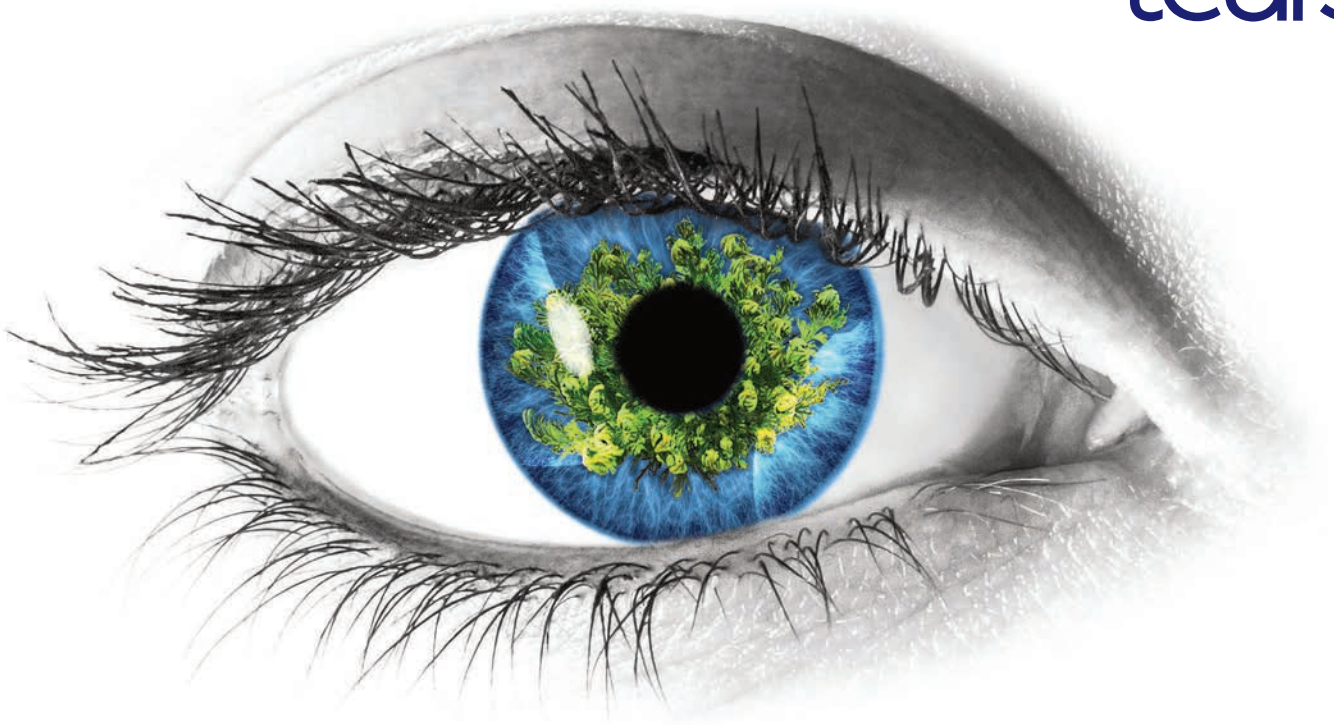

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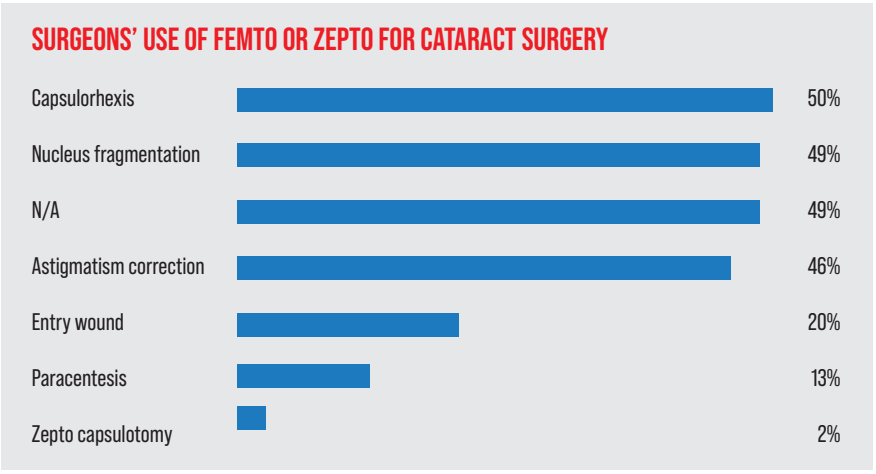
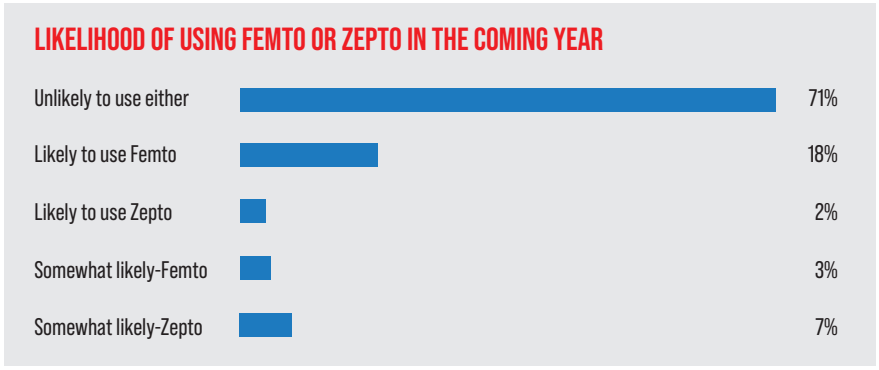
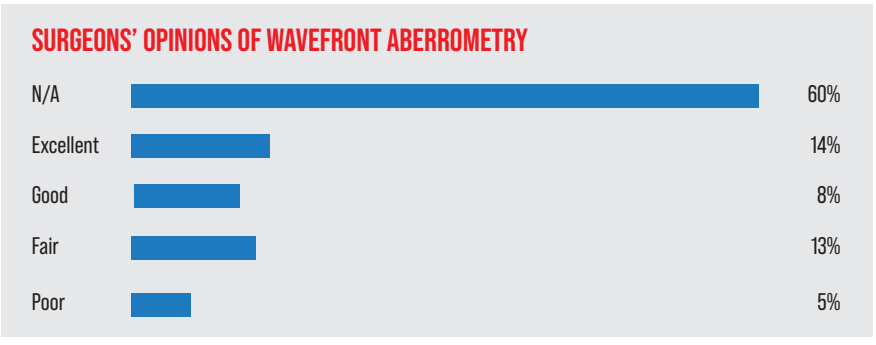
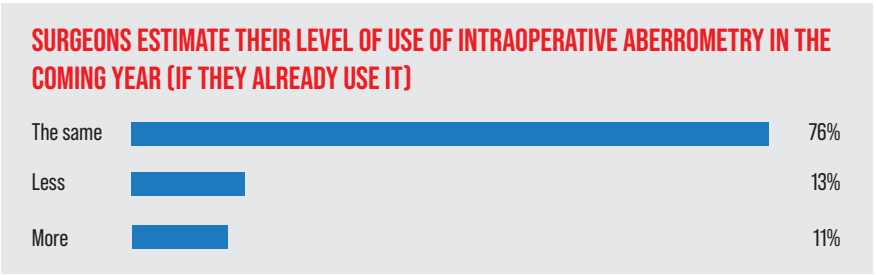
Reference: 1. Jones L, Downie L, Korb D, et al. TFOS Dews II Management and Therapy Report. The Ocular Surface Jul 2017; 575-628.









In the non-Yamane scleral-fixation camp, surgeons like the approach's "good centration and stability," according to Los Angeles surgeon Michael Colvard.

A cataract surgeon from New Jersey likes the method's staying power in the eye. "9-0 prolene doesn't fracture even after 20 years," she says.

Tech Choices

Two of the high-tech devices available to surgeons for a while have been the femtosecond laser for use in cataract surgery and the intraoperative aberrometer. Surgeons on the survey appear to use the former somewhat more than the latter, however.

• ***Femtosecond laser-assisted cataract surgery.*** Fifty-one percent of the surgeons say they use the femto for some aspect of cataract surgery. The most popular use is for the creation of the capsulhorhexis (50 percent of FLACS users), followed by nucleus fragmentation (49 percent) and astigmatism correction (46 percent) (surgeons could choose more than one response). The full list of the uses and their percentages appears in the graph to the left.

"The femtosecond laser produces excellent, reproducible results," says a surgeon from Atlanta. "It's more precise, and makes surgery easier." Dr. Piracha sees pros and cons to the laser. "I like the perfect capsulorhexis and fragmentation," he says. "The AKs aren't perfect, however, due to alignment and measurement issues."

"I like the femto for its decrease in phaco power required for dense lenses, the precision of placing toric IOLs when combined with Cassini for iris registration, and for a perfect capsulorhexis, particularly for multifocal IOLs," states a surgeon from Virginia. Another surgeon agrees, saying the use of the femtosecond results in "less ultrasound and less endothelial damage in shallow chambers."

Taking a slightly different technological path, Ronald Wise, MD, of Denver uses the Zepto capsulotomy device. He says he appreciates the "round, central rhexis" it creates.

In terms of the surgeons' FLACS volumes, a fifth of the surgeons say they're volumes are increasing, 7 percent say they're decreasing, and

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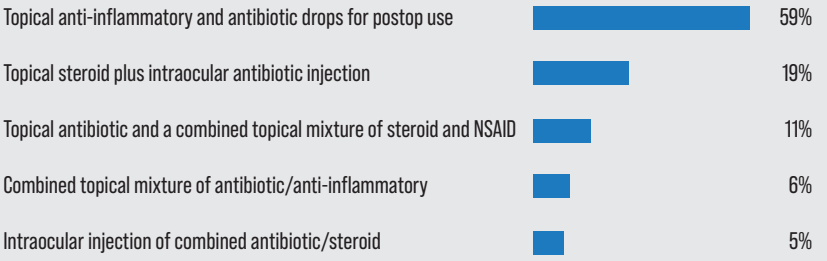
1. Cionni RJ, Pei R, Dimalanta R, et al. Evaluating red reflex and surgeon preference between nearly-collimated and focused beam microscope illumination systems. *Transl Vis Sci Technol.* 2015;4(4):7.

PREFERRED METHOD FOR CONTROLLING POSTOP INFLAMMATION AND PREVENTING INFECTION



a quarter of the surgeons say they're staying the same.

Looking ahead at FLACS'/Zepto's future uptake, 71 percent of the respondents who don't currently use the technology say they're unlikely to use either of them. Eighteen percent say they're likely and 3 percent are somewhat likely to use the femtosecond. Two percent are likely and 7 percent are just somewhat likely to try the Zepto.

Surgeons lay out the reasons they're not interested: "Cost, availability, and [the fact that I] could do the steps by hand that the laser can do," says a surgeon from Washington, D.C.

"I don't need it, and haven't seen any data suggesting improved outcomes," opines a Michigan surgeon.

"This is great technology that solves no problem we were having previously," says a surgeon from Ohio. An ophthalmologist from Oklahoma agrees, saying, "We have a very quick, successful, easy method already."

Another surgeon, from Florida, says he's somewhat likely to try the technology. "I would somewhat like either in certain instances," he says. One surgeon says he's interested in the Zepto, but hasn't had any experience with it yet.

• ***Intraoperative aberrometry.*** Sixty percent of the respondents don't use intraoperative aberrometry. Of the surgeons who do use it, 14 percent think it's excellent, 8 percent would call it good, 13 percent think it's fair, and 5 percent think it's poor.

"I've been using it for 10 years," says Florida's Dr. Stephenson. "It improves my outcomes." Frank Burns, MD, of Louisville, Kentucky, agrees. "It helps with most IOL powers in post-refractive patients (post-LASIK, post-PRK and post-RK), and also helps with toric IOL alignment," he says. San Diego's Steven Fish, MD, can see the benefit, but only in certain spots. "It's helpful post-refractive surgery," he says. "Otherwise, modern formulas do a good job at predicting outcomes, so I rarely use it."

"It's stressful when it doesn't agree [with your calculations], says a surgeon from Maryland. "Lots of variables can affect the reading intraoperatively."

A surgeon from Tennessee has cooled on the technology. "I used to use it, but with improved preop biometry and formulas, it's not necessary anymore," she says.

Other Techniques

Surgeons also commented on specific technique/technologies as well as gave their best pearls for cataracts.

• ***Pupil management during surgery.*** Fifty-two percent of the respondents use intracameral epinephrine/lidocaine injection ("Epi-Shugarcaine") to help promote a wide pupil during surgery. Nineteen percent use mechanical pupillary dilation, usually via a Malyugin ring, and 17 percent use Omidria (an injection of phenylephrine/ketorolac from Omeros).

• ***Postop inflammation management/infection prevention.*** Most surgeons (59 percent) still prescribe topical anti-inflammatory and antibiotics for postop use. Nineteen percent prescribe topical steroids but give the antibiotics via an injection, and 11 percent prescribe a topical antibiotic and a topical combination of a steroid and an NSAID.

• ***Surgeons' pearls.*** The surgeons were also asked to give their single best piece of surgical advice. Here are some of the answers:

— "Use of good, old-fashioned immersion A Scan and keratometry can still give you great results. Just use the appropriate IOL calculation." (Lancaster's Dr. Lee)

— "Treat dry eye and astigmatism." (Dr. Stephenson)

— "Always have a Plan B and, for complicated cases, a Plan C. Though rare, if things don't go to plan, it is usually better to take the time to assess the situation, ensure a safe outcome, and a happy ending ... even if it means a longer surgery or a slower recovery. If you're asking yourself the question [about a possible complicating factor], then place that CTR and stain with triamcinolone to check for vitreous. Always be assessing and re-assessing." (Jimmy Y. Hu, MD, of Manhattan)

— "Hydrodisect well. Make sure the nucleus is rotating well and make a round, 5-mm capsulorhexis that overlaps the implant." (Bradenton's Dr. Adler)

— "Drop your wrist, flatten your I/A tip and rotate the eye toward you for subincisional cortex removal." (Anonymous)

— "Use a Malyugin ring in small pupil IFIS." (Denver's Dr. Wise)

— "Every step builds on the previous step. Be precise and efficient." (St. Louis' Dr. Cohen)

— "Treat every patient like your mother." (David G. Gross, MD, Merrillville, Indiana). ◀

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Reference: 1. Leibowitz HM, Hyndiuk RA, Lindsey C, et al. Fluorometholone acetate: clinical evaluation in the treatment of external ocular inflammation. *Ann Ophthalmol*. 1984;16(12):1110-1115.

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Shake Well Before Using. One to two drops instilled into the conjunctival sac(s) four times daily. During the initial 24 to 48 hours, the dosage may be safely increased to two drops every two hours. If no improvement after two weeks, consult physician. Care should be taken not to discontinue therapy prematurely.

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Contraindicated in acute superficial herpes simplex keratitis, vaccinia, varicella, and most other viral diseases of the cornea and conjunctiva; mycobacterial infection of the eye; fungal diseases; acute purulent untreated infections, which like other diseases caused by microorganisms, may be masked or enhanced by the presence of the steroid; and in those persons who have known hypersensitivity to any component of this preparation.

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For topical ophthalmic use only. Not for injection.

Intraocular Pressure Increase
Prolonged use may result in glaucoma, damage to the optic nerve, and defects in visual acuity and visual field. It is advisable that the intraocular pressure be checked frequently.

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Use of corticosteroids may result in cataract formation.

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Topical ophthalmic corticosteroids may slow corneal wound healing. In those diseases causing thinning of the cornea or sclera, perforation has been known to occur with chronic use of topical steroids.

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Use in the treatment of herpes simplex infection requires great caution.

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Use of corticosteroids may suppress the host response and thus aid in the establishment of secondary ocular infections. Acute purulent infections of the eye may be masked or exacerbated by the presence of steroid medication.

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Do not touch dropper tip to any surface, as this may contaminate the suspension.

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Vision may be temporarily blurred following dosing with FLAREX. Care should be exercised in operating machinery or driving a motor vehicle.

ADVERSE REACTIONS
Clinical Trials Experience
Glaucoma with optic nerve damage, visual acuity and field defects, cataract formation, secondary ocular infection following suppression of host response, and perforation of the globe may occur.

