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December 2017
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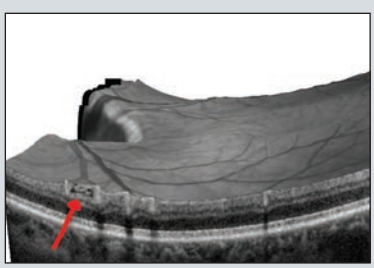

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BromSite®
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Indications and Usage

BromSite® (bromfenac ophthalmic solution) 0.075% is a nonsteroidal anti-inflammatory drug (NSAID) indicated for the treatment of postoperative inflammation and prevention of ocular pain in patients undergoing cataract surgery.

Recommended Dosing

One drop of BromSite® should be applied to the affected eye twice daily (morning and evening) 1 day prior to surgery, the day of surgery, and 14 days postsurgery.

Important Safety Information

- **Slow or Delayed Healing:** All topical nonsteroidal anti-inflammatory drugs (NSAIDs), including BromSite®, may slow or delay healing. Topical corticosteroids are also known to slow or delay healing. Concomitant use of topical NSAIDs and topical steroids may increase the potential for healing problems.
- **Potential for Cross-Sensitivity:** There is the potential for cross-sensitivity to acetylsalicylic acid, phenylacetic acid derivatives, and other NSAIDs, including BromSite®. Therefore, caution should be used when treating individuals who have previously exhibited sensitivities to these drugs.
- **Increased Bleeding Time of Ocular Tissue:** With some NSAIDs, including BromSite®, there exists the potential for increased bleeding time due to interference with platelet aggregation. There have been reports that ocularly applied NSAIDs may cause increased bleeding of ocular tissues (including hyphemas) in conjunction with ocular surgery. It is recommended that BromSite® be used with caution in patients with known bleeding tendencies or who are receiving other medications which may prolong bleeding time.
- **Keratitis and Corneal Effects:** Use of topical NSAIDs may result in keratitis. In some susceptible patients, continued use of topical NSAIDs may result in epithelial breakdown, corneal thinning, corneal erosion, corneal ulceration or corneal perforation. Patients with evidence of corneal epithelial breakdown should immediately discontinue use of topical NSAIDs, including BromSite®, and should be closely monitored for corneal health. Patients with complicated ocular surgeries, corneal denervation, corneal epithelial defects, diabetes mellitus, ocular surface diseases (e.g., dry eye syndrome), rheumatoid arthritis, or repeat ocular surgeries within a short period of time may be at increased risk for corneal adverse events which may become sight threatening. Topical NSAIDs should be used with caution in these patients. Post-marketing experience with topical NSAIDs also suggests that use more than 24 hours prior to surgery or use beyond 14 days postsurgery may increase patient risk for the occurrence and severity of corneal adverse events.
- **Contact Lens Wear:** BromSite® should not be administered while wearing contact lenses. The preservative in BromSite®, benzalkonium chloride, may be absorbed by soft contact lenses.
- **Adverse Reactions:** The most commonly reported adverse reactions in 1% to 8% of patients were anterior chamber inflammation, headache, vitreous floaters, iritis, eye pain, and ocular hypertension.

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

NSAID=nonsteroidal anti-inflammatory drug.

Reference: 1. BromSite® [package insert]. Cranbury, NJ: Sun Pharmaceutical Industries, Inc.; 2016.

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SUN OPHTHALMICS

BromSite® (bromfenac ophthalmic solution) 0.075%
Brief Summary

INDICATIONS AND USAGE
BromSite® (bromfenac ophthalmic solution) 0.075% is indicated for the treatment of postoperative inflammation and prevention of ocular pain in patients undergoing cataract surgery.

CONTRAINDICATIONS
None

WARNINGS AND PRECAUTIONS
Slow or Delayed Healing
All topical nonsteroidal anti-inflammatory drugs (NSAIDs), including BromSite® (bromfenac ophthalmic solution) 0.075%, may slow or delay healing. Topical corticosteroids are also known to slow or delay healing. Concomitant use of topical NSAIDs and topical steroids may increase the potential for healing problems.

Potential for Cross-Sensitivity
There is the potential for cross-sensitivity to acetylsalicylic acid, phenylacetic acid derivatives, and other NSAIDs, including BromSite® (bromfenac ophthalmic solution) 0.075%. Therefore, caution should be used when treating individuals who have previously exhibited sensitivities to these drugs.

Increased Bleeding Time of Ocular Tissue
With some NSAIDs, including BromSite® (bromfenac ophthalmic solution) 0.075%, there exists the potential for increased bleeding time due to interference with platelet aggregation. There have been reports that ocularly applied NSAIDs may cause increased bleeding of ocular tissues (including hyphemas) in conjunction with ocular surgery.

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

Keratitis and Corneal Reactions
Use of topical NSAIDs may result in keratitis. In some susceptible patients, continued use of topical NSAIDs may result in epithelial breakdown, corneal thinning, corneal erosion, corneal ulceration or corneal perforation. These events may be sight threatening. Patients with evidence of corneal epithelial breakdown should immediately discontinue use of topical NSAIDs, including BromSite® (bromfenac ophthalmic solution) 0.075%, and should be closely monitored for corneal health.

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

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

Contact Lens Wear
BromSite® should not be administered while wearing contact lenses. The preservative in BromSite®, benzalkonium chloride, may be absorbed by soft contact lenses.

ADVERSE REACTIONS
The following serious adverse reactions are described elsewhere in the Brief Summary:
- Slow or Delayed Healing
- Potential for Cross-Sensitivity
- Increased Bleeding Time of Ocular Tissue
- Keratitis and Corneal Reactions
- Contact Lens Wear

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

The most commonly reported adverse reactions in 1–8% of patients were: anterior chamber inflammation, headache, vitreous floaters, iritis, eye pain and ocular hypertension.

USE IN SPECIFIC POPULATIONS
Pregnancy
Risk Summary
There are no adequate and well-controlled studies in pregnant women to inform any drug associated risks. Treatment of pregnant rats and rabbits with oral bromfenac did not produce teratogenic effects at clinically relevant doses.

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

Data
Animal Data
Treatment of rats with bromfenac at oral doses up to 0.9 mg/kg/day (195 times a unilateral daily human ophthalmic dose on a mg/m^2 basis, assuming 100% absorbed) and rabbits at oral doses up to 7.5 mg/kg/day (3243 times a unilateral daily dose on a mg/m^2 basis) produced no structural teratogenicity in reproduction studies. However, embryo-fetal lethality, neonatal mortality and reduced postnatal growth were produced in rats at 0.9 mg/kg/day, and embryo-fetal lethality was produced in rabbits at 7.5 mg/kg/day. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

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

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

Geriatric Use
There is no evidence that the efficacy or safety profiles for BromSite® differ in patients 65 years of age and older compared to younger adult patients.