Postmarketing Experience
The following reaction has been identified during postmarketing use of FLAREX in clinical practice. Because reactions are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. The reaction, which has been chosen for inclusion due to either its seriousness, frequency of reporting, possible causal connection to FLAREX, or a combination of these factors, includes dysgeusia.

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Fluorometholone has been shown to be embryocidal and teratogenic in rabbits when administered at low multiples of the human ocular dose. Fluorometholone was applied ocularly to rabbits daily on days 6-18 of gestation, and dose-related fetal loss and fetal abnormalities including cleft palate, deformed rib cage, anomalous limbs, and neural abnormalities, such as encephalocele, craniorachischisis, and spina bifida, were observed. There are no adequate and well-controlled studies of fluorometholone in pregnant women, and it is not known whether fluorometholone can cause fetal harm when administered to a pregnant woman. Fluorometholone should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Lactation
Systemically administered corticosteroids appear in human milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects. It is not known whether topical administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in human milk. Because many drugs are excreted in human milk, caution should be exercised when FLAREX is administered to a nursing woman.

Pediatric Use
Safety and effectiveness in pediatric patients have not been established.

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

NONCLINICAL TOXICOLOGY
Carcinogenesis, Mutagenesis, Impairment of Fertility
No studies have been conducted in animals or in humans to evaluate the possibility of these effects with fluorometholone.

PATIENT COUNSELING INFORMATION
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The preservative in FLAREX, benzalkonium chloride, may be absorbed by soft contact lenses. Contact lenses should be removed during instillation of FLAREX but may be reinserted 15 minutes after instillation.

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PHACO: TECHNOLOGY SHAPES TECHNIQUE

A look at cataract removal techniques using the latest machines.

CHRISTINE LEONARD
SENIOR ASSOCIATE EDITOR

Today's phacoemulsification machines are packed with innovative features such as advanced fluidics and IOP control, all in the name of enhancing the safety and efficiency of cataract removal procedures. No two systems are exactly alike, however. In this article, we'll take a look at several cataract surgeons' techniques using different phacoemulsification systems and how the technological advances are making a difference.

Veritas (Johnson & Johnson Vision)

Jason J. Jones, MD, medical director of the Jones Eye Clinic in Sioux City, Iowa, has been using Veritas since its preliminary market release in early May 2021. With Veritas, he reports increasing his effective bottle height to around 115 cm for venturi quadrant removal, noting that "The forced infusion plus physical bottle height [during this stage] offers some extra stability."

He says Veritas' dual pump system is convenient, allowing him to easily switch between peristaltic and venturi. "I use peristaltic for my chop because it's still very efficient for whatever I might need it for, whether that's a dense or a soft nucleus," he says. "If you're on a venturi setting and have a very soft cataract, you still want to chop it. You need to be able to chop things with control, and then when those pieces are liberated, you want something with good response and very high performance."

Dr. Jones also reports less fatigue using the new foot pedal, which has a flat rather than angled design.

Dr. Jones shares his cataract removal technique with Veritas: He begins his cases by irrigating with lidocaine and epinephrine. Then he fills the anterior chamber with dispersive viscoelastic (Healon EndoCoat, Johnson & Johnson Vision) and stabilizes the eye through the paracentesis with his instruments. Next, he marks the cornea for centration. He makes his capsulorhexis using Utrata forceps and hydrodissects with a Chang cannula.

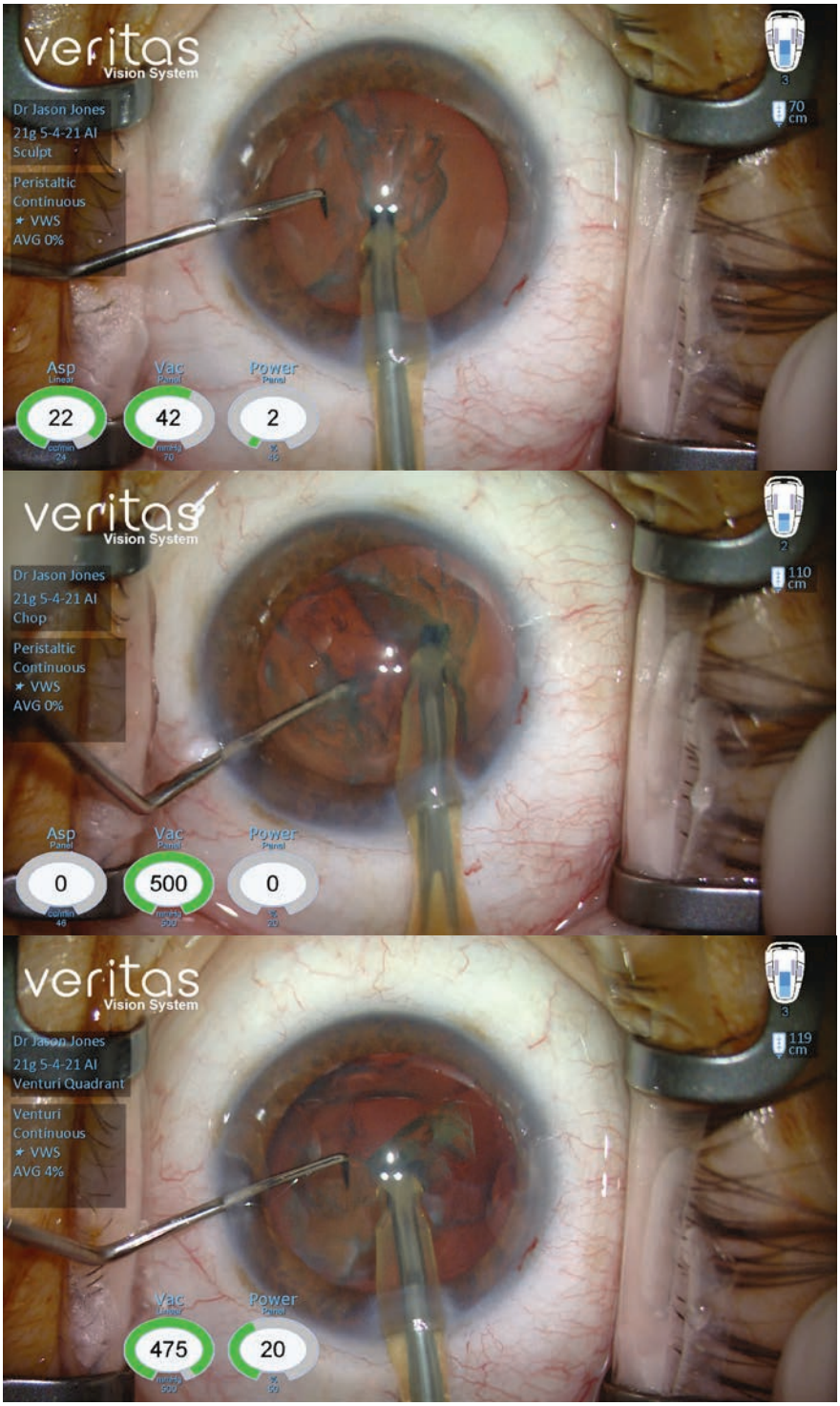
He begins cataract removal in the sculpt setting with fairly low vacuum and aspiration (*Figure 1*). "This is a peristaltic setting," he explains. "I use it to clean off the anterior cortex from the surface of the nucleus within the capsulorhexis."

Afterwards, he switches to a chop setting (also peristaltic) and buries the tip. He listens for the machine's pulsing sounds. "When you achieve an occlusion state, the sound becomes noticeably higher," he says. "Veritas doesn't give you an occlusion bell, but it's very easy to listen for the level that indicates I have a grasp on a piece of cataract. The Veritas' tones are more pleasant to listen to than those of previous machines—for me and for the patients.

"I then use a small amount of phaco energy to get in, and then I do a vertical chop," he continues. "I maneuver my chopper away from me, plunge it into the nucleus and bring it toward my

This article has no commercial sponsorship.

Dr. Jones is a speaker and consultant for Johnson & Johnson Vision. He also does paid research and clinical studies for J&J Vision. **Dr. Shafer** is a consultant for Alcon. **Dr. Page** is a consultant for Bausch + Lomb and Johnson & Johnson Vision. **Dr. Parker** reports no relevant financial disclosures.



Jason Jones, MD

Figure 1. Jason Jones, MD, performs cataract removal surgery using the Veritas (Johnson & Johnson Vision). Shown here: sculpt (top), chop (middle) and venturi quadrant removal (bottom).

phaco tip. The crack will elaborate on its own. When the two devices come close to each other, I separate them while paying attention to a posterior separation, so it's more of a pivot of instruments from their incision fulcrum than a translational movement. I want to get that crack through the posterior plane, but also subincisionally and distally from me.

"I now have essentially two nuclei to deal with," he continues. "This typically helps to rotate the nuclei counterclockwise. I'll usually do two more chops on each hemi-nucleus for a total of six pieces. As I rotate the nucleus around to get to the last piece, I'll chop it while I'm still in occlusion holding.

"Then, I touch my button to advance, and go right into my venturi quadrant removal and start to take out pieces," he says. "I use my chopper to help enucleate pieces out of the capsular bag, but typically they're pretty well-liberated from each other as well as from the capsular bag, so they kind of tumble out pretty nicely. I rotate the second hemi-nucleus to the other side, away from me again, and complete the case of phacoemulsification."

He adds that as he gets to that last piece, he switches from the vertical chopper to a more blunt instrument that he developed, which is on the other end of his chopper. "This way, if I need to touch the capsule or something comes close to it, it's less risky from a safety standpoint. I rotate the chopper in my hand, put it back in the paracentesis and finish manipulation of it up to the phaco tip."

He then switches out his second instrument and goes back in with dispersive viscoelastic. "I lay a stripe of viscoelastic in the anterior chamber," he says. "To do that properly, I need to come down to foot-position zero because any irrigation is going to shoot the viscoelastic out of the wound. Basically, I replace the anterior chamber volume with viscoelastic. This provides better stability and nicer tension overall to the anterior chamber with less collapse."

If he has any formed cortex left, he goes in with irrigation/aspiration and pulls it out in venturi

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mode. "Having remaining cortex is pretty uncommon—about 10 to 15 percent of the time I do need to get some small piece out of the capsular bag, but otherwise I go in with a silicone-tip cannula on a 5-cc syringe to irrigate and polish off the central posterior capsule," he explains. "After that, I go in with a 27-gauge cannula 5-cc syringe and irrigate into the fornix of the bag."

To eliminate any cortical remnants, he reenters the main wound and sweeps around to a 12 o'clock position. He says it's reassuring to clean these chunks out since the iris obscures the view, hiding any leftover material. "I take the same 27-gauge cannula and go into the paracentesis," he continues. "I go subincisionally over to my right; now I've done about three-quarters of the capsular fornix. Next, I go back with a Chang cannula 5-cc syringe, which isn't like hydrodissection, but I use the angled cannula to go and clean the inferior subincisional fornix and sweep around to my incisional left to irrigate out 360 degrees of capsular fornix."

He then puts in dispersive viscoelastic. "To inflate the capsular bag, I curette the capsular bag for lens epithelial cell removal from the subcapsular region of the anterior leaflet," he says. After placing the IOL, he removes the viscoelastic with irrigation/aspiration.

"Be sure to rotate the lens and go behind it as well," he notes. "I go under one side, rotate the lens and go on the other side. It's amazing how often there's a thin layer of viscoelastic still on the opposite side of the lens. It's nice to get all of that out. Be sure to get all of the viscoelastic out of the anterior chamber as well. I irrigate into the fornices of the angle using a 27-gauge cannula, hydrate my wounds, check my incisions and ensure they're dry, and then the case is completed."

CataRhex3 (Oertli Instrumente AG)

Jack S. Parker, MD, PhD, of Parker Cornea in Birmingham, Alabama, says the Swiss-made CataRhex3, though unassuming in its appearance, is a highly dependable, safe and intuitive machine. "We originally purchased a CataRhex for mission trips to Nicaragua about 10 years ago," he says. "It's the size of a carry-on. It performed admirably on those trips." Now, Dr. Parker uses his CataRhex3 for routine, in-office cataract surgery.

His approach with the CataRhex3 employs two techniques not commonly performed. First, he pre-chops the nucleus with a prechopper. "This allows me to divide the nucleus into two or four pieces prior to inserting the phaco handpiece into the eye," he says. "It reduces the amount of total ultrasound energy in the eye."

Secondly, Dr. Parker performs one-handed phaco. "I like to do phacoemulsification without a second instrument inside the eye," he says. "There's nothing usually there to help me grab pieces or keep the posterior capsule back. I believe that if you can just use the phaco handpiece, as opposed to the phaco handpiece and a secondary instrument, the chamber stability is a little better. The CataRhex3's phaco tip is also larger than most others. This gives you a better ability to grip pieces.

"Many people prefer a second instrument because they're worried about the posterior capsule trampolining up into the phaco tip," he continues, "but what I've found using Oertli's machine is that the chamber stability is good enough that you don't necessarily need a second instrument in the eye. I feel that when all of my attention is just on the phaco handpiece and not divided between phaco and something else in the eye, it's a more pleasant, safe and controlled experience."

He says the machine employs only longitudinal, as opposed to torsional phaco. "This was a philosophical choice by the Oertli engineers," he says. He says the thinking was that longitudinal phaco may be safer than torsional phaco because the tip "moves predictably back and forth and is less likely to cause inadvertent damage to surrounding structures."

Additionally, the CataRhex3 is now available with Speep, Oertli's pump innovation that offers more precise control of flow and vacuum, according to the company.

Dr. Parker points out that CataRhex3's reliability offers peace of mind. "When I'm operating at the hospital, it's not uncommon for there to be something wrong with a phaco machine, and we'll have to bring in another and set it up," he says. "We don't have a backup for the CataRhex3 in

Oertli Instrumente AG

Oertli's CataRhex3 is portable and reliable, says Jack S. Parker, MD, who performs one-handed phaco and in-office surgery with this machine.

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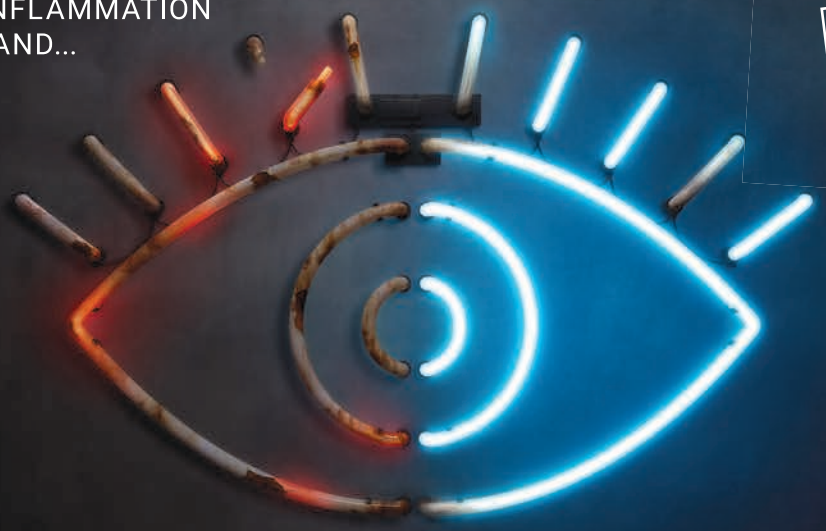

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Indications and Usage

For steroid responsive inflammatory ocular conditions of the palpebral and bulbar conjunctiva, cornea, and anterior segment of the globe and chronic anterior uveitis, corneal injury from chemical, radiation or thermal burns, or penetration of foreign bodies for which a corticosteroid is indicated and where the risk of superficial bacterial ocular infection is high or where there is an expectation that potentially dangerous numbers of bacteria will be present in the eye.

Important Safety Information

CONTRAINDICATIONS:
Most viral disease of the cornea and conjunctiva including epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, and varicella, and also in mycobacterial infection of the eye and fungal disease of ocular structures. Hypersensitivity to any components of the medication.

WARNINGS & PRECAUTIONS:

- **IOP increase –** Prolonged use may result in glaucoma with damage to the optic nerve, defects in visual acuity and fields of vision. IOP should be monitored.
- **Aminoglycoside sensitivity –** Sensitivity to topically applied aminoglycosides may occur.
- **Cataracts –** Posterior subcapsular cataract formation may occur.
- **Delayed healing –** May delay healing and increase the incidence of bleb formation. Perforations of the cornea or sclera have occurred. Slit lamp biomicroscopy, and fluorescein staining should be conducted.
- **Bacterial infections –** May suppress host response and increase secondary ocular infections. In acute purulent conditions, steroids may mask infection or enhance existing infection. If signs and symptoms fail to improve after 2 days, the patient should be re-evaluated.
- **Viral infections –** Use with history of herpes simplex requires great caution. The course and severity of many viral infections of the eye (including herpes simplex) may be exacerbated.
- **Fungal infections –** Fungal infections of the cornea may occur and should be considered in any persistent corneal ulceration.
- **Use with systemic aminoglycosides –** Total serum concentration of tobramycin should be monitored.

ADVERSE REACTIONS:
The most frequent adverse reactions (<4%) to topical ocular tobramycin are hypersensitivity and localized ocular toxicity, including eye pain, eyelid pruritus, eyelid edema, and conjunctival hyperemia.

The reactions due to the steroid component are increased intraocular pressure with possible development of glaucoma, and infrequent optic nerve disorder; subcapsular cataract; and impaired healing.

The development of secondary infection has occurred. Fungal infections of the cornea may occur. Secondary bacterial ocular infection following suppression of host responses also occurs.

Non-ocular adverse events (0.5% to 1%) included headache and increased blood pressure.

Please see Brief Summary of Full Prescribing Information on the adjacent page.

[a]Randomized, investigator-masked, active-controlled, parallel-group trial conducted at 7 private practice clinical sites in the United States with 122 adult patients who had moderate to severe blepharitis/blepharoconjunctivitis.[1]

[b]Multicenter, double-blind, parallel-group, single-dose study of 987 patients receiving a single dose of TOBRADEX ST or TobraDex ophthalmic suspension.[2]

References: 1. Torkildsen GL, Cockrum P, Meier E, et al. *Curr Med Res Opin.* 2011;27(1):171-178.
2. Scoper SV, Kabat AG, Owen GR, et al. *Adv Ther.* 2008;25(2):77-88.

Santen

TOBRADEX® ST (tobramycin/dexamethasone ophthalmic suspension) 0.3%/0.05%

Brief Summary

This Brief Summary does not include all the information needed to use TOBRADEX ST safely and effectively. Please see Full Prescribing Information for TOBRADEX ST at MyTobraDexST.com.

INDICATIONS AND USAGE

TOBRADEX ST is a topical antibiotic and corticosteroid combination for steroid-responsive inflammatory ocular conditions for which a corticosteroid is indicated and where superficial bacterial ocular infection or a risk of bacterial ocular infection exists.

Ocular steroids are indicated in inflammatory conditions of the palpebral and bulbar conjunctiva, cornea and anterior segment of the globe where the inherent risk of steroid use in certain infective conjunctivitides is accepted to obtain a diminution in edema and inflammation. They are also indicated in chronic anterior uveitis and corneal injury from chemical, radiation or thermal burns, or penetration of foreign bodies.

The use of a combination drug with an anti-infective component is indicated where the risk of superficial ocular infection is high or where there is an expectation that potentially dangerous numbers of bacteria will be present in the eye.

DOSAGE AND ADMINISTRATION

Recommended Dosing: Instill one drop into the conjunctival sac(s) every four to six hours. During the initial 24 to 48 hours, dosage may be increased to one drop every 2 hours. Frequency should be decreased gradually as warranted by improvement in clinical signs. Care should be taken not to discontinue therapy prematurely.

CONTRAINDICATIONS

Nonbacterial Etiology: TOBRADEX ST is contraindicated in most viral diseases of the cornea and conjunctiva including epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, and varicella, and also in mycobacterial infection of the eye and fungal diseases of ocular structures.

Hypersensitivity: Hypersensitivity to any component of the medication.

WARNINGS AND PRECAUTIONS

IOP increase: Prolonged use of corticosteroids may result in glaucoma with damage to the optic nerve, defects in visual acuity and fields of vision. IOP should be monitored.

Aminoglycoside sensitivity: Sensitivity to topically applied aminoglycosides may occur.

Cataracts: May result in posterior subcapsular cataract formation.

Delayed healing: May delay healing and increase the incidence of bleb formation after cataract surgery. In those diseases causing thinning of the cornea or sclera, perforations have been known to occur with the use of topical steroids.

Bacterial infections: 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 infection. If signs and symptoms fail to improve after 2 days, the patient should be re-evaluated.

Viral infections: Treatment in 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 with long-term use. Fungal invasion must be considered in any persistent corneal ulceration.

Use with systemic aminoglycosides: Use with systemic aminoglycoside antibiotics requires monitoring for total serum concentration of tobramycin.

ADVERSE REACTIONS

The most frequent adverse reactions to topical ocular tobramycin (TOBREX®) are hypersensitivity and localized ocular toxicity, including eye pain, eyelids pruritis, eyelid edema, and conjunctival hyperemia. These reactions occur in less than 4% of patients. Similar reactions may occur with the topical use of other aminoglycoside antibiotics.

Non-ocular adverse events occurring at an incidence of 0.5% to 1% included headache and increased blood pressure.

The reactions due to the steroid component are: increased intraocular pressure (IOP) with possible development of glaucoma, and infrequent optic nerve disorder; subcapsular cataract; and impaired healing.

Secondary Infection.

The development of secondary infection has occurred. Fungal infections of the cornea are particularly prone to develop with long-term use. Fungal invasion must be considered in any persistent corneal ulceration. Secondary bacterial ocular infection following suppression of host responses also occurs.

USE IN SPECIFIC POPULATIONS

Pregnancy and Nursing Mothers

There are no adequate and well controlled studies in pregnant women. TOBRADEX® ST ophthalmic suspension should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Caution should be exercised when TOBRADEX® ST is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in pediatric patients below the age of 2 years have not been established.

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

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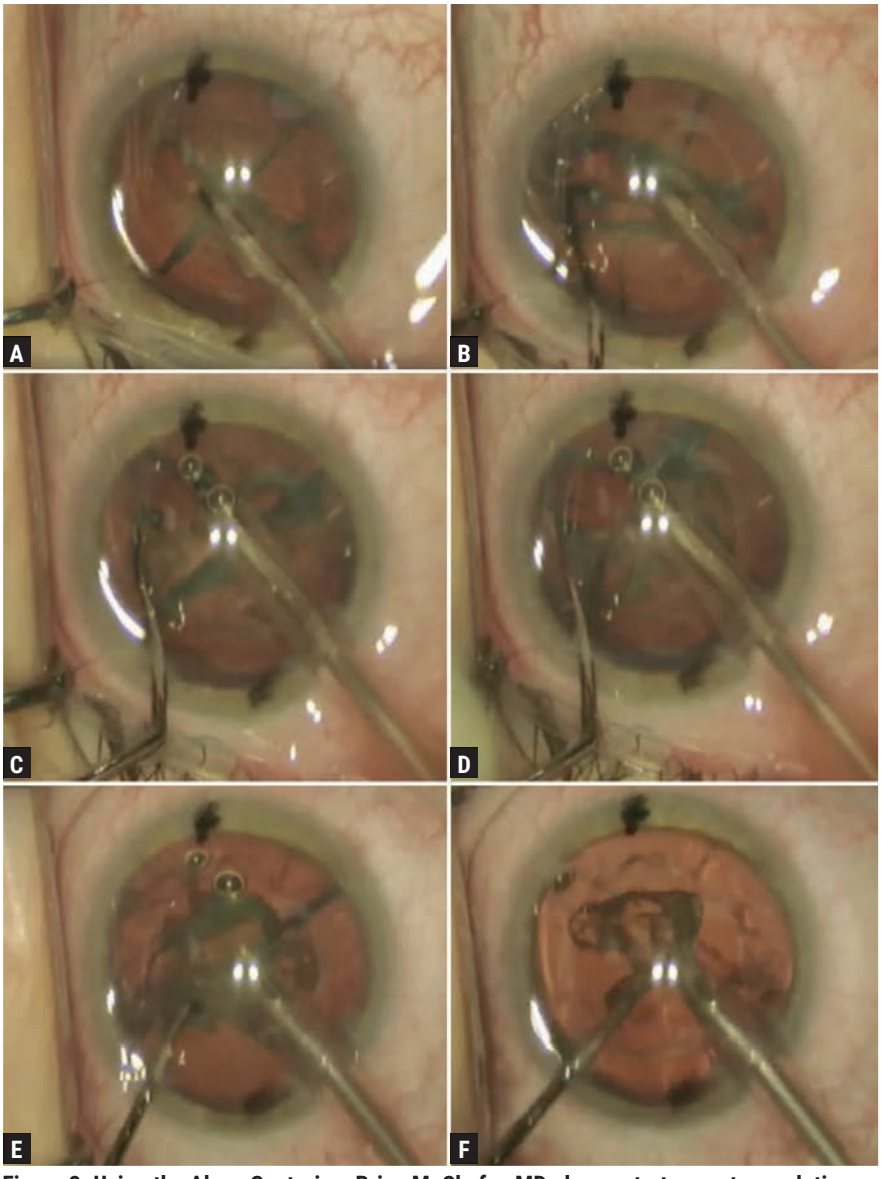
Centurion (Alcon)

Brian M. Shafer, MD, of Chester County Eye Care in Malvern, Pennsylvania, uses the Alcon Centurion with the Active Sentry handpiece. He says the new IOP-sensing technology in the tip of the handpiece offers greater safety for preventing post-occlusion surge.

"The Centurion system complements my approach well," he says. "Active Fluidics and Active Sentry allow me to adjust the pressure by clicking a button rather than waiting for the bottle to change its physical height. It's safer, and it also benefits beginner surgeons since chamber stability isn't as guaranteed based on technique."

He says he employs either a divide-and-conquer (about 90 percent of the time) or a stop-and-chop technique, depending on the type of cataract he's faced with. "I have many different settings depending on what I experience intraoperatively with each unique cataract," he says. "The Centurion allows for a lot of adaptability based on the lens itself."

Dr. Shafer shares his approach: "After completing a capsulorhexis and hydrodissection, I begin my standard divide-and-conquer technique by rotating the nucleus 360 degrees to ensure complete movement," he begins. "Next, I set my phaco setting to sculpt, which provides high phaco power, low vacuum and a low flow rate (*Figure 2*). This allows for a lot of energy to be delivered directly to the center of the nucleus without displacing it too much. I sculpt deeply, and then I use a second instrument to crack the nucleus.



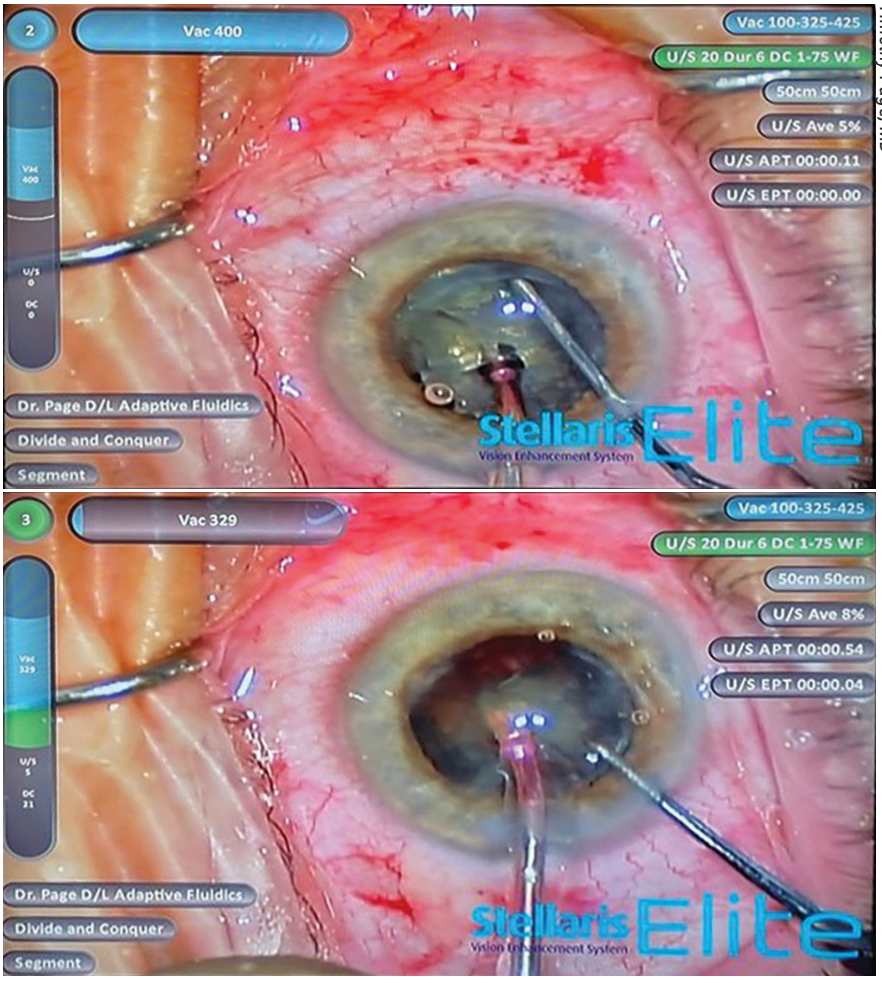
Brian M. Shafer, MD

Figure 2. Using the Alcon Centurion, Brian M. Shafer, MD, demonstrates center sculpting (A), cracking the nucleus into two hemi-pieces (B), cracking the first hemisphere into quadrants (C), cracking the final hemisphere into quadrants (D), emulsifying the first quadrant (E) and emulsifying the final quadrant (F).

Using the second instrument, I spin the nucleus 90 degrees and continue to sculpt into that second hemisphere. I crack it into a quadrant, spin it 180 degrees, sculpt again and crack it. I'm left with four quadrants."

At this point in the procedure, he switches his settings to ultrasound 1 on the Centurion. "This setting has a higher flow rate, higher vacuum and slightly lower phaco power," he explains. With a second instrument he gets behind a quadrant and shifts it into the center portion of the capsular bag. He maintains occlusion of that quadrant using fluidics and ensures it stays in the proper position during emulsification with his second instrument.

After the first quadrant is completely emulsified, he moves on to the second quadrant. "I use the second instrument to position the quadrant toward my phaco tip," he says. "Maintaining the ultrasound 1 setting, I emulsify that piece



Timothy Page, MD

Figure 3. Timothy Page, MD, says that the Stellaris' (Bausch + Lomb) dual-linear function allows the surgeon to increase vacuum when needed, such as during removal of the first quadrant, which is made easier with higher vacuum (top). Once the quadrant is in the central safety zone, he lowers the vacuum level (bottom). In the pitch position, the pressure gradients and the risk of surge are reduced.

as well. Then I spin the nucleus around and do the exact same thing with the final two quadrants."

He says that it's often difficult to achieve a good crack on certain lenses, such as the softer ones. For these cases, he switches to a stop-and-chop technique with a soft-chop. "When I start out my technique, I still begin by sculpting in the center using the same approach as described above, but instead of making four quadrants, I spin the nucleus so I have two hemispheres. I reach my second instrument around, beneath the anterior capsule, and I go to the equator of the lens and do what I call a soft chop."

For Dr. Shafer's soft chop, he impales the hemisphere with his phaco tip, brings his second instrument to the phaco tip and makes a soft, horizontal chop with no phaco power engaged. "That divides the hemisphere into quadrants," he says. "I spin it around and do the same thing with the other hemisphere."

With a soft lens, he says the epi-nucleus setting is better suited than ultrasound 1. "The epi-nucleus setting has a higher vacuum rate, slightly lower flow rate and lower phaco power," he says. "This allows for maintaining excellent occlusion while aspirating the quadrant with minimal phaco energy delivered. It's just not necessary to emulsify that piece."

For very dense lenses, he switches to his dense setting, which increases the amount of phaco power delivered to the cataract. "Greater phaco power is important to ensure you can cut through a very dense lens," he says. "In other circumstances, if the lens is pretty hard or if I just don't have my usual equipment, I'll use the chop setting.