NONCLINICAL TOXICOLOGY
Carcinogenesis, Mutagenesis and Impairment of Fertility
Long-term carcinogenicity studies in rats and mice given oral doses of bromfenac up to 0.6 mg/kg/day (129 times a unilateral daily dose assuming 100% absorbed, on a mg/m^2 basis) and 5 mg/kg/day (540 times a unilateral daily dose on a mg/m^2 basis), respectively revealed no significant increases in tumor incidence.

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

Bromfenac did not impair fertility when administered orally to male and female rats at doses up to 0.9 mg/kg/day and 0.3 mg/kg/day, respectively (195 and 65 times a unilateral daily dose, respectively, on a mg/m^2 basis).

Rx Only
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REVIEW NEWS
Volume XXIV • No. 12 • December 2017

Study: Steroid/NSAID Combo Best For Preventing CME

A randomized, controlled multicenter study has demonstrated that combination topical drop therapy is more effective for preventing cystoid macular edema after cataract surgery in nondiabetic patients than either corticosteroid or NSAID monotherapy; in diabetic eyes, postop combination drop therapy plus a subconjunctival injection of triamcinolone acetonide perioperatively is superior to postop eye drops alone or with combinations involving intravitreal bevacizumab at close of surgery. Lead author Rudy Nuijts, MD, PhD, professor of ophthalmology at the University Eye Clinic Maastricht UMC+, The Netherlands, presented the findings of the PREMED (PREvention of Macular EDema after cataract surgery) study at the 35th Congress of the European Society of Cataract and Refractive Surgeons in October.

"The aim of the ESCRS PREMED study was to provide evidence-based recommendations that could serve as a basis for clinical guidelines on the prevention of CME after cataract surgery," explains study author Laura Wielders, MD, PhD. PREMED looked at two groups of patients who underwent standard phacoemulsification cataract surgery with IOL implantation at 12 centers throughout the EU. There were 914 nondiabetic patients and 213 with diabetes. Patients with proliferative diabetic retinopathy and marked DME were excluded. Patients with monocular function, elevated CME risk or previous surgery in the study eye were excluded from both groups.

For this study, funded by the ESCRS, the nondiabetic patients were randomized to four treatment groups: topical NSAID monotherapy (bromfenac 0.09%); corticosteroid monotherapy (dexamethasone 0.1%); or combined-drop therapy. The primary outcome measure was mean central macular subfield thickness measured by OCT at six weeks postoperatively versus baseline. Secondary outcomes included the occurrence of CME (an increase in CMST of 10 percent or more over baseline with cystic changes noted on OCT) and clinically significant CME at six and 12 weeks postoperatively (defined as CME on OCT plus less than 0.2 logMAR of CDVA improvement over baseline).

At six weeks, the dexamethasone group had the highest CMST measurements, 9.6 µm greater than those of the combined-drop patients. The incidence of clinically significant CME in the dual-drop therapy group was 1.5 percent at 12 weeks, compared with the NSAID monotherapy group (3.6 percent) and the corticosteroid monotherapy group (5.1 percent).

The 213 diabetic patients all received dual-drop therapy, and were randomized to receive either no additional treatment; 40 mg subconjunctival triamcinolone acetonide at close of surgery; 1.25 mg intravitreal bevacizumab; or both injections. Among the patients who received a TA injection on top of combination-drop therapy, there were no cases of CME. The addition of bevacizumab didn't affect macular thickness in any significant way. The patients who got subconjunctival TA had a CSMT measurement that was 12.3 µm less at six weeks than in those who did not; at 12 weeks they measured 9.7 µm less than the eyes that didn't receive TA.

Jeffrey Whitman, MD, president and chief surgeon of Key-Whitman Eye Center, with offices in Dallas and Fort Worth, Texas, says, "This study's early findings show us that what had been rumored is true: using both a steroid drop and an NSAID drop topically, starting two days preop and continuing postoperatively, makes a statistically significant difference in bringing the incidence of CME closer to zero in normal patients. Before, there was no paper to substantiate it, but now we have a clinical trial that demonstrates it.

"For diabetic patients," Dr. Whitman continues, "if you're afraid to inject triamcinolone or tri-moxi intravitreally, this study says that you can put it in subconjunctivally—along with your topical drop regimen of steroid and NSAID—and you're going to have an excellent effect in terms of preventing diabetic macular edema and CME."

Dr. Wielders urges careful decision-making with regard to diabetic eyes, though. "Based on the results of this study, it is not recommended to administer subconjunctival TA in all diabetic patients undergoing cataract surgery, given the low overall incidence of postoperative CME (4.5 percent), and considering the higher incidence of developing an increased IOP after subconjunctival TA injection (7.1 percent)," she says. REVIEW

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REVIEW Editor's Page

Walter C. Bethke, Editor in Chief

In the Interest Of Time

With 2017 soon drawing to a close, it's only natural to start thinking about things we could do differently—or better—in 2018. And, as the grains in the hourglass dwindle, our thoughts turn to what might be our most valuable resource: time—specifically how much time we have and what we intend to do with it.

In this month's issue of *Review*, the concept of time—in particular, how you can make the most of it in your practice—is the common thread that runs through our articles.

In Associate Editor Liam Jordan's feature on the lost art of patient communication *(pg. 20)*, almost every expert on the subject, physician and practice-management guru alike, emphasizes that it's not just the amount of time with a patient that matters, but what you and your staff do with the time you have with each person. Quality trumps quantity: Explaining every detail of the eye is less-effective than pinpointing a patient's concerns and addressing them fully, yet efficiently.

Then, in Senior Associate Editor Kristine Brennan's article on navigating the murky waters of disability insurance *(pg. 24)*, the specter of time hangs over the entire discussion, since the concept of such insurance acknowledges that today might be your last one in practice. Make the most of it. In addition, if the unthinkable happens and you find yourself unable to work, time again emerges as a key factor: How long will you be out of the game and will your policy cover you during that time?

Finally, on page 30, Senior Editor Christopher Kent sits down with glaucoma experts and parses out the features of visual field and optical coherence tomography instruments to help you make the most of them when tracking the progression of the disease.