"Most of my technique uses a combination of longitudinal and torsional power at the phaco tip," he continues. "I use a lot of torsional power when breaking up my lenses using the divide-and-conquer technique, but if I'm going to chop, I switch to a longitudinal technique to drive the phaco tip into the center of the hemisphere. Then, I use very high vacuum (around 400 to 500 mmHg) with no phaco power being delivered, and I pass my second instrument to complete either a vertical or horizontal chop. I don't do that too often anymore, but I do have that setting available if the situation presents itself."

Stellaris (Bausch + Lomb)

Timothy Page, MD, in practice at Oakland Ophthalmic Surgery in Birmingham, Michigan, and Beaumont Hospital in Royal Oak, Michigan, says the Stellaris is well-suited to the chop technique because of its exceptional holding power and fluidics that prevent post-occlusion surge.

"It's a high-performance phaco system," he says. "The microphaco needle has an hourglass design. The lumen is very small, and this offers greater visibility, especially when performing complex cases. It tapers quickly from a diameter of about 790 µm to 500 µm. This small diameter acts as a flow restrictor, preventing large boluses of fluid from rushing out

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Dr. Page's main technique is a vertical chop. "The Stellaris needle has a nice, flared tip, which gives me a lot of surface area to engage the nucleus," he says. "I hold the nucleus in place in foot-position two with my foot pedal and use the chopper to do a vertical chop technique. I create two hemispheres and then make my first quadrant."

He says removing the first quadrant from the capsular bag is usually the most difficult, but the Stellaris' dual-linear function helps to facilitate this maneuver (*Figure 3*). "The dual-linear foot pedal enables you to swing your foot to the left or right, depending how you program it, so you can get extra vacuum to pull a piece of cataract out of the capsule and into the safe zone," he explains. "It helps to reduce the gradient between very high pressures in the eye during occlusion and low pressures when the occlusion clears. I often apply an extra 100 mmHg of vacuum this way. Then, I'll go back in my linear phase and emulsify the nucleus using only 30-percent phaco power and 300-mmHg vacuum. The Stellaris uses venturi, which is highly efficient."

For dense cataracts, he increases his phaco power to about 40 to 50 percent. However, he notes that this setting won't necessarily translate to other machines, due to the Stellaris' long stroke length. "When you're at 50 percent on the Stellaris, you're pulling a stroke length of about 70 µm," he says. "The whole travel length on other machines may be about 80 to 90 µm at 100 percent; you don't need the same amount of power on the Stellaris. The Stellaris also has a low oscillation rate at 28.5 kHz, which reduces the chances of phaco wound burn. I've rarely gone up to 50 percent on this machine."

He adds that the disposable CapsuleGuard I/A handpiece with a silicone tip for cortex removal helps to ensure safety. "I've never ruptured a capsule using this handpiece," he says. "The cannula is a good millimeter away from the port, so it's highly unlikely that you could ever aspirate the capsule up far enough that it would touch metal and rupture.

"If you've wanted to use chop and master the chop techniques, but are having difficulty with a peristaltic system, I recommend trying the Stellaris because of its flared phaco needle and ease of holding the nucleus," Dr. Page says. "The dual-linear function will help you hold everything in place and remove the first quadrant without having to use high levels of vacuum throughout the rest of nuclear disassembly."

EVA Phaco-Vitrectomy System (DORC)

The upgraded EVA system from Dutch Ophthalmic Research Centre enables cataract, vitrectomy and combined procedures. For cataract surgeons, the system features an integrated, redesigned footswitch, which the company says is easier to operate, and a modifiable foot bed so surgeons can choose their optimal foot position. The wireless footswitch is also dual-linear, allowing for independent control of and quick transitions between aspiration and phaco. There are eight programmable switches.

The system has a 19-inch touch-screen user interface, voice feedback, an integrated stylus holder and infrared remote control as well as multi-language functionality.

DORC says the EVA's Vacuflow fluidics system with Valve Timing Intelligence (VTi) provides a three-times faster rise time (300 msec; 0 to 680 mmHg@0 cc/min 10 to 90 percent) than traditional venturi and reduces pulsations in peristaltic mode. Flow mode is 0 to 90 ml/min. EVA uses a gravity-based infusion system with an integrated IV pole.

DORC

DORC's EVA Phaco-Vitrectomy system has a redesigned footswitch with dual-linear function for independent control of aspiration and phaco during cataract surgery.

EVA's phaco pulse mode is 250 pps for phacoemulsification and fragmentation. Its oscillation rate is 40 kHz and its stroke length is 100 µm at 100 percent. EVA's phaco system features needle detection, auto tuning and the company's advanced fluidics technology.

No matter which machine you use, experts say it's a good idea to enlist your company representative when adjusting to a new model. "Sit down with your company representative and go through some cases," says Dr. Shafer. "For example, if you have too much chatter during quadrant removal, it's often because your power is a little too high and it's creating cavitation bubbles. Your company representative can adjust your power a little lower or increase your vacuum to ensure you maintain occlusion. Tell your representative what you're experiencing and ask for their feedback. Everyone's technique is a little different." ◀

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THE DME PIPELINE: WHAT'S NEXT?

Now that faricimab has been approved, the spotlight falls on the next batch of agents in the research queue.

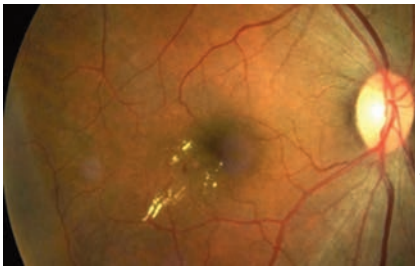
MICHELLE STEPHENSON
CONTRIBUTING EDITOR

The pipeline for diabetic macular edema treatments has expanded in recent years, with several promising products in various phases of clinical trials. The big news in DME treatment, however, is the FDA approval of Roche's Vabysmo (faricimab-svoa) in late January.

Vabysmo targets and inhibits two disease pathways linked to a number of vision-threatening retinal conditions by neutralizing angiopoietin-2 (Ang-2) and vascular endothelial growth factor-A (VEGF-A). It's the only FDA-approved injectable eye medication for neovascular age-related macular degeneration and DME that improves and maintains vision with treatment intervals up to four months apart in the first year following four initial monthly doses. Treatment intervals are based on the patient's anatomy and vision outcomes.[1]

The approvals were based on positive results from four Phase III studies, which consistently showed that patients treated with Vabysmo given at intervals of up to four months achieved non-inferior vision gains versus aflibercept given every two months in the first year. Vabysmo was well-tolerated in all four studies, with conjunctival hemorrhage being the most common adverse reaction reported (7 percent).[1]

According to Chicago's Jennifer I. Lim, MD, faricimab is going to make an impact on treatment. "It has an exceptionally long durability compared to other drugs," she says. "The clinical trials are truly relevant for today's retina specialist because they incorporate an adjustment of the dosing intervals based on disease activity after loading in the case of AMD, or a personalized treatment-interval arm in the case of the DME trials. So one can actually use the study to model how you will apply the treatment for your patients. I think the most exciting thing about faricimab is that more than 50 percent of patients can go about four months after loading. Also, more than 80 percent can go 12 weeks or more. That's huge! Additionally, the OCT data show that the faricimab eyes had a better drying effect. In other words, there was less edema within the retina, and more eyes had complete resolution of fluid. That biomarker result explains the extended durability. I think that's really exciting."



All images: David Boyer, MD

Figure 1. An eye with clinically significant macular edema.

While Vabysmo has achieved FDA approval, other promising treatments remain in the pipeline.

KSI-301 (Kodiak Sciences)

KSI-301 is an investigational anti-VEGF therapy built on Kodiak's Antibody Biopolymer Conjugate Platform. It's designed to maintain potent and effective drug levels in ocular tissues for longer than currently available agents.[2] In early February, Kodiak completed enrollment in its GLEAM and GLIMMER Phase III clinical

This article has no commercial sponsorship.

Dr. Boyer has a financial interest in Adverum Biotechnologies, Genentech, Graybug Vision, Roche and Novartis. **Dr. Kaiser** is a consultant to Kodiak, Oxurion, Regeneron, Novartis, RegenxBio, Ocuphire and Allergan. **Dr. Lim** is a consultant to Genentech and Novartis. She has previously done research for or received grants from Genentech, Roche and Graybug. **Dr. Stone** is an investigator for the Kodiak and Genentech trials.

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trials, which are global, multicenter, randomized studies designed to evaluate the efficacy, durability and safety of KSI-301 in patients with treatment-naïve DME. In each of these studies, patients are randomized to receive either intravitreal KSI-301 on an individualized dosing regimen every eight to 24 weeks after only three loading doses, or intravitreal aflibercept every eight weeks after five loading doses. Each study is expected to enroll approximately 450 patients worldwide; the primary endpoint is the change from baseline in best-corrected vision at a year. Patients will be treated and followed for two years.

"KSI-301 is a very-long-acting anti-VEGF," explains the Cleveland Clinic's Peter K. Kaiser, MD. "It lasted six months or longer in approximately two-thirds of patients in its Phase Ib study, and diabetic patients were able to go even longer. It still requires intravitreal injections, of course, and they're testing diabetic retinopathy and DME at the same time."

Thomas W. Stone, MD, who is in practice in Lexington, Kentucky, adds, "Through our studies, we feel there is potential with this molecule. It's an anti-VEGF, and physically it's a thicker liquid, like cold maple syrup or molasses. Patients tolerate the injections well, and it's probably the next anticipated agent that's going to find a place on your shelf."

Brolucizumab

Brolucizumab (Beovu) (Novartis) is a VEGF-A inhibitor. In its Phase III trials (KESTREL and KITE), brolucizumab 6 mg showed robust visual gains and anatomical improvements with an overall favorable benefit/risk profile in patients with DME, compared with aflibercept.[3]

These studies were double-masked, 100-week, multicenter, active-controlled, randomized trials. Study participants were randomized 1:1:1 to brolucizumab 3 mg/6 mg or aflibercept 2 mg in KESTREL (n=566) or 1:1 to brolucizumab 6 mg or aflibercept 2 mg in KITE (n=360). Patients in the brolucizumab groups received five loading doses every six weeks followed by dosing every 12 weeks, with optional adjustment to every eight weeks if disease activity was identified. The primary endpoint was best-corrected visual acuity (BCVA) change from baseline at Week 52.

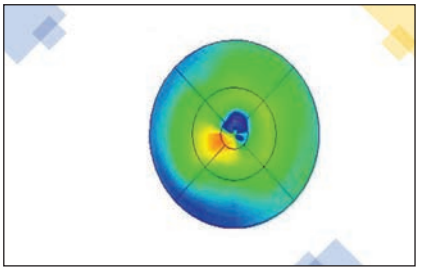

Figure 2. OCT of the eye from Figure 1 showing thickening of the retina.

At Week 52, brolucizumab 6 mg was found to be noninferior to aflibercept in mean change in BCVA from baseline. More subjects achieved central subfield thickness less than 280 µm, and fewer had persisting subretinal and/or intraretinal fluid versus aflibercept. More than half of brolucizumab 6 mg subjects were maintained on every 12 weeks dosing after loading. In KITE, brolucizumab 6 mg showed superior improvements in change of central subfield thickness from baseline from week 40 to week 52 versus aflibercept. The incidence of serious ocular adverse events was 3.7 percent for brolucizumab 3 mg, 1.1 percent for brolucizumab 6 mg, and 2.1 percent for aflibercept in KESTREL; it was 2.2 percent for brolucizumab 6 mg and 1.7 percent for aflibercept in KITE.

"Beovu is a great drug for drying up the retina, and that's been shown in clinical trials for age-related macular edema and DME," says Dr. Lim. "The clinical trials did show the inflammatory responses are less likely to be seen in diabetes than in AMD. However, because we've seen that it can cause a severe retinal vasculitis, I personally am not willing to take the risk."

Dr. Stone agrees. "Beovu has had problems with safety," he says. "In the nAMD trials, more than 4 percent of patients experienced some form of inflammation with the shot, with a smaller subset of less than 1 percent of patients experiencing occlusive vasculitis with permanent vision loss. So, when it first came out, we were using it. Then, when we saw safety issues, everybody pulled back. Now, we're only using it if we don't have another option."

Susvimo (Genentech)

The FDA recently approved Genentech's Susvimo, formerly known as the port delivery system (PDS) with ranibizumab, for the treatment of patients with wet AMD who have previously responded to at least two anti-VEGF injections.

It continuously provides 100 mg/mL ranibizumab injections intravtreally via an ocular implant, which is surgically inserted into the eye during a one-time, outpatient procedure and then is refilled every six months.

"The PDS is currently in studies for diabetes," Dr. Lim says. "In the future, it may be another option for people who need frequent injections, or for proliferative retinopathy that requires anti-VEGF, not just macular edema from diabetes."

GB-102 (Graybug Vision)

GB-102 is a VEGF receptor-1 agonist that's currently in Phase II clinical trials. The company conducted an open-label, single-injection trial in patients with macular edema, with a primary endpoint of the safety and tolerability of two dose levels of GB-102 (1 and 2 mg with optimized formulation).[4] The study included six centers in the United States that enrolled 21 patients who had received at least three prior injections of anti-VEGF and who had at least some response within the past 24 months.

At enrollment, patients required, on average, eight injections per year to control their disease. Eligible patients received GB-102 (1 or 2 mg) at day one and were followed monthly.

There were no drug-related non-ocular adverse events in the trial. The 2-mg dose was associated with medi-

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cation present in the anterior chamber in five of 11 patients. Most adverse events occurred in these patients, including two serious adverse events in a single patient. It's believed that too many microparticles were injected in the 2-mg dose (approximately 2 million) to allow adequate aggregation. As a result, the company has discontinued the development of the 2-mg dose.[4]

The GB-102 1-mg dose met its primary endpoint of safety and tolerability, with seven of 10 patients demonstrating no adverse events. None of the patients had inflammation, and all adverse events were mild to moderate and resolved without long-term consequences. The microspheres aggregated well in the 1-mg dose and formed a depot at the bottom of the eye. As the depot eluted drug, the size decreased, and at six months there was only a small amount of the depot left.

ADVM-022 (Adverum)

ADVM-022 is a VEGF-A inhibitor in Phase II clinical trials. It's an adeno-associated viral vector encoding aflibercept that's been optimized for intravitreal delivery and strong protein expression.

Long-term expression and efficacy of ADVM-022-derived aflibercept were evaluated in a laser-induced choroidal neovascularization model in non-human primates.[5] Ocular safety was evaluated, following long-term suppression of VEGF, by clinical scoring (inflammatory parameters) as well as OCT and electroretinography. Intravitreal administration of ADVM-022 was well-tolerated and resulted in sustained aflibercept levels in ocular tissues. Additionally, administration of ADVM-022 13 months before laser-induced choroidal neovascularization prevented the occurrence of clinically relevant CNV lesions, to the same degree as a bolus of aflibercept given at the time of the laser. These results demonstrate that a single intravitreal administration of ADVM-022 may provide a safe and effective long-term treatment option for DME and may ultimately improve patients' visual outcomes.

Clinical trials are currently under way to evaluate the safety and efficacy of a single intravitreal injection of ADVM-022.

KVD001 (KalVista)

KVD001 is an intravitreally administered plasma kallikrein inhibitor that's completed a Phase II clinical trial in patients with DME.[6]

The clinical trial evaluated the safety and efficacy of KVD001 in patients who have received previous anti-VEGF therapy, yet continue to experience reduced visual acuity and significant edema. The primary efficacy endpoint in the trial was change in best-corrected visual acuity at 16 weeks compared to sham. The 6-µg dose showed a difference of +2.6 letters versus sham, which wasn't statistically significant, and the 3-µg dose showed a difference of +1.5 letters. No significant differences were observed in the secondary endpoints of central subfield thickness or the diabetic retinopathy severity scale. KVD001 was safe and well-tolerated with

(Continued on p. 73)

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IOP Elevation Following Retinal Procedures

A number of these procedures, including anti-VEGF injections, can trigger a rise in IOP. A retinal specialist offers advice.

BASIL K. WILLIAMS JR. MD
CINCINNATI

As every ophthalmologist knows, elevated intraocular pressure is a risk factor for glaucoma progression. Unfortunately, many retina-related procedures, including anti-VEGF injections and some surgical interventions, can cause an increase in IOP.

In most cases, the increase is temporary, so although the pressure can become quite high, consequences are usually minimal or nonexistent. However, susceptibility to damage in some patients can cause even a brief rise in pressure to be consequential; and in other patients, the brief pressure spike can be followed by a long-term IOP increase. Thus, to avoid glaucoma-related complications, it behooves us to identify patients who may be more susceptible to damage in this situation.

As a retina specialist, I know that my glaucoma colleagues are aware of this issue, and there's usually good communication between the retina and glaucoma teams. However, sometimes a patient is sent to a glaucoma specialist only after the pressure has been elevated for a while. For that reason, spreading awareness of this issue can be helpful.

Here, I'd like to share some of what we know about this concern, the patients who may be at risk, and what we can do to prevent negative consequences from arising—and treat them if they do. In particular, I'll discuss anti-VEGF injections, vitrectomy surgery with or without tamponade, the use of a scleral buckle and the use of panretinal photocoagulation laser. (I won't discuss intravitreal or periocular steroid injections, because those are well known to cause an increase in IOP, and they've been extensively documented and discussed elsewhere.)

Anti-VEGF Injections

The idea of anti-VEGF medications comes from the oncology world. The premise was that tumors required a prominent blood supply to continue growing, and it was determined that this angiogenesis was a VEGF-mediated process. Retina specialists rapidly made the association that certain intraocular conditions like age-related macular degeneration were also VEGF-mediated processes. This led to the clinical trials studying ranibizumab, the off-label use of bevacizumab and ultimately the development of aflibercept.

Today, intravitreal injections of anti-VEGF drugs are increasingly common. The IRIS Registry shows that 524,485 patients received 2,419,931 injections in 2016 alone. However, that increasing number of injections has drawn attention to their potential drawbacks—including the potential IOP-related consequences of injecting a volume of material into the eye.

From the beginning, everyone understood that pushing fluid into the eye can cause the pressure to increase in the short term. So, when we first started doing injections, doctors wouldn't let the patient leave the office immediately afterwards; they'd repeatedly check the pressure for 30 or 40 minutes to make sure the pressure had come back down to a reasonable range before allowing the patient to go home.

For a long time it was thought that those short-term post-injection pressure spikes were the only issue.[1-3] (For example, in one study IOP increased during the first hour post-injection and then dropped to only 2 to 3 mmHg higher than the baseline level within 60 minutes in most patients.[3]) But over time, subset analyses of the data from several clinical trials made it apparent that some of these patients did have long-term increases in IOP—presumably triggered by the injections.[4-6]

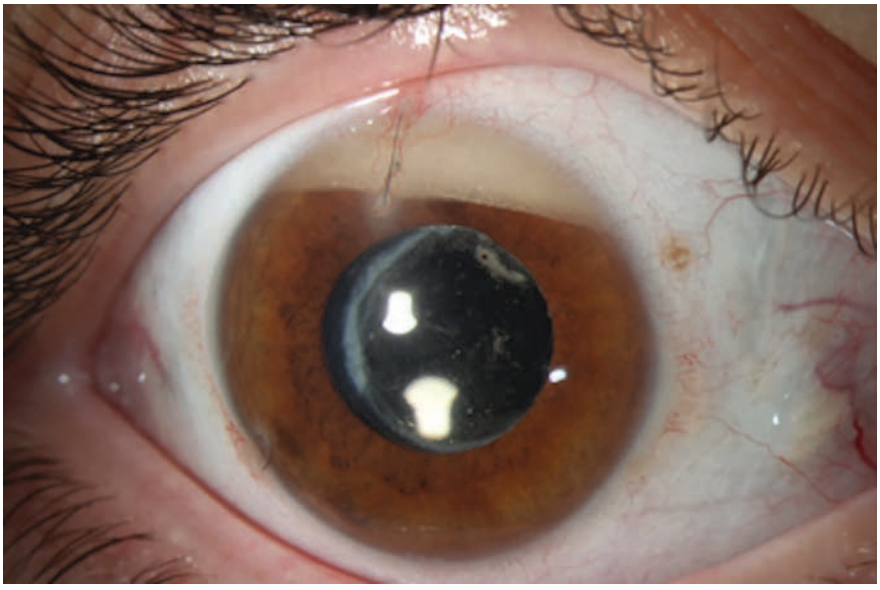
These factors raised a number of questions: Are glaucoma patients more likely to be affected long-term? Does the injection duration and/or frequency matter? Does anti-VEGF medication choice matter? Does the patient's underlying diagnosis matter? Does injection technique matter? And do preventive techniques work?

Who's at Risk?

At-risk populations were assessed in a meta-analysis of five relevant, randomized controlled trials.[7] (Related trials that weren't included in this meta-analysis were not random-

This article has no commercial sponsorship.

Dr. Singh is a professor of ophthalmology and chief of the Glaucoma Division at Stanford University School of Medicine. **Dr. Netland** is Vernah Scott Moyston Professor and Chair at the University of Virginia in Charlottesville.



Emulsified silicone oil that has migrated to the anterior chamber, resulting in a secondary increase in intraocular pressure.

ized and had enormous variation in the medications used, the number of injections given, and how they defined "increased pressure," making them difficult to analyze.) All of the randomized controlled trials included had at least three months of follow-up.

The meta-analysis revealed:

• About 5 percent of the injected patients seemed to be at risk for a sustained increase in IOP.

• The specific anti-VEGF medication used didn't seem to make a difference.

• A patient's susceptibility didn't change no matter how long the patient was followed.

• The underlying indication for the injection didn't seem to make a difference in the amount of pressure increase.

• Patients with a history of glaucoma were more likely to have a long-term pressure rise than their peers. That's not a surprise, because if patients already have glaucomatous damage they're more likely to be affected by a spike in IOP, such as the acute rise in pressure that follows an injection.

More recently, researchers used the IRIS Registry database to look at data from 23,776 patients who got injections either for macular degeneration or for macular edema associated with vein occlusion or diabetes, in 2013, 2014 and 2015.[8] This was a well-designed study that involved patients who got injections in one eye but not the other, making it possible to use the other eye as a control. The study authors included patients who received multiple injections of bevacizumab, ranibizumab or aflibercept; they assessed the change in IOP at the one-year mark to see how many of those patients had a significant increase in IOP. (A significant increase was defined as a rise of 6 mmHg over baseline to a pressure above 21 mmHg.)

Their findings included:

• For all groups there was a mean decrease in IOP of almost 1 mmHg in the treated eye and 0.2 mmHg in the fellow (untreated) eye.

• At one year about 2.6 percent of patients had a clinically significant increase in pressure in the treated eye. (About 1.5 percent of patients had a clinically significant pressure increase in the control eye as well.)

• There was a statistically significant difference in pressure increase associated with ranibizumab and bevacizumab compared to aflibercept (a 2.8-percent increase for the first two drugs, but a 1.9-percent increase for the latter). However, it's hard to know why this difference occurred or what the clinical significance might be.

Our group has also investigated some other factors that could, in theory, impact whether IOP increases following an injection. One such factor is the way in which the surgeon deals with the possibility of reflux of fluid from the injection site. Basically, when you give an injection into the eye, there tends to be some reflux at the injection site because the pressure gets so high. (One study found that, following an intravitreal injection, there was an almost 20 mmHg difference in IOP between eyes that experienced reflux and those that didn't.[9])

Since then, we've given more weight to the fact that reflux is a way for the pressure to more rapidly equilibrate. Patients who have no reflux—or in whom reflux is prevented—have a much greater increase in IOP immediately afterwards.

Mitigating the Pressure Increase

Of course, there are numerous ways to manage an increase in intraocular pressure, some of which can be useful in this situation. For example, we know that giving topical antihypertensive drops 20 or 30 minutes before the injection reduces the amount of pressure increase following an injection. *(See graph, p. 65.)*

Another management option is to perform an anterior chamber paracentesis and withdraw some aqueous fluid from the anterior chamber either prior to or immediately following the injection; this blunts the rise in IOP that you get from the intravitreal injection. However, it's important to know that anterior chamber taps have the potential to lead to complications. There have been occasional reports of unintended consequences such as hitting the lens when creating an anterior chamber paracentesis, so it's important to consider the risk/benefit ratio

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INDICATION

EYSUVIS is a corticosteroid indicated for the short-term (up to two weeks) treatment of the signs and symptoms of dry eye disease.

IMPORTANT SAFETY INFORMATION

Contraindication:

EYSUVIS, 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, and also in mycobacterial infection of the eye and fungal diseases of ocular structures.

Warnings and Precautions:

Delayed Healing and Corneal Perforation: Topical corticosteroids have been known to delay healing and cause corneal and scleral thinning. Use of topical corticosteroids in the presence of thin corneal or scleral tissue may lead to perforation. The initial prescription and each 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.

Intraocular Pressure (IOP) Increase: Prolonged use of corticosteroids may result in glaucoma with damage to the optic nerve, as well as defects in visual acuity and fields of vision. Corticosteroids should be used with caution in the presence of glaucoma. Renewal of the medication order should be made by a physician only after examination of the patient and evaluation of the IOP.

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

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

Viral Infections: Use of a corticosteroid medication in the treatment of patients with a history of herpes simplex requires great caution. Use of ocular corticosteroids 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 corticosteroid application. Fungus invasion must be considered in any persistent corneal ulceration where a corticosteroid has been used or is in use.

Adverse Reactions:

The most common adverse drug reaction following the use of EYSUVIS for two weeks was instillation site pain, which was reported in 5% of patients.

Please see Brief Summary of Prescribing Information for EYSUVIS on the next page.

References: 1. Brazzell RK, Zickl L, Farrelly J, et al. Prevalence and characteristics of dry eye flares: a patient questionnaire survey. Presented at: AAO 2019; October 12-15, 2019; San Francisco, CA. **2.** Brazzell RK, Zickl L, Farrelly J, et al. Prevalence and characteristics of symptomatic dry eye flares: results from patient questionnaire surveys. Poster presented at: AAOPT 2019; October 23-27, 2019; Orlando, FL. **3.** 2020 Study of Dry Eye Sufferers. Conducted by Multi-sponsor Surveys, Inc.

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

Risk of Contamination—Do not to allow the dropper tip to touch any surface, as this may contaminate the suspension.

Contact Lens Wear—The preservative in EYSUVIS may be absorbed by soft contact lenses. Contact lenses should be removed prior to instillation of EYSUVIS and may be reinserted 15 minutes following administration.

ADVERSE REACTIONS

Adverse reactions associated with ophthalmic corticosteroids 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.

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 most common adverse reaction observed in clinical trials with EYSUVIS was instillation site pain, which was reported in 5% of patients.

USE IN SPECIFIC 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 1.4 times the recommended human ophthalmic dose (RHOD) and to pregnant rats at doses 34 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 3.4 times the RHOD. Maternal toxicity was observed in rats at doses 347 times the RHOD, and a maternal no observed adverse effect level (NOAEL) was established at 34 times the RHOD.

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 (1.4 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 (5.6 times the RHOD). At 3 mg/kg (41 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 (83 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 (34 times the RHOD); and cleft palate, agnathia, cardiovascular defects, umbilical hernia, decreased fetal body weight and decreased skeletal ossification at 50 mg/kg (347 times the RHOD). Embryofetal lethality (resorption) was observed at 100 mg/kg (695 times the RHOD). The NOAEL for developmental toxicity in rats was 0.5 mg/kg (3.4 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 (3.4 times the clinical dose), reduced survival was observed in live-born offspring. Doses ≥ 5 mg/kg (34 times the RHOD) caused umbilical hernia/incomplete gastrointestinal tract. Doses ≥ 50 mg/kg (347 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 EYSUVIS and any potential adverse effects on the breastfed infant from EYSUVIS.

Pediatric Use—Safety and effectiveness in pediatric patients have not been established.

Geriatric Use—No overall differences in safety and effectiveness have been observed between elderly and younger adult 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 thymidine kinase (tk) assay, in a chromosome aberration test in human lymphocytes, or *in vivo* in the single dose mouse micronucleus assay. Treatment of male and female rats with 25 mg/kg/day of loteprednol etabonate (174 times the RHOD based on body surface area, assuming 100% absorption) prior to and during mating caused pre-implantation loss and decreased the number of live fetuses/live births. The NOAEL for fertility in rats was 5 mg/kg/day (34 times the RHOD).

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before employing this strategy.

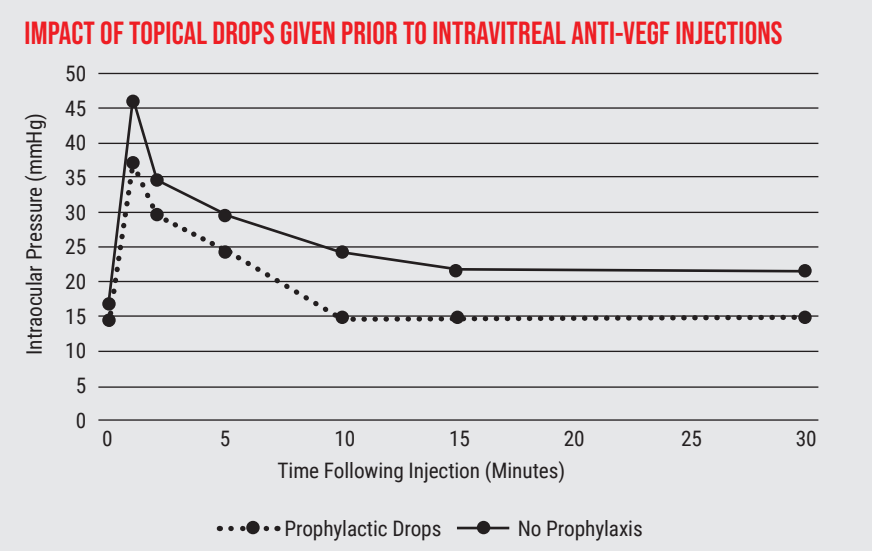
In general, I wouldn't consider creating a paracentesis routinely; the rate of developing a sustained increase in pressure following an injection is so low that this probably isn't warranted. On the other hand, there are select patients for whom using this approach routinely might be beneficial. If you have a patient with a history of glaucoma, and either the pressure has started to go up or the glaucoma specialist is starting to see changes in the visual field, it might be worth performing an anterior chamber tap to mitigate any pressure increase. In these individuals, having the pressure go from the 10- to 15-mmHg range up to 30 or 40 mmHg—even just for 15 or 20 minutes—could cause some lasting damage to the nerve. I have five or six patients like this for whom I routinely perform an anterior chamber tap before an injection, because they've had long-lasting increases in pressure previously.

To summarize what we know about the connection between anti-VEGF injection and long-term IOP increases:

- Glaucoma patients are most likely to be at risk.
- The underlying reason a given patient needs anti-VEGF injections doesn't seem to make a difference.
- The way the injection is performed can make a difference.
- It's not yet clear whether the choice of anti-VEGF drug or the frequency of injections makes a difference.
- Steps taken to lower pressure before or after the injection are effective.

Retinal Surgeries: Vitrectomy

Several retinal surgeries are sometimes followed by increased IOP. In particular, this is sometimes seen following vitrectomy, with or without a tamponade; following the placing of a scleral buckle; and after panretinal laser photocoagulation. Let's look more closely at each of these.