In the article, Duke University professor Felipe A. Medeiros, MD, PhD, highlights how important it is that ophthalmologists make the most of the time they spend with their glaucoma patients, because the number of visits is almost always limited. In the real world, constant follow-up often isn't possible, even though it might hasten the detection of progression. "It's important to remember that having a patient come in three or four times a year for testing might be a significant burden for [him]," Dr. Medeiros says. "That has to be balanced against the need to detect progression." In effect, ophthalmologists are exhorted to get the most accurate, artifact-free imaging and visual field tests they can—and then study them. Make those precious few follow-up visits count.

This Editor's Page deals with the idea of maximizing your time at work, but there's a whole other side of the discussion that addresses how to make the most of life's moments with spouses, family and friends.

To tackle that question, though, I'm going to need some more time.

Happy holidays from everyone at *Review*!

—Walt Bethke, Editor in Chief

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AMD = Age-related Macular Degeneration; DME = Diabetic Macular Edema; DR = Diabetic Retinopathy; RVO = Retinal Vein Occlusion.

INDICATIONS AND IMPORTANT SAFETY INFORMATION

INDICATIONS

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

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

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

ADVERSE REACTIONS

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

Please see adjacent Brief Summary.

*Best-corrected visual acuity.
†Early Treatment Diabetic Retinopathy Study–Diabetic Retinopathy Severity Scale: an established grading scale for measuring the severity of DR.

Reference: 1. EYLEA® (aflibercept) Injection full U.S. Prescribing Information. Regeneron Pharmaceuticals, Inc. May 2017.

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EYLEA®
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For Intravitreal Injection

BRIEF SUMMARY—Please see the EYLEA package insert for full Prescribing Information.

1 INDICATIONS AND USAGE

EYLEA is a vascular endothelial growth factor (VEGF) inhibitor indicated for the treatment of:

Neovascular (Wet) Age-Related Macular Degeneration (AMD); Macular Edema Following Retinal Vein Occlusion (RVO); Diabetic Macular Edema (DME); Diabetic Retinopathy (DR) in Patients with DME

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 Dosage and Administration (2.7) and 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 [*see Dosage and Administration (2.7)*].

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

6 ADVERSE REACTIONS

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

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

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

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

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

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

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

	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). 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.

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 [*see Clinical Pharmacology (12.1)*], 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 [*see Nonclinical Toxicology (13.1)*].

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.

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

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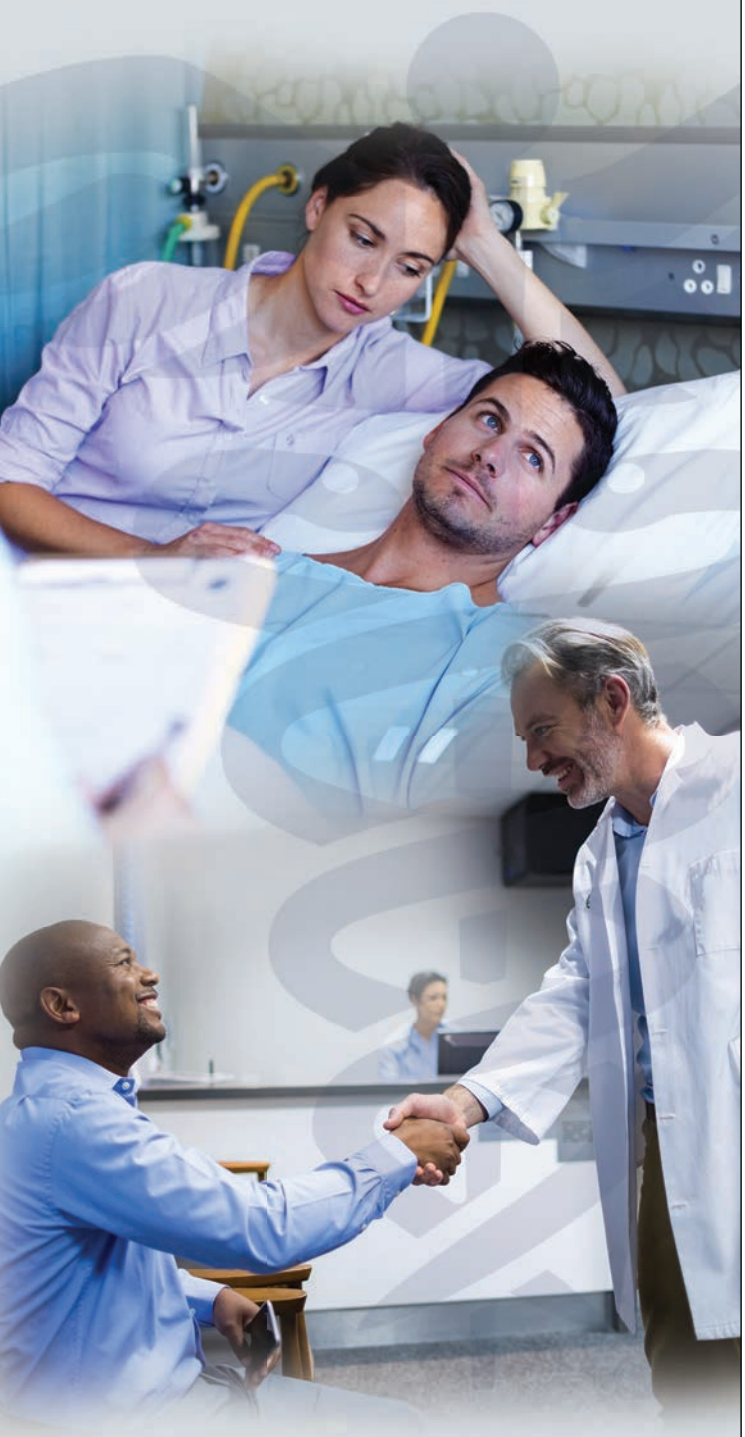
Issue Date: June 2017
Initial U.S. Approval: 2011

Based on the May 2017 EYLEA® (aflibercept) Injection full Prescribing Information.