One way to limit the pressure rise following anti-VEGF injections is to give prophylactic topical drops before the injection. (Data drawn from a review conducted by Peter Bracha, MD, et al, 2018.[9])

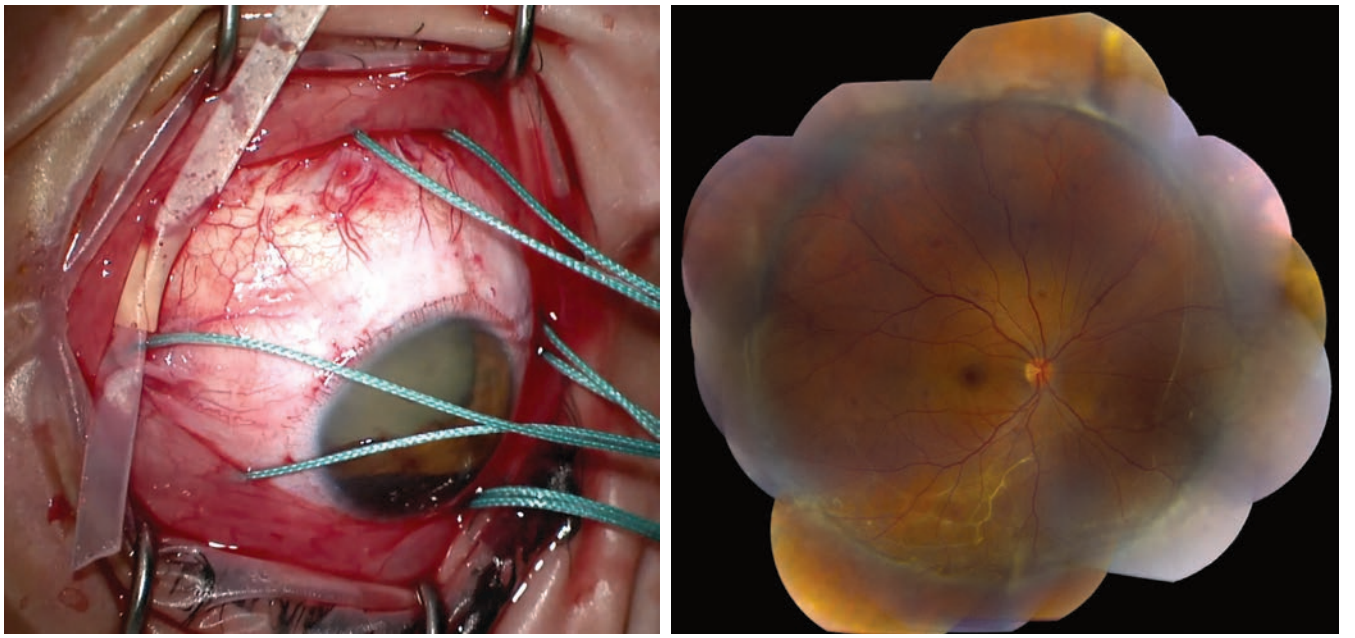
A 2019 population-based study looked at the likelihood of glaucoma developing in age-matched patients who underwent scleral buckle, scleral buckle with vitrectomy, or vitrectomy only.[10] The data showed that about 9 percent of patients undergoing a vitrectomy, with or without a scleral buckle, ultimately developed some level of glaucoma. (For comparison, only 1 percent of the general population who didn't undergo any of these surgical interventions developed glaucoma.) The study concluded that vitrectomy can be associated with increased IOP.

There's reason to believe that using a gas or oil injection (i.e., a tamponade) to help keep the retina flat postoperatively may contribute to the rise in pressure. (More about the reasons for that shortly.) However, in this study, many of the patients had epiretinal membranes, meaning they would definitely not have received a tamponade. Those patients still showed an increased rate of developing glaucoma after the surgery.

What might explain this? Sometimes anterior vitreous is left in the eye, especially in phakic patients. That can allow aqueous misdirection to occur, where the ciliary body can become rotated; the pressure can go up significantly, the anterior chamber can shallow and uveal effusions can happen. Sometimes this can lead to extensive damage.

A chronic increase in IOP following vitrectomy is probably related to inflammation. Significant anterior chamber inflammation may occur in diabetic patients, or when the surgery was lengthy; that inflammation can result in blockage of the trabecular meshwork. Normally, once the inflammation calms down, the pressure drops. However, if the inflammation continues for a while, posterior synechiae can develop, causing pupillary block. That can prevent aqueous from leaving the eye, resulting in a pressure increase.

Furthermore, in some of the conditions that lead to the need for vitrectomy in the first place, such as diabetic retinopathy or vein occlusions that have led to neovascularization, inflammation from the surgery can cause the neovascularization to worsen. That can block the angle and cause the pressure to increase. Finally, some level of oxidative stress happens during the surgery. That can cause some inflammation, or even direct damage to the



Left: An intraoperative image of a 360-degree-encircling scleral buckle with sleeve in place, before tightening the band. Right: A montage color fundus photo of a patient with a history of a chronic inferior retinal detachment and subretinal fibrotic bands, demonstrating retinal reattachment after scleral buckle placement.

trabecular meshwork, which will increase the resistance and reduce the outflow.

Tamponades

Tamponades, often used after vitrectomy to hold retinal tissue in place while it heals, can also cause elevated IOP in some situations. Sometimes the tamponade is accomplished with a gas bubble inside the eye, sometimes with silicone oil. Each option has its own caveats.

The two main types of gas that are used—sulfur hexaflouride and perflouropropane—are both expansile gases that in certain concentrations gradually increase in volume over time. (The former doubles in volume by 24 hours at 25-percent concentration; the latter quadruples in volume by 48 hours at 18-percent concentration.) This can be advantageous, because gas gradually dissipates from the eye; if the gas that remains is gradually expanding, the support it provides will continue for a longer time.

However, this characteristic can backfire. If you put too much gas into the eye, the tendency to expand can cause an increase in IOP. Or, if the concentration you use is incorrect, that can affect the volume doubling or quadrupling time and cause the pressure to increase. (A similar problem can occur if the patient travels via airplane; the change in altitude during flight changes the expansile properties of the gas, increasing the likelihood that the gas will expand more than we want it to. That's why we always tell patients that they can't fly with a gas bubble in the eye.)

The benefit of using a gas tamponade is that it dissolves on its own, so there's no need for additional surgery to remove it. However, there are some situations—such as when there's a significant amount of scarring or a lot of damage to the retina—in which you need a longer-lasting tamponade. In that situation, silicone oil may be the best choice. It's beneficial in the sense that it will stay in the eye until you do another surgery to remove it, and it will keep the retina attached while it's in there. However, there are some potential toxic effects. For example, if the oil flows in front of the iris it can block and eventually close the trabecular meshwork.

There's also the issue that the oil can sometimes break down or emulsify if it remains in the eye for an extended period. In that situation, some of it may seep forward and block the trabecular meshwork, eventually causing trabecular meshwork scarring and long-term damage. *(See image, p. 62.)* That's another reason we try to avoid using silicone oil if we can, reserving it for advanced cases with significant disease.

If the oil does end up interfering with outflow and the IOP increases, there are several possible ways to proceed:

- ***Topical anti-hypertensives are often helpful.*** In one series of 450 eyes with long-term silicone oil endotamponade, 11 percent developed increased IOP; most (78 percent) were treated only with glaucoma medications.[11]
- ***Create an inferior peripheral iridotomy.*** If the patient in this situation is pseudophakic, this is another approach that may help. (Usually a PI isn't necessary in a phakic eye because a natural lens is larger than a pseudophakic lens; it tends to do a good job of keeping the oil in the back of the eye.) The PI allows

Apellis is exploring the role of complement in Geographic Atrophy[1]

C3 is the linchpin of complement overactivation in GA.[2-7]

All three complement pathways converge at C3 and it drives multiple downstream effects — inflammation, opsonization, and formation of the membrane attack complex — all of which can ultimately lead to retinal cell death. Increased levels of complement activity have been found not just in the lesion itself, but also in the area just outside the lesion, known as the pre-lesion.[2-9]

Scan the code to explore new territory with us at pre-lesion.com

Apellis

1. Katschke KJ Jr, et al. *Sci Rep*. 2018;8(1):13055. 2. Mastellos DC, et al. *Trends Immunol*. 2017;38(6):383-394. 3. Ricklin D, et al. *Immunol Rev*. 2016;274(1):33-58. 4. Heesterbeek TJ, et al. *Invest Ophthalmol Vis Sci*. 2020;61(3):18. 5. Seddon JM, et al. *Nat Genet*. 2013;45:1266-1370. 6. Yates JRW, et al. *N Engl J Med*. 2007;357(6):553-561. 7. Smailhodzic D, et al. *Ophthalmology*. 2012;119(2):339-346. 8. Boyer DS, et al. *Retina*. 2017;37:819-835. 9. Park DH, et al. *Front Immunol*. 2019;10:1007.

aqueous to come from behind the iris to in front of the iris and the pupil, where it helps to push back and block the oil from coming forward. It's a little counterintuitive.

Because oil floats, it would tend to rise in the anterior chamber and block a superior PI. So, the PI would be placed inferiorly in one of these patients.

• ***Remove or replace the oil.*** If the oil in an eye is starting to emulsify, and the retina is now stable, then you can perform surgery to remove the oil. However, if the retina has appreciable scar tissue, or it appears that it may re-detach, then you may need to do an oil exchange. (In this situation you may need to do this periodically as the oil breaks down.)

• ***Place a tube.*** Sometimes this works to relieve the elevated pressure. However, although a tube would normally be placed superiorly, in this situation an inferior quadrant is recommended, for the same reason we'd place a PI inferiorly.[12] Oil rises, so if you place the tube superiorly, the oil can go into the tube and either migrate out of the eye through the tube or block the tube completely.

In addition to inferior quadrant placement of the implant, viscoelastic during surgery can prevent intraoperative loss of oil while the patient is in the supine position. Patients may need longer-duration treatment with steroids during the postoperative period.[12]

• ***Perform cyclophotocoagulation.*** If you can't remove the oil, this can help by partially shutting down the ciliary body so it doesn't produce as much aqueous. However, this option is pro-inflammatory, so it can create issues of its own.

Scleral Buckle and Laser

Another retinal treatment that can result in an elevated IOP is the placement of a scleral buckle, in which we place a band 360 degrees around the eye. Usually, the squeezing of the eye elevates the pressure, but only in the short term. That can cause the anterior chamber to shallow, but it's rare that the shallowing is so significant that it causes angle closure. However, sometimes the buckle can be so tight that it affects the blood flow to the eye; that ischemia can lead to inflammation and choroidal effusions or neovascularization, either of which can increase the IOP.[13]

Usually, corticosteroids, topical anti-hypertensives and cycloplegia are sufficient to address the IOP increase caused by a scleral buckle. Laser iridoplasty may be needed in rare cases. It's rare that the encircling band needs to be loosened or removed because of the pressure increase.

The final treatment on the list is the use of panretinal photocoagulation for proliferative diabetic retinopathy. In that case, the laser can be pro-inflammatory and cause the choroid to swell a little bit, pushing everything forward. If the lens-iris diaphragm is pushed forward,

that can lead to angle closure. Furthermore, it's possible for the laser to damage the short ciliary nerves, causing decreased ciliary muscle tone, as well as the release of prostaglandins.

Usually, these effects are transient because the amount of laser and inflammation is fairly limited. As a result, you can often achieve prophylaxis by using a dilating drop and steroid drops.

Working Wisely

As our treatments evolve and proliferate, we must always be on the lookout for unintended consequences of their use—including elevations in IOP. By remaining aware, being careful and maintaining good communication between specialties, we can help ensure that all our patients get the best outcomes possible.

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ERM After Vitrectomy For RRD Repair

Researchers in Japan studied patient records to analyze the factors related to the development of epiretinal membranes after pars plana vitrectomy surgery for the repair of retinal detachment.

The investigators reviewed 2,239 cases treated with PPV for RRD repair registered in the Japan Retinal Detachment Registry between February 2016 and March 2017. They used univariate analysis to analyze associations of 13 baseline characteristics and eight surgical procedures with ERM formation. The researchers report that ERM had developed in 104 cases (4.6 percent) by six months.

They found that drainage retinotomy was significantly associated with ERM (odds ratio: 2.22 [95% confidence interval: 1.50-3.31]; $p<0.001$). In the propensity score-matched analysis (n=492 in each group), the researchers confirmed a significant difference in the incidence of ERM after six months of vitrectomy (8.3 percent and 2.6 percent in cases with and without drainage retinotomy, respectively; OR 3.35 [95% CI 1.77-6.33]; $p<0.001$).

The researchers say that, though a drainage retinotomy is now less frequently used because of the increased use of microincision vitrectomy surgery with a wide-angle viewing system, and the availability of perfluorocarbon liquid, 677 cases (30.3 percent) still underwent drainage retinotomy between 2016 and 2017 in the J-RD Registry. They say that knowledge of the increased risk of macular pucker after a drainage retinotomy may help surgeons reconsider its application and case selection. In addition, they say, prophylactic ILM peeling may be necessary in the cases that undergo drainage retinotomy, to avoid a reoperation for ERM removal.

Am J Ophthalmol 2022;234: 20–27.
Ishikawa K, Akiyama M, Mori K.

Predicting the Outcome of SLT

Researchers in New Delhi, India, sought to evaluate whether the presence of angle dysgenesis—defined as the absence of Schlemm's canal and/or the presence of a hyperreflective membrane over the trabecular meshwork, as determined on anterior segment optical coherence tomography (ADoA)—could be a predictive factor in determining the outcome of selective laser trabeculoplasty treatment.

They conducted a prospective clinical cohort study involving 35 patients with juvenile-onset open-angle glaucoma and uncontrolled intraocular pressure, who didn't show angle dysgenesis on gonioscopy. After evaluation for ADoA using AS-OCT, the subjects underwent SLT. Successful SLT treatment was defined as a reduction of IOP by 20 percent or more from the pre-laser value at six-month follow-up, without any further IOP-lowering medication or surgery. (One repeat SLT during the six-month period was admissible.)

A successful reduction in IOP at six-month follow-up was then correlated with the extent of ADoA. Furthermore, the number of AS-OCT B-scans in which Schlemm's canal was identified as present were quantified.

Findings included:

- In comparison to pre-SLT IOP, 57.1 percent of eyes (20/35) showed a more than 20-percent reduction in IOP at six months, with a mean reduction of 7.6 ±1.8 mmHg (29.6 percent).
- When all three observers agreed, SC was identified in 90 percent of eyes that were succesfully treated (18/20), vs. 26.6 percent of eyes that failed (4/15) ($p<0.001$).
- All five eyes with a hyperreflective membrane showed treatment failure ($p<0.001$).
- All 19 eyes in which SC was present in more than 50 percent of ASOCT B scans showed treatment success ($p<0.001$).
- On a bias-reduced regression analysis, the identification of SC on any two consecutive scans increased the chances of SLT treatment success at six months by 8.3 times. The identification of SC in more than 50 percent of AS-OCT scans was associated with a 21.4 times greater chance of success.

The authors concluded that the presence of SC on AS-OCT is a strong predictor for successful IOP reduction after SLT in JOAG eyes.

Am J Ophthalmol 2022;234:126-137.
Varshney T, Azmira K, Gupta S, et al.

Vision After Macula-off vs. Macula-on Detachment Repair

Researchers in the United Kingdom recently investigated the relationship between retinal anatomic characteristics, visual acuity and perimetric retinal sensitivity in patients following retinal reattachment surgery, finding that the central outer nuclear layer and outer retinal segment thinning correlated with decreased retinal

sensitivity and may be explained by rhegmatogenous retinal detachment photoreceptor death. They noted there was greater thinning following macula-off RRD compared with macula-on RRD.

The study assessed 13 macula-on and eight macula-off patients before and six months after vitreoretinal surgery. The researchers recorded the OCT thickness of the outer nuclear layer, outer retinal segment, retinal pigment epithelium to the ellipsoid zone, and external limiting membrane to the ellipsoid zone at six months post-op. They then compared their findings with BCVA and retinal sensitivity.

The mean outer nuclear layer thickness was higher after macula-on RRD compared with macula-off (97.7 µm vs. 73.1 µm). Central outer nuclear layer thickness was strongly associated with retinal sensitivity and less strongly with BCVA. In all RRD eyes, every 1-µm decrease in outer nuclear layer thickness correlated with a 0.052-dB decrease in retinal sensitivity, and every 1-µm decrease in outer retinal segment thickness was associated with a 0.062-dB reduction in retinal sensitivity. The other thickness measurements didn't correlate with BCVA post-retinal reattachment surgery.

The researchers said they believe that retinal detachment causes photoreceptor apoptosis and that foveal cone morphology after reattachment correlates with VA.

"The associations between outer nuclear layer thickness and retinal sensitivity and visual acuity support the hypothesis that photoreceptor apoptosis after macula-off retinal detachment contributes to reduced visual function," they noted in their paper.

However, because they used clinical examination to distinguish macula-off and macula-on RRD, it's possible that some macula-on RRD patients might have had subclinical subretinal fluid in the macula. This possibility limits the study's ability to make distinctions between the relationships in macula-on as opposed to macula-off RRD.

Graefes Arch Clin Exp Ophthalmol 2022, Jan 26. [Epub ahead of print].
Rasool S, Kaushik M, Chaudhary R, et al.

Color-vision Deficiency and Myopia in Children

Scientists explored the relationship between color vision deficiency, myopia progression and axial elongation in Chinese primary school children during a five-year cohort study.

A total of 2,849 grade one students (ages 7.1 ±0.4 years) from 11 primary schools were enrolled and followed for five years. Cycloplegic autorefraction and axial length were measured annually. Color vision testing was performed annually using Ishihara's test and the City University color vision test.

Here are some of the findings:

- The prevalence of color vision deficiency was 1.68 percent (2.81 percent in boys and 0.16 percent in girls).
- Color-deficient cases consisted of 91.6 percent deutan and 8.3 percent protan.
- The cumulative incidence of myopia was 35.4 percent (17/48) in the color-vision deficiency group, which was lower than 56.7 percent (1,017/1,794) in the normal group (p=0.004).
- The change in spherical equivalent refraction in the color vision deficiency group (-1.81 D) was also significantly lower than that in the normal group (-2.41 D) (p=0.002).

Scientists wrote that the lower incidence and slower progression of myopia in children with color vision deficiency over the five-year follow-up period suggests that color-deficient individuals were less susceptible to myopia onset and development.

IOVS 2022;2;63:2:2.
Gan J, Li SM, Atchison DA, et al.

Retinal Imaging May Help Predict Heart-attack Risk

New research suggests retinal imaging may be capable of identifying patients at high risk for heart attack based on retinal biomarkers associated with cardiac function, such as retinal blood vessel density and tortuosity.

To predict incident myocardial infarction, the researchers used a combination of retinal images and patient metadata to estimate left ventricle mass and end-diastolic volume in 5,663 qualifying subjects. Their models employed cardiovascular magnetic resonance imaging (end-diastolic, short-axis view), retinal imaging and demographic data from the U.K. Biobank imaging study.

They found the following, based solely on retinal images and demographic data:

- Mean left ventricle mass was 4.4 g.
- Mean left ventricular end-diastolic volume was 3.02 ml.
- Risk of myocardial infarction had an area under the curve of 0.8, a sensitivity of 0.74 and a specificity of 0.71.

"Our results indicate that one could identify patients at high risk of future myocardial infarction from retinal imaging available in every optician and eye clinic," the authors wrote in their paper. They noted that using cardiac indices and demographic data together (vs. using demographic data alone) can improve the prediction of heart attack incidence.

They tested their method on the AREDS dataset as well, reporting a slightly lower performance, but an overall discrimination capacity similar to that of established cardiovascular disease risk assessment models. "This highlights the potential for our approach to be employed as a second referral tool in eye clinics/opticians to identify patients at risk of future myocardial infarction events," they wrote.

Nature Machine Intel 2022;4:55-1.
Diaz-Pinto A, Ravikumar N, Attar R, et al.

DME Pipeline

(Continued from p. 60)

no drug-related serious adverse events.

The Rest of the Field

According to Dr. Lim, gene therapy is further down the pipeline. "I'm a little bit cautious about gene therapy, not just because some inflammatory reactions can develop, but primarily because you can't shut it down," she says. "Once you put an 'anti-VEGF factory' genetically into the eye, it's going to keep producing anti-VEGF, and we know that we need some VEGF for viability of tissues. So, until we learn how to modulate the 'factory' and learn more about the long-term outcomes, I'm less excited about that for diabetic applications."

David S. Boyer, MD, in practice in Los Angeles, believes that a multifactorial approach may be best. "You have longer-acting steroids that may be able to last six months," he notes. "We know steroids work, but they have a number of potential risks. Pills are interesting because if you have a pill that will reduce the diabetic retinopathy severity, it may also play a role systemically in kidney function or even neuropathy. So, I think, if you could take a pill rather than getting a shot, there may be greater acceptance. Several oral medications attacking different pathways (REF-1, connexin-43 channels, CCR5 eotaxin inhibitor, AOC3, CB receptor or the kallikrein pathway) are under development."

He adds that drops are being studied, but drops are exceedingly difficult to get to the back of the eye in a concentration sufficient to cause a marked improvement on a consistent basis. "They do work, but they're inconsistent, in that only 30 percent to 50 percent of patients improve," he says. "There have been several improvements in the delivery system of drops that may allow us to use drops in the future. Treatment comes down to several things: trying to reduce the treatment burden of the VEGFs; trying to reduce the number of patients who don't respond to therapy at the present time; and trying to treat earlier in the course of the disease to prevent vision-threatening complications. The earlier we can treat, the better chance we have of people keeping their vision. So, I think it's a multifactorial approach. Some are treating the macular edema, and some are treating to reduce the diabetic retinopathy severity so we can go earlier and possibly prolong or reduce the chances of the patient progressing." ◀

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Setting Up Today's Cataract & Refractive Surgeons for Success

By Thomas Harvey, MD

Optical biometry has long been a staple in the planning and follow-up of cataract and refractive surgeries, and like all technologies in healthcare today, biometers continue to evolve. While we may once have expected the biometer to simply provide information on axial length, keratometry, and anterior chamber depth to calculate for intraocular lens (IOL) powers, today's systems go well beyond these basics. For example, the Aladdin HW 3.0 Optical Biometer and Corneal Topographer (Topcon Healthcare; Tokyo, Japan) provides nine different parameter calculations in one device, and it does so on an instrument that is easy to use and has a conveniently small footprint.

For cataract and refractive practices with increasing surgical volumes looking to maximize workflow efficiency, or to add greater functionality and additional IOL calculation formulas, a new biometer featuring advanced technology such as state-of-the-art corneal topography and dynamic pupillometry can help to bring the practice to the next level. My practice has seen firsthand the benefits such a device can yield since we added the Aladdin a year ago.

Aladdin Optical Biometer and Corneal Topographer: At A Glance

The Aladdin HW 3.0 Optical Biometer and Corneal Topographer provides low coherence interferometry biometric readings for axial length, central corneal thickness, anterior chamber depth and crystalline lens thickness. Placido-ring topography provides anterior corneal curvature, shape and wavefront (Zernike) analysis. In addition, white-to-white and dynamic pupillometry are also offered. The device performs all relevant measurements to assist in IOL calculation and surgical planning, with different IOL calculation formulas, including the Barrett Suite, the Olsen formula, as well as other formulas for post-refractive surgery and toric IOL power calculations.

Supporting the Practice with the Right Technology

While most biometers are moving to a component model in this day and age, the Aladdin continues to be an entirely mobile, multi-modal device. The device offers a touch screen experience and software integration that eliminates the need for a keyboard and mouse.

> The efficiency of the Aladdin HW 3.0 for potential IOL upgrades to premium IOLs is one of its greatest advantages. Within seconds, I know exactly what is needed for the patient to achieve his or her visual goals. This is dictated into my EMR notes, including the exact model, power, and orientation of the lens. Even with post-corneal refractive surgery, the time savings are monumental.— Thomas Harvey, MD

While some will question the lack of swept-source OCT technology, I have found the device is more than capable of measuring axial length through my cataract patients. In addition, its native Placido topography capabilities provide detailed corneal information. Thanks to the onboard Barrett Suite, I can calculate toric implants faster than ever before. This device has increased the efficiency of my practice, is reproducible, simple to operate, and provides all the data I need.

Helping Cataract & Refractive Procedures to "Shine"

We use the Aladdin HW 3.0 for all anterior segment surgery applications. Our refractive surgeons love Placido topography, and this device provides top-shelf images with no extra time investment. Of course, cataract surgery is our number one procedure, and Aladdin shines with its biometry capacity. The software is a great tool to help me educate patients on astigmatism and its potential impact on uncorrected acuity.

Other benefits of the device include reducing the time to upgrade a basic IOL implant and calculate for a premium IOL option to less than one minute, and generating fewer transcription errors since all of the information is housed in the software. Our enhancement and explantation rate for premium IOL implants is less than 1% due to the accuracy of the device.

We also use the Aladdin for some refractive procedures, including laser vision correction, phakic IOLs, and refractive lens exchanges. It has excellent keratoconus detection software, which can help with potential ectasia patients. The automatic photopic and mesopic pupil information is valuable in both refractive and premium IOL surgeries.

Accelerating Toric and Multifocal IOL Calculation

I still remember the days when we would take information from the standard contact or immersion biometer using autorefractor/keratometer data and a topographic printout, to enter into online calculators to select our IOL powers. Not only was this process labor-intensive and prone to transcription errors, but it had to be done after the patient left the building, meaning if there was an error the patient had to come back to be remeasured.

With the Aladdin HW 3.0, I now have all upgraded implants calculated by the time the patient sees the scheduler. It literally takes seconds compared to more than 15 minutes per patient previously. This allows the entire team to be more efficient in sending orders and avoiding unnecessary callbacks and billing errors.

This device has been an "upgrade machine" in my practice: when the onboard topography plus Barrett Toric Calculator says 2 diopters of toricity correction is needed, I can educate the patient on the spot, so immediate value is realized and the ability to upgrade to a premium IOL increases so that the patient receives the best option for uncorrected visual correction postoperatively. The dynamic pupillometry data assists me in ruling-out patients that might not be good candidates for multifocal IOLs, helping to avoid patient dissatisfaction after the surgery.

Reaping Practice Benefits

The efficiency of the Aladdin HW 3.0 for potential upgrade patients is one of its greatest advantages. Within seconds, I know exactly what is needed for the cataract patient to achieve his or her visual goals. This is dictated into my EMR notes, including the exact model, power, and orientation of the lens. Even with post-corneal refractive surgery, the time savings are monumental.

Essential Tools for Today's Cataract & Refractive Practice

Today's fast-paced and competitive cataract and refractive surgical environment means that surgeons need the right tools to swiftly and efficiently move patients toward the best visual procedure that will ensure optimal results. These tools are no longer luxuries, but requirements for an advanced surgical practice.

At the heart of every cataract surgery procedure is the need to perform biometry of different ocular structures. To be able to obtain detailed corneal information using an advanced Placido topography system that can read 6,200 points on the cornea, as well as crystalline lens thickness, white-to-white, anterior chamber depth, and dynamic and static pupillometry in a single measurement offers valuable insights—all in one place.

Moreover, the availability of numerous IOL calculations via different formulas, including the Barrett Suite and Olsen formula, opens the door to improved refractive results in all types of eyes. Using standard toric IOL calculators adjusted by the Abulafia-Koch formula can significantly reduce errors in predicting residual astigmatism.[1] And having a toric IOL calculator built into the existing software not only saves time but can prevent errors, helping to pave the way for a successful cataract surgery.

All of these capabilities are now integrated into one device, the Aladdin HW 3.0 Optical Biometer and Corneal Topographer from Topcon Healthcare (Tokyo, Japan). The device provides cataract and refractive surgeons with advanced technology to aid them in achieving successful procedures and a more efficient practice.

1. Abulafia A, Koch DD, Wang L, et al. New regression formula for toric intraocular lens calculations. J Cataract Refract Surg. 2016 May;42(5):663-71.

I have found the device to be on par with popular swept-source biometers in the US in terms of reproducibility for basic IOL implantation as well as premium IOLs. There are so many good biometers today, but I cannot understand why anyone would pay twice as much for another machine that is more time-consuming, offers fewer features, and takes up the entire corner of a room.

We chose the Topcon Aladdin HW 3.0 for its total package of portability, performance, and price. It is the one irreplaceable device for our cataract and refractive surgery patients.

Thomas Harvey, MD, is a fellowship-trained eye surgeon, specializing in surgical vision correction and medical ophthalmology, and owner of Independent Vision Group, based in Eau Claire, Wis.

PRODUCT NEWS

New items on the market to improve clinical care and strengthen your practice.

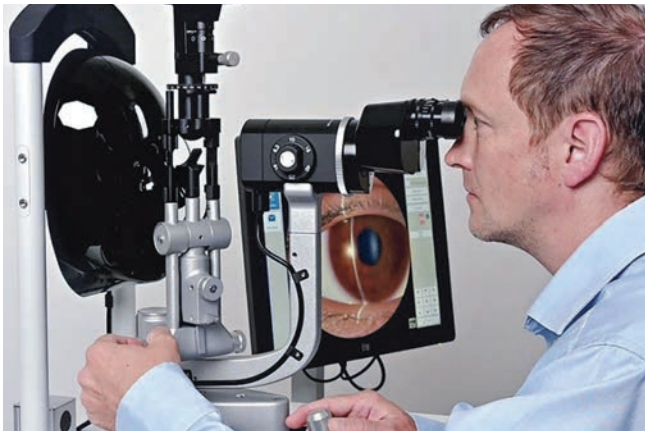
TRAINING

Slit Lamp Simulator Goes Gonio

Haag-Streit says its EyeSi Slit Lamp Simulator now offers a gonioscopy module.

The simulator integrates virtual reality technology into the original hardware of a BQ 900 model slit lamp and simulates all functions of the real slit lamp, the company says. Looking through the simulator's biomicroscope and using the slit lamp controls, trainees see the visualization of a virtual patient's eyes. Software modules provide various patients presenting with healthy eyes or clinically relevant pathologies. For visualization of the iridocorneal angle, a gonioscopy lens mimic is now available with the new gonioscopy module. Haag-Streit says pathologies included in the new module include pseudoexfoliation syndrome, iris nevus and iris melanoma. To practice grading the angle, the Shaffer-Kanski and Spaeth classification systems are available.

For information, visit https://www.vrmagic.com/medical-simulators/eyesi-slit-lamp.



OCULAR SURFACE

Generic Restasis Approved

Viatris recently announced that its subsidiary, Mylan Pharmaceuticals, has received approval from the FDA for its Abbreviated New Drug Application (ANDA) for Cyclosporine Ophthalmic Emulsion 0.05%, the first generic version of Allergan's dry-eye drug Restasis. The company says the drug will be "launched immediately."

For information, visit viatris.com.

EYEWEAR AND OPTICAL

New AR Coating Improves Contrast Sensitivity

A common complaint from spectacle wearers—and whoever may be talking to them—is the distracting reflections caused by light rays "bouncing off" the lenses of their glasses. Thankfully, lens manufacturers have long used anti-reflective coatings to reduce reflections and improve overall visual quality. One such company, Shamir Optical, recently launched a new AR coating called Glacier Expression that it touts as something even better than existing products.

According to Shamir, people wearing glasses coated with Glacier Expression demonstrated a 25-percent increase in contrast sensitivity vs. standard AR coating (no brand was specified), leading to improved reaction times during daily activities such as night driving. The company says the new coating also improves how wearers look to others—thereby improving person-to-person connection—and how their eyes feel, by reducing eyestrain.

In addition, Shamir Insight just announced an update to its Autograph Intelligence progressive lens design that the company says better reflects real-world visual needs, particularly during computer use. Visit https://shamir.com/us.

Stay on Top of Patients' Vision Plans

If you've got an optical shop in your office, First Insight has coupled its EHR system MaximEyes with GPN's EdgePro financial analysis software to help you keep better track of your business. First Insight says this new integration provides eye-care professionals with "real-time practice analytics that will empower doctors and staff to learn more about their business while maximizing revenue."

With the EDGEPro and MaximEyes integration, doctors and staff use an application programming interface that

automatically pulls data from the practice management system into EDGEPro nightly, so it's ready when they need it, the company says. First Insight says, "EDGEPro lets you customize dashboards, find lost opportunities, manage frame boards, analyze managed vision care (MVC) plans and track staff performance."

For information, visit https://www.first-insight.com/blog/edgepro-practice-analytics-maximeyes-empowers-eyecare/.

▸ TESTING AND PLANNING

Glaucoma- and Retina-specific Testing Protocols

Recently, M&S Technologies announced a roll-out of six new enhancements for their Clinical Trial Suite (CTS), the DVA-5000, that the company says specifically address the needs of glaucoma and retina trial sponsors and researchers. The company claims that these automated testing protocols are more efficient and accurate than traditional testing methods.