REGENERON

REVIEW® of Ophthalmology

December 2017 • Volume XXIV No. 12 | reviewofophthalmology.com



Cover Focus

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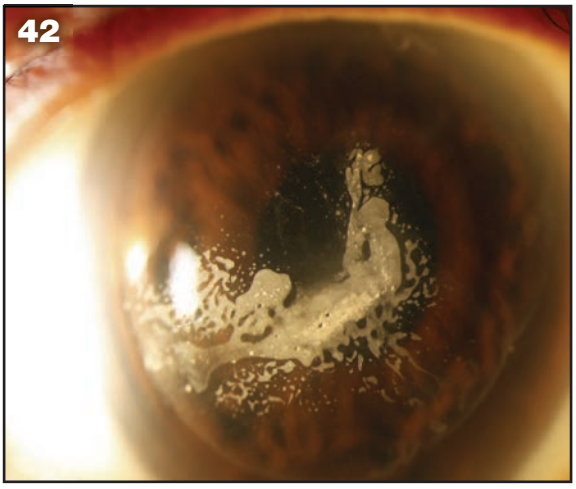
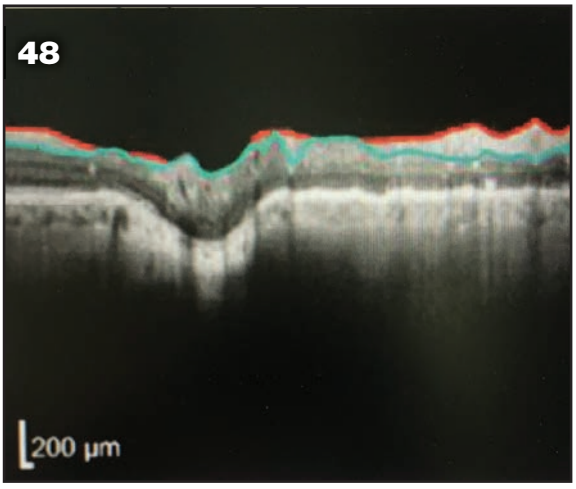
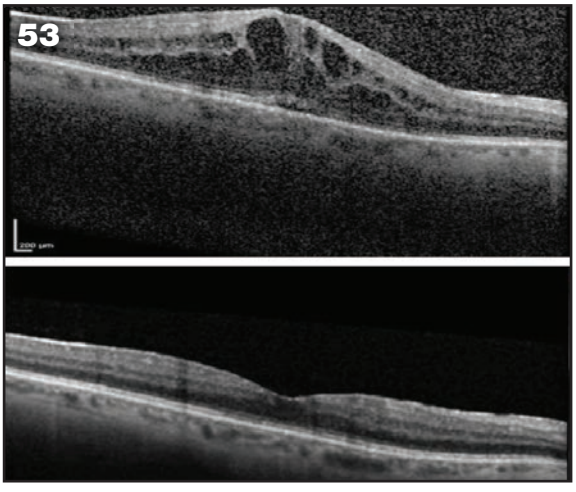
Departments

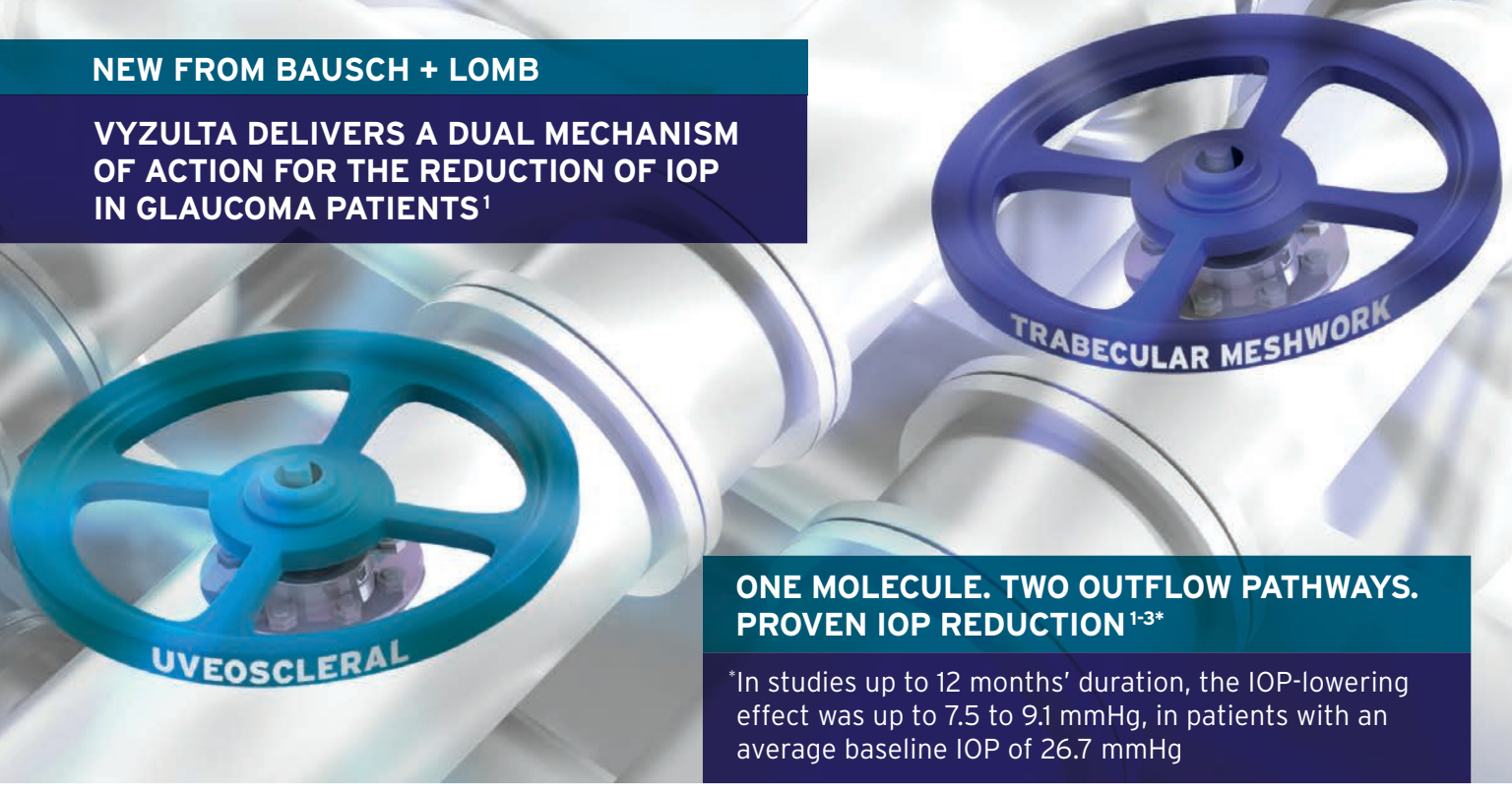






NEW FROM BAUSCH + LOMB

VYZULTA DELIVERS A DUAL MECHANISM OF ACTION FOR THE REDUCTION OF IOP IN GLAUCOMA PATIENTS[1]



ONE MOLECULE. TWO OUTFLOW PATHWAYS. PROVEN IOP REDUCTION[1-3*]

*In studies up to 12 months' duration, the IOP-lowering effect was up to 7.5 to 9.1 mmHg, in patients with an average baseline IOP of 26.7 mmHg

INDICATION

VYZULTA™ (latanoprostene bunod ophthalmic solution), 0.024% is indicated for the reduction of intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension.

IMPORTANT SAFETY INFORMATION

- Increased pigmentation of the iris and periorbital tissue (eyelid) can occur. Iris pigmentation is likely to be permanent
- Gradual changes to eyelashes, including increased length, increased thickness, and number of eyelashes, may occur. These changes are usually reversible upon treatment discontinuation
- Use with caution in patients with a history of intraocular inflammation (iritis/uveitis). VYZULTA should generally not be used in patients with active intraocular inflammation
- Macular edema, including cystoid macular edema, has been reported during treatment with prostaglandin analogs. Use with caution in aphakic patients, in pseudophakic patients with a torn posterior lens capsule, or in patients with known risk factors for macular edema

IMPORTANT SAFETY INFORMATION (CONTINUED)

- There have been reports of bacterial keratitis associated with the use of multiple-dose containers of topical ophthalmic products that were inadvertently contaminated by patients
- Contact lenses should be removed prior to the administration of VYZULTA and may be reinserted 15 minutes after administration
- Most common ocular adverse reactions with incidence ≥2% are conjunctival hyperemia (6%), eye irritation (4%), eye pain (3%), and instillation site pain (2%)

For more information, please see Brief Summary of Prescribing Information on next page.

References:

1. VYZULTA Prescribing Information. Bausch & Lomb Incorporated. 2017.
2. Weinreb RN, Sforzolini BS, Vittitow J, Liebmann J. Latanoprostene bunod 0.024% versus timolol maleate 0.5% in subjects with open-angle glaucoma or ocular hypertension: the APOLLO study. *Ophthalmology*. 2016;123(5):965-973.
3. Medeiros FA, Martin KR, Peace J, Sforzolini BS, Vittitow JL, Weinreb RN. Comparison of latanoprostene bunod 0.024% and timolol maleate 0.5% in open-angle glaucoma or ocular hypertension: the LUNAR study. *Am J Ophthalmol*. 2016;168:250-259.

For more information about VYZULTA and how it works, visit vyzultanow.com

VYZULTA™
(latanoprostene bunod ophthalmic solution), 0.024%

BAUSCH + LOMB

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BRIEF SUMMARY OF PRESCRIBING INFORMATION

This Brief Summary does not include all the information needed to use VYZULTA safely and effectively. See full Prescribing Information for VYZULTA.

VYZULTA™ (latanoprostene bunod ophthalmic solution), 0.024%, for topical ophthalmic use.

Initial U.S. Approval: 2017

1 INDICATIONS AND USAGE

VYZULTA™ (latanoprostene bunod ophthalmic solution) 0.024% is indicated for the reduction of intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension.

4 CONTRAINDICATIONS

None

5 WARNINGS AND PRECAUTIONS

5.1 Pigmentation

VYZULTA™ (latanoprostene bunod ophthalmic solution), 0.024% may cause changes to pigmented tissues. The most frequently reported changes with prostaglandin analogs have been increased pigmentation of the iris and periorbital tissue (eyelid).

Pigmentation is expected to increase as long as latanoprostene bunod ophthalmic solution is administered. The pigmentation change is due to increased melanin content in the melanocytes rather than to an increase in the number of melanocytes. After discontinuation of VYZULTA, pigmentation of the iris is likely to be permanent, while pigmentation of the periorbital tissue and eyelash changes are likely to be reversible in most patients. Patients who receive prostaglandin analogs, including VYZULTA, should be informed of the possibility of increased pigmentation, including permanent changes. The long-term effects of increased pigmentation are not known.

Iris color change may not be noticeable for several months to years. Typically, the brown pigmentation around the pupil spreads concentrically towards the periphery of the iris and the entire iris or parts of the iris become more brownish. Neither nevi nor freckles of the iris appear to be affected by treatment. While treatment with VYZULTA™ (latanoprostene bunod ophthalmic solution), 0.024% can be continued in patients who develop noticeably increased iris pigmentation, these patients should be examined regularly *[see Patient Counseling Information (17) in full Prescribing Information]*.

5.2 Eyelash Changes

VYZULTA may gradually change eyelashes and vellus hair in the treated eye. These changes include increased length, thickness, and the number of lashes or hairs. Eyelash changes are usually reversible upon discontinuation of treatment.

5.3 Intraocular Inflammation

VYZULTA should be used with caution in patients with a history of intraocular inflammation (iritis/uveitis) and should generally not be used in patients with active intraocular inflammation as it may exacerbate this condition.

5.4 Macular Edema

Macular edema, including cystoid macular edema, has been reported during treatment with prostaglandin analogs. VYZULTA should be used with caution in aphakic patients, in pseudophakic patients with a torn posterior lens capsule, or in patients with known risk factors for macular edema.

5.5 Bacterial Keratitis

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

5.6 Use with Contact Lens

Contact lenses should be removed prior to the administration of VYZULTA because this product contains benzalkonium chloride. Lenses may be reinserted 15 minutes after administration.

6 ADVERSE REACTIONS

The following adverse reactions are described in the Warnings and Precautions section: pigmentation (5.1), eyelash changes (5.2), intraocular inflammation (5.3), macular edema (5.4), bacterial keratitis (5.5), use with contact lens (5.6).

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

VYZULTA was evaluated in 811 patients in 2 controlled clinical trials of up to 12 months duration. The most common ocular adverse reactions observed in patients treated with latanoprostene bunod were: conjunctival hyperemia (6%), eye irritation (4%), eye pain (3%), and instillation site pain (2%). Approximately 0.6% of patients discontinued therapy due to ocular adverse reactions including ocular hyperemia, conjunctival irritation, eye irritation, eye pain, conjunctival edema, vision blurred, punctate keratitis and foreign body sensation.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no available human data for the use of VYZULTA during pregnancy to inform any drug associated risks.