M&S' CTS modules already feature multiple visual acuity and contrast sensitivity function testing algorithms, all of which adhere to the ANSI and ISO standards and are recognized by the Food and Drug Administration for all clinical trial phases, including PMA trials. The company says that using their testing protocols can save trial sponsors and researchers significant time, as well as reduce the risk of erroneous data due to human error by calculating results automatically. CTS test results are available as a letter score, logMAR acuity notation, decimal score and Snellen equivalent. The company says that secure reports are immediately available in XML or CSV format to export to a reading center or other location.

For information, visit mstech-eyes.com.

LKC Technologies Launches Enhanced PhNR Protocol

LKC has launched a protocol enhancement for the RETeval, a handheld, full-field, non-mydriatic ERG testing device, that the company says helps hone the accuracy of the machine.

LKC says the new algorithm provides a 4-times improvement in test/retest variability, and a normative reference range that's 1.7-times narrower. The result is a "more sensitive tool aiding in the detection of abnormal ganglion cell function," the company states.

The company says the device is easy-to-use and comes with a large reference data set for straightforward interpretation. It requires no corneal contact, dilation or anesthetic for most tests, including this new PhNR protocol, LKC says.

For information, visit https://lkc.com/products/reteval/.

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A 53-year-old woman presents with a choroidal mass in the right eye.

MARK S. PYFER, MD, AND CAROL L. SHIELDS, MD
PHILADELPHIA

Presentation and Initial Work-up

Two months prior to presentation, the patient noticed intermittent flashes of light in both eyes. She initially presented to her primary ophthalmologist, who discovered a hypopigmented choroidal lesion in the mid-periphery of the right eye. There was concern for amelanotic choroidal melanoma, and she was referred to the Ocular Oncology Service for further evaluation. Upon presentation to the clinic, she reported intermittent photopsia in both eyes, without floaters. She denied changes in vision, loss of vision, metamorphopsia, pain or other symptoms.

Medical History

Upon initial review, she reported a past medical history of type 2 diabetes mellitus, hypertension, hyperlipidemia, osteoarthritis, kidney stones and vertigo. Her current medications included metformin, sitagliptin, glimepiride, insulin detemir, lisinopril, atorvastatin, aspirin, magnesium, naproxen and meclizine. She denied a personal history of skin cancer or other known malignancy. She reported a surgical history of bilateral cataract extraction two years earlier, right breast mass biopsy (reportedly benign), hysterectomy for fibroids 18 years ago and left oophorectomy for ovarian cyst 16 years ago.

Family history was significant for glaucoma (maternal grandmother, mother, sister), breast cancer (sister, multiple aunts), colon cancer (maternal grandmother, paternal grandfather), and unspecified brain tumor (maternal grandmother). Social history was negative for tobacco, alcohol or other substance use.

What is your diagnosis? What further work-up would you pursue? The diagnosis appears on p. 80.

A PUBLICATION BY REVIEW of OPHTHALMOLOGY

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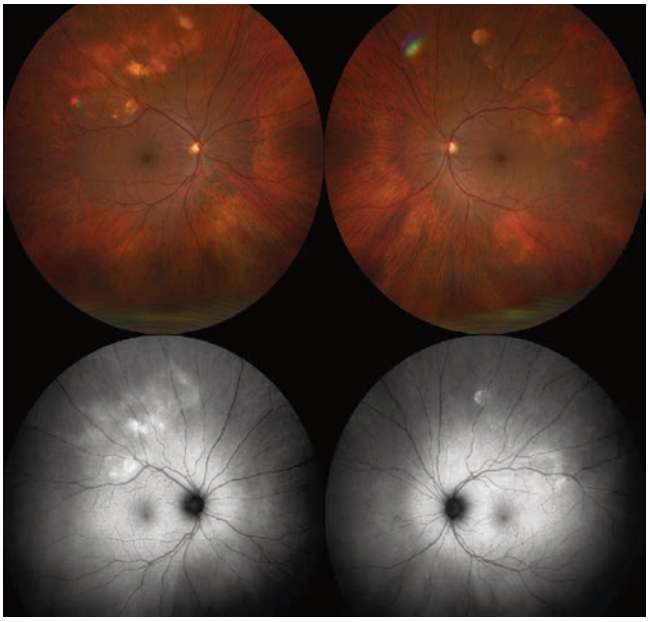

Figure 1. (Top) Color fundus photos demonstrate geographic, yellow/white choroidal mass in the superotemporal mid-periphery of both eyes. (Bottom) FAF shows the lesions to be hyper-autofluorescent.

Ocular examination demonstrated a visual acuity of 20/20 in each eye. Pupils were found to be 3 mm, round and reactive without a relative afferent pupillary defect in either eye. Intraocular pressure was 13 mmHg and 18 mmHg in the right and left eye, respectively. Extraocular motility and confrontation visual fields were full in both eyes. External examination was within normal limits and there was no evidence of melanocytosis or iris heterochromia in either eye. Slit lamp examination revealed posterior chamber intraocular lenses with mild posterior capsular opacification in both eyes.

Dilated fundus examination of the right eye demonstrated a geographic, yellow/white choroidal mass in the superotemporal mid-periphery measuring 10x7 mm *(Figure 1)*. In the left eye, similar lesions were noted in the superotemporal mid-periphery measuring 12x7 mm (*Figure 1*). Examination was also notable for partial posterior vitreous detachment in the right eye. Otherwise, the vitreous, optic disc, vessels, macula and peripheral retina were within normal limits in both eyes.

To further evaluate these amelanotic lesions, the patient underwent fundus autofluorescence imaging, optical coherence tomography and B-scan ultrasonography of both eyes. FAF showed hyper-autofluorescence

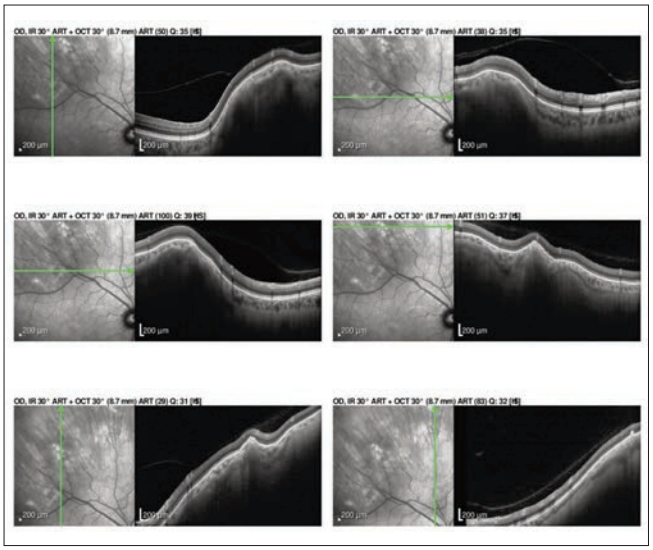

Figure 2. Enhanced depth imaging OCT of the lesions show abrupt rounded and jagged scleral thickening with overlying choroidal and retinal external compression in both eyes.

in the distribution of the lesions in both eyes *(Figure 1)*. OCT demonstrated normal retinal thickness and architecture in the macula. However, enhanced-depth OCT imaging of the lesions revealed abrupt, round, jagged scleral thickening with overlying choroidal and retinal external compression in both eyes *(Figure 2)*. B-scan demonstrated the lesions to be placoid and markedly hyperechoic with dense shadowing in both eyes, suggestive of calcification (*Figure 3*).

Based on these findings, the patient was diagnosed with sclerochoroidal calcification in both eyes.

Upon more targeted questioning, the patient reported that five years prior she was found to have hypercalcemia on routine laboratory evaluation. Subsequent studies showed elevated urine calcium levels and elevated serum parathyroid hormone (PTH). She declined treatment at that time, but two years later was again found to have elevated serum calcium and PTH levels. She was diagnosed with a benign parathyroid adenoma which was surgically removed with resolution of the hypercalcemia.

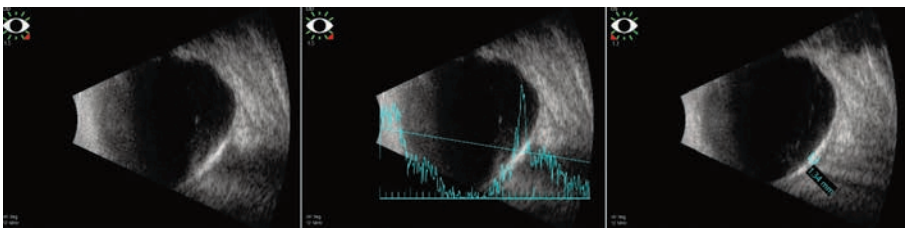

Figure 3. B-scan demonstrates the lesions to be placoid and markedly hyperechoic with a large A-scan spike and dense shadowing in both eyes.

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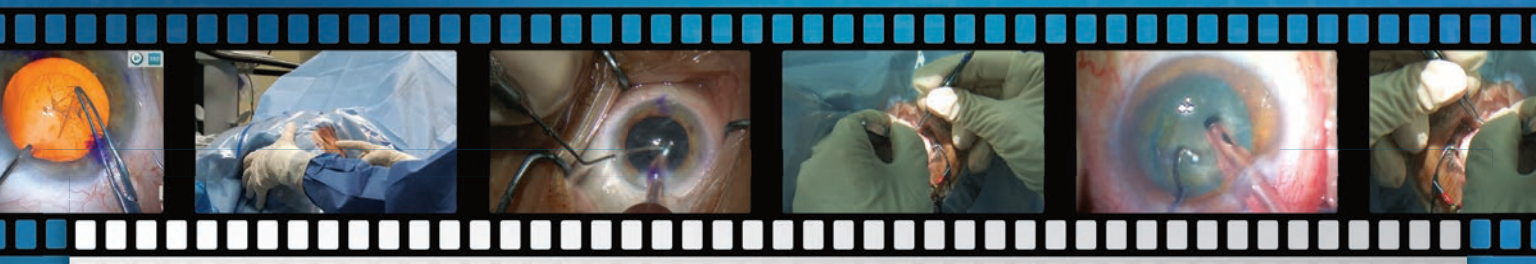

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Episode 75:
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Video Overview:
This relatively young patient with clinically obvious pseudoexfoliation and a poorly dilating pupil undergoes phacoemulsification after pupil enlargement and anterior capsule staining.

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Richard J. Mackool, MD

I am happy to announce an exciting addition as we continue into our seventh year of Mackool Online CME. This year, with the generous support of several ophthalmic companies, my son Dr. RJ Mackool and I will share the honor of presenting our surgical cases to you. Together we will continue to demonstrate the technologies and techniques that we find to be most valuable to our patients, and that we hope are helpful to many of our colleagues.

I will continue to narrate all of the cases, even as we share the surgical duties and thereby expand the variety of the cases that we bring to you. As before, one new surgical video will be released monthly, allowing our colleagues the opportunity to earn CME credits or just observe the case. New viewers are able to obtain additional CME credit by reviewing previous videos that are located in our archives.

I thank the many surgeons who have told us that they have found our CME program to be valuable and instructive; I appreciate your comments, suggestions and questions. Thanks again for joining us on Mackool Online CME.

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Discussion

Sclerochoroidal calcification (SCC) is a benign, uncommon condition in which calcium is deposited in the post-equatorial sclera, with secondary compression of the choroid and retina. Given its rarity, the true prevalence of SCC is unclear, but one estimate placed its incidence at around three to six cases per million. The mean age of presentation in one large case series of 118 affected patients was 69 years of age.

Nearly all cases of SCC are asymptomatic from an ophthalmic perspective and discovered on routine fundus examination.[1] Rarely, patients present with visual loss or metamorphopsia from retinal complications (discussed below). On dilated fundus exam, SCC typically appears as a yellow/white, flat/placoid lesion(s) at the level of the sclera.[2,3] Variable degrees of atrophy in the overlying choroid and retinal pigment epithelium impart a geographic or multifocal appearance.[2] The most common location for SCC is the superotemporal quadrant of the midperiphery, or just outside the retinal vascular arcades.[2] While it can be unilateral, SCC is frequently bilateral and somewhat asymmetric.[1,2]

Due to the rarity of this condition, several studies have focused on similar-appearing conditions such as choroidal nevus, choroidal melanoma, choroidal lymphoma, choroidal metastasis, choroidal osteoma and focal choroiditis.[2,3] In one reported case, a patient received radiation for suspected prostate cancer metastases that later were determined to be idiopathic SCC.[4]

The diagnosis of SCC is made with a combination of imaging modalities, most importantly indirect ophthalmoscopy and B-scan ultrasonography. On B-scan, SCC is intensely reflective, with dense shadowing visible even on low gain.[1,2,3] OCT, FAF and fluorescein angiography are also frequently obtained. Enhanced depth imaging OCT has been used to categorize SCC into four "mountain-like" types based on their characteristic appearance.[5] OCT is also useful for assessing disruption of the overlying choroid, RPE and retinal layers. FAF can be variable, but typically shows hyper-autofluorescence with occasional patches of hypo-autofluorescence. This has been postulated in some cases to represent local disruption of the RPE, either from direct pressure or disruption of underlying choroidal circulation.[1] FA can again be variable, but typically shows hyperfluorescence with persistent late staining.[1,2,3] FA is perhaps most useful in identifying surrounding CNV.

Once the diagnosis of SCC is made, there is no direct ophthalmic treatment and the patient is observed. In the vast majority of cases, no ill effects arise in the retina or in the patient's vision.[2] However, case reports of choroidal neovascularization associated with SCC support routine monitoring of all identified lesions.[6,7]

Most importantly, an ophthalmologist should be aware of the systemic associations with SCC, as this diagnosis frequently requires additional medical evaluation. While most reported cases are idiopathic, 21 percent of patients with SCC in one case series were found to have a systemic cause.[2] Examples of conditions that can result in metastatic calcium deposition include hyperparathyroidism, elevated vitamin D, renal transport abnormalities, pseudogout, various malignancies and sarcoidosis.[8] Of these, the most commonly associated with SCC appear to be parathyroid adenoma, Gitelman syndrome and Bartter syndrome. In the previously mentioned case series, these conditions occurred in 15 percent, 11 percent and 2 percent of patients, respectively. In addition to harm from an undiagnosed underlying condition, hypercalcemia itself is associated with significant morbidity. Kidney stones, polyuria, constipation, nausea/vomiting, pancreatitis, depression, psychosis and CNS disturbance are symptoms of hypercalcemia and primary hyperparathyroidism. This is remembered with the mnemonic "stones, bones, groans, thrones, and psychiatric overtones."[2] Therefore, patients diagnosed with SCC should undergo screening with serum and urine studies including calcium, phosphorus, magnesium, potassium, calcitonin and parathyroid hormone.

In conclusion, sclerochoroidal calcification is an important ophthalmic finding to recognize. Frequently asymptomatic, SCC can be identified by its classic yellow/white geographic appearance, frequent bilateral and superotemporal distribution, and classic appearance on ultrasound, OCT, FAF, and FA imaging. It is important to distinguish SCC from more sinister ocular neoplasia, as SCC typically only needs routine ophthalmic surveillance. Nevertheless, all patients diagnosed with SCC should undergo thorough metabolic evaluation given its unique association with systemic electrolyte derangement. The patient presented above demonstrates a classic example of sclerochoroidal calcification in the setting of hypercalcemia secondary to a parathyroid adenoma. She currently follows with ophthalmology and endocrinology. At the time of this writing, she has shown no evidence of hypercalcemia recurrence, choroidal neovascularization or other ophthalmic complication of SCC. ◀

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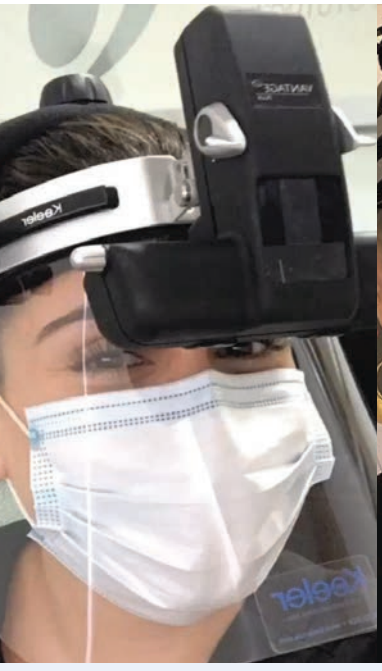


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