Latanoprostene bunod has caused miscarriages, abortion, and fetal harm in rabbits. Latanoprostene bunod was shown to be abortifacient and teratogenic when administered intravenously (IV) to pregnant rabbits at exposures ≥ 0.28 times the clinical dose. Doses ≥ 20 µg/kg/day (23 times the clinical dose) produced 100% embryofetal lethality. Structural abnormalities observed in rabbit fetuses included anomalies of the great vessels and aortic arch vessels, domed head, sternebral and vertebral skeletal anomalies, limb hyperextension and malrotation, abdominal distension and edema. Latanoprostene bunod was not teratogenic in the rat when administered IV at 150 mcg/kg/day (87 times the clinical dose) *[see Data]*.

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 latanoprostene bunod daily by intravenous injection on gestation days 7 through 19, to target the period of organogenesis. The doses administered ranged from 0.24 to 80 mcg/kg/day. Abortion occurred at doses ≥ 0.24 mcg/kg/day latanoprostene bunod (0.28 times the clinical dose, on a body surface area basis, assuming 100% absorption). Embryofetal lethality (resorption) was increased in latanoprostene bunod treatment groups, as evidenced by increases in early resorptions at doses ≥ 0.24 mcg/kg/day and late resorptions at doses ≥ 6 mcg/kg/day (approximately 7 times the clinical dose). No fetuses survived in any rabbit pregnancy at doses of 20 mcg/kg/day (23 times the clinical dose) or greater. Latanoprostene bunod produced structural abnormalities at doses ≥ 0.24 mcg/kg/day (0.28 times the clinical dose). Malformations included anomalies of sternum, coarctation of the aorta with pulmonary trunk dilation, retroesophageal subclavian artery with absent brachiocephalic artery, domed head, forepaw hyperextension and hindlimb malrotation, abdominal distention/edema, and missing/fused caudal vertebrae.

An embryofetal study was conducted in pregnant rats administered latanoprostene bunod daily by intravenous injection on gestation days 7 through 17, to target the period of organogenesis. The doses administered ranged from 150 to 1500 mcg/kg/day. Maternal toxicity was produced at 1500 mcg/kg/day (870 times the clinical dose, on a body surface area basis, assuming 100% absorption), as evidenced by reduced maternal weight gain. Embryofetal lethality (resorption and fetal death) and structural anomalies were produced at doses ≥ 300 mcg/kg/day (174 times the clinical dose). Malformations included anomalies of the sternum, domed head, forepaw hyperextension and hindlimb malrotation, vertebral anomalies and delayed ossification of distal limb bones. A no observed adverse effect level (NOAEL) was established at 150 mcg/kg/day (87 times the clinical dose) in this study.

8.2 Lactation

Risk Summary

There are no data on the presence of VYZULTA 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 VYZULTA, and any potential adverse effects on the breastfed infant from VYZULTA.

8.4 Pediatric Use

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

8.5 Geriatric Use

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Latanoprostene bunod was not mutagenic in bacteria and did not induce micronuclei formation in the *in vivo* rat bone marrow micronucleus assay. Chromosomal aberrations were observed *in vitro* with human lymphocytes in the absence of metabolic activation.

Latanoprostene bunod has not been tested for carcinogenic activity in long-term animal studies. Latanoprost acid is a main metabolite of latanoprostene bunod. Exposure of rats and mice to latanoprost acid, resulting from oral dosing with latanoprost in lifetime rodent bioassays, was not carcinogenic.

Fertility studies have not been conducted with latanoprostene bunod. The potential to impact fertility can be partially characterized by exposure to latanoprost acid, a common metabolite of both latanoprostene bunod and latanoprost. Latanoprost acid has not been found to have any effect on male or female fertility in animal studies.

13.2 Animal Toxicology and/or Pharmacology

A 9-month toxicology study administered topical ocular doses of latanoprostene bunod to one eye of cynomolgus monkeys: control (vehicle only), one drop of 0.024% bid, one drop of 0.04% bid and two drops of 0.04% per dose, bid. The systemic exposures are equivalent to 4.2-fold, 7.9-fold, and 13.5-fold the clinical dose, respectively, on a body surface area basis (assuming 100% absorption). Microscopic evaluation of the lungs after 9 months observed pleural/subpleural chronic fibrosis/inflammation in the 0.04% dose male groups, with increasing incidence and severity compared to controls. Lung toxicity was not observed at the 0.024% dose.

Distributed by:

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Bridgewater, NJ 08807 USA

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Laser Focus on New Technology

An update on products for therapy and phaco that have been recently cleared by the FDA.

Kristine Brennan, Senior Associate Editor

As the world's population ages, retinal disease, glaucoma and cataracts are expected to correspondingly increase in prevalence, and access to ophthalmic laser treatments is growing around the world. Market Scope estimated in July that 2017 global revenues for ophthalmic lasers and related accessories and maintenance would reach $422 million, and that laser sales would comprise 63 percent of that total, while another 22 percent would be related to maintenance and 11 percent would go toward single-use endoprobes.[1] The latter half of the year saw two new photocoagulator lasers and a new software package and hardware upgrade for a femtosecond laser all receive FDA 510(k) clearances. Here's a brief snapshot of each of these newcomers.

Easyret Photocoagulator

This 577-nm yellow laser by Quantel (Clermont-Ferrand, France) received FDA clearance in late July 2017. The manufacturer's proprietary ELBA fiber laser cavity forms the Easyret's resonator; the laser delivers a 577-nm yellow wavelength in a uniform tophat spot profile to treat ocular diseases such as chronic central serous chorioretinopathy, diabetic retinopathy, diabetic macular edema, branch retinal vein occlusion and associated macular edema; choroidal neovascularization; and retinopathy of prematurity. The Easyret is also indicated for trabeculoplasty in open-angle glaucoma and iridotomy in angle-closure glaucoma.

The manufacturer claims that the Easyret's size and ergonomic setup make it a suitable, durable alternative to solid-state lasers. The Easyret is available with either a Haag Streit- or Zeiss-type slit lamp.

A large touch-screen interface lets users program the appropriate power, pulse, duration, spot size, and treatment beam intensity level for the therapy at hand:

- ***SingleSpot treatment mode:*** Traditional focal photocoagulation in one spot, in single, repeat, painting or continuous-delivery modes.
- ***MultiSpot treatment mode:*** Multiple consecutive laser spots treated automatically per a preselected customizable treatment pattern (square, macular grid, triple arc, circle or single spot).
- ***SubLiminal treatment mode:*** The manufacturer's proprietary subthreshold micropulse setting divides energy delivery into pulse envelopes with fully customizable on/off durations per laser shot. The company says this affords a high level of control over the thermal effect on targeted tissue.

For more information, visit www.quantel-medical.com.

Quantel says that the Easyret is a low-maintenance, ergonomic alternative to solid-state lasers.

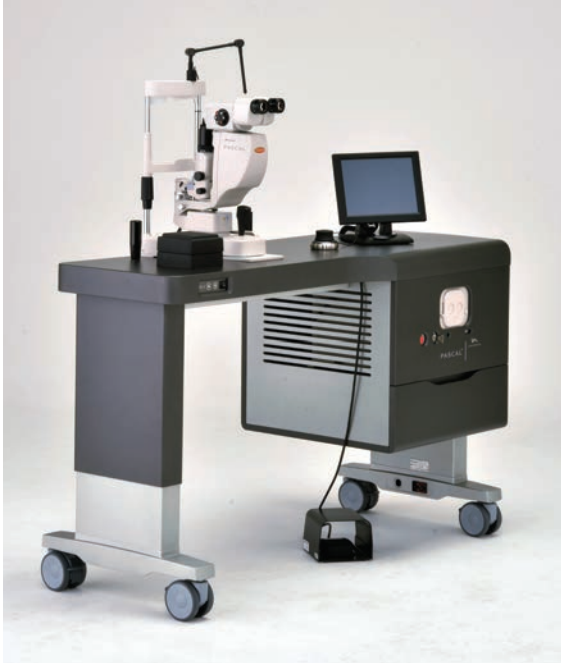
This article has no commercial sponsorship.

PASCAL Synthesis TwinStar Laser

In October 2017, Topcon (Livermore, Calif.), announced that the latest addition to its line of PASCAL (PAttern SCAnning Laser) technology, the PASCAL Synthesis TwinStar Ophthalmic Laser Scanning System, received 510(k) clearance from the FDA. The Synthesis TwinStar is an update on its predecessor, the green/yellow Synthesis. The TwinStar combines a 638-nm red wavelength module with a 577-nm yellow one to treat anterior- and posterior-segment ocular pathologies using focal or scattered photocoagulation.

The newly incorporated red wavelength is intended for targeting the choroid with single-spot treatments. Spot diameters can be set at 50 or 200 µm. The yellow wavelength is intended to perform single-spot photocoagulation in the posterior segment (retina, choroid) as well as pattern-scanning photocoagulation in the non-macular retina. It has settings for single-spot treatment, four spot sizes and a selection of patterns.

The TwinStar also incorporates the Synthesis' proprietary optional Endpoint Management software for use with the 577-nm yellow module. Endpoint Management allows the user to titrate laser delivery at subthreshold energy levels. This application may help minimize collateral tissue damage in patients who require multiple laser treatments, and may help surgeons and patients feel more comfortable about initiating treatment earlier in the course of disease by helping to limit the potential for cumulative damage. For more information, visit www.topconmedical.com.



Topcon's newly-cleared TwinStar laser combines a 638-nm red module with a 577-nm yellow laser module for treatment versatility.

In addition to a new 3.3 software package for the Victus femtosecond laser, Bausch + Lomb has updated some ergonomic features to aid workflow.

Victus Femtosecond Laser 3.3 Software

Bausch + Lomb (Bridgewater, N.J.) recently got 510(k) clearance from the FDA for a new software package and some hardware modifications for its Victus femtosecond laser that the company hopes will enhance its utility and ease of use in the OR.

The Victus is an Nd:glass solid-state laser in a console that has a computerized interface for the user, and a proprietary Verafit patient interface that keeps the eye still and cornea flat to help the anterior capsulotomy go smoothly and safely. The Victus generates sub-picosend pulses that repeat at 15 kHz. The spot diameter of the beam is less than 6 µm at the target location.

The new 3.3 software platform has a centration feature to guide capsulotomy and lens fragmentation that allows surgeons to choose centration on the pupil, limbus, lens apex, or other location he or she selects. It also adds a grid lens-fragmentation pattern to its menu of phacoemulsification options. For refractive surgery, the 3.3 software package features automatic pupil centration to aid in making flaps. The improved platform comes with some upgrades to the Victus' hardware, too: an S60 bed helps with workflow in the OR by swinging out farther away from the laser so that patients can get in and out more easily.

For more information, visit www.victuslaser.com. REVIEW

1. Market Scope press release. Ophthalmic lasers expected to generate $422 million in 2017. July 6 2017. https://market-scope.com/pressrelease/ophthalmic-lasers-expected-to-generate-422-million-in-2017/. Retrieved October 25 2017.

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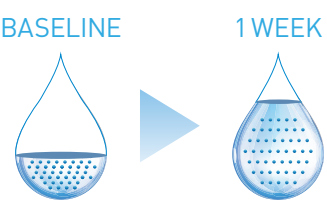

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Paul M. Larson, MBA, MMSc, COMT, COE, CPC, CPMA

"Targeted Probe and Educate" Reviews

How to protect yourself from the new TPE reviews.

Q What are Targeted Probe and Educate reviews?

A These are another form of Medicare claims data-driven reviews done by your Medicare Administrative Contractor. A pilot, less targeted, program began in 2014 involving one MAC. In June 2016 it became more targeted, and in July 2017, it expanded to three more MACs; it will expand to all MACs by the end of 2017. CMS notes that the pilot "… combined a review of a sample of claims with education to help reduce errors in the claims submission process. CMS called this medical review strategy "Probe and Educate." CMS believes the results of this program have been favorable, based on the decrease in the number of claim errors after providers received education."

Q Why are these being implemented now in addition to all the other types of reviews already present?

A As alluded to above, because of the decrease in error rates on claims and the documentation to support them, CMS felt the program was successful. On the TPE webpage,[1] they explained their rationale for moving to a more focused approach: "CMS is now further improving this strategy by moving from a broad Probe and Educate program to a more targeted one. When performing a medical review as part of Targeted Probe and Educate, MACs focus on specific providers/suppliers within the service rather than all provider/suppliers billing a particular service."

Q How many charts might this entail?

A CMS notes that this will involve 20 to 40 claims per provider, per item or service, or per round. There will be up to three rounds of review.

Q Why are there three rounds of TPE reviews?

A CMS refers to each of the rounds as a "probe." They note that "This term is intended to convey that the number of claims reviewed is relatively small in comparison with previous provider-specific review where the number of claims reviewed for an individual provider may have been much larger. After each round, providers are offered individualized education based on the results of their reviews." CMS says that if providers do well on early rounds, they are less likely to go through subsequent rounds. They state, "Whereas previously the first round of [other types of] reviews were of all providers for a specific service, the TPE claim selection is provider/supplier-specific from the onset. This eliminates burdens to providers who, based on data analysis, are already submitting claims that are compliant with Medicare policy."

Q How do the MACs choose what gets reviewed?

A CMS "will select claims for items/services that pose the greatest financial risk to the Medicare trust fund and/or those that have a high national error rate. MACs will focus only on providers/suppliers who have the highest claim-error rates or billing practices that vary significantly out from their peers. These providers/suppliers and specific items/services are identified by the MAC through data analysis."

Q How is the decision to perform subsequent reviews made?

A CMS notes, "Providers/supplier may be removed from the review process after any of the three rounds of probe review, if they demonstrate

(Continued on page 66)

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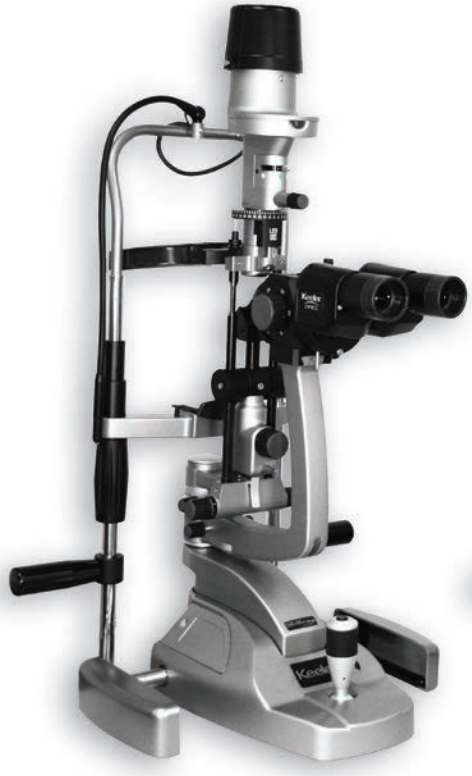

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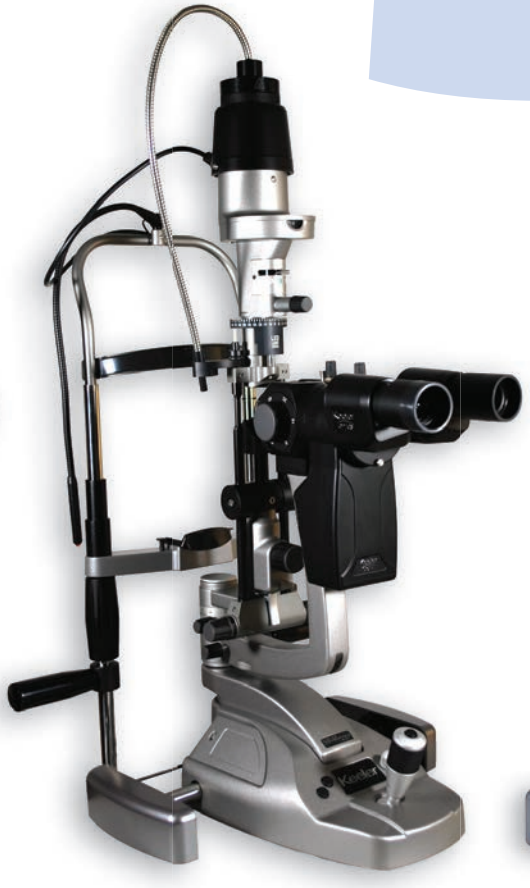

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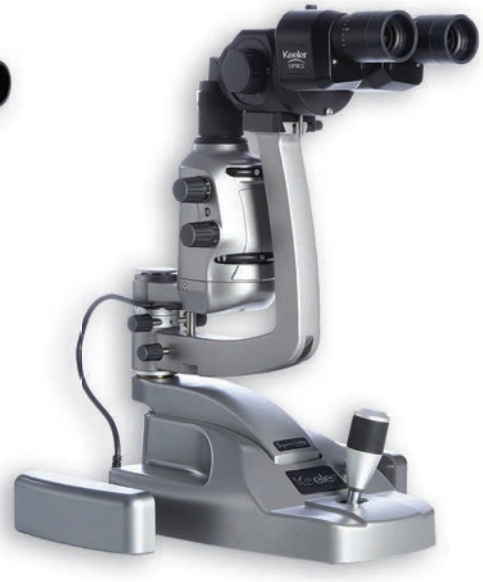

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The Lost Art of Talking to the Patient

Liam Jordan, Associate Editor

How to get physicians, staff and patients on the same page.

Today's technological advancements are a tremendous asset to the modern ophthalmologist. New devices and surgical techniques are developing and gaining approval at an amazing rate. However, one must be careful to listen to what's most important amid the din of technological advancement: the patient. Talking with a patient is becoming a more and more antiquated notion, when practices can run almost entirely digitally with doctors simply filling out check boxes to fulfill their regulatory requirements.

In this article, we'll discuss the pitfalls that physicians face when talking with patients, and how to streamline communications to make a practice as efficient as possible, while still putting the patient first.

Practices' Pitfalls

Perhaps the best place to begin is where practices go wrong and what mistakes to avoid when building a relationship with patients. Maureen Waddle, a principal and senior consultant with BSM Consulting, says she has seen practices falter when it comes to doctor-patient communications. "Historically, practices go wrong when doctors speak too clinically or medically with the patients and have challenges regarding how to phrase things for someone who is not medically trained," she says. "In recent years another problem is the fact that computers have the techs and doctors turning their backs to patients to do data entry. They're too focused on checking the right boxes to meet whatever the regulatory requirements are, so they can't give their focus or attention to the patient to engage them or listen to them."

John Pinto, of J. Pinto and Associates, an ophthalmic practice management consulting firm, also shares two extreme examples of failure to communicate with patients. "There's a lot of latitude in this area. In practice A, the doctor would walk into the room, not say hello to the patient, do the slit

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lamp exam, dictate his findings to the scribe, and then walk out. He would not say hello, goodbye, shake hands or describe the condition to the patients," Mr. Pinto explains. "Upon the doctor's departure, the scribe would then become the health educationist, and say, 'The doctor has described that you have a cataract, and here's what that is and how we can help you with that.' Then they would escort the patient to the surgical counselor when that was indicated.

"Now in practice B, in the same kind of suburban environment and patient demographic, the doctor would walk in, without a scribe in the room," he continues. "He would spend at least a half an hour, up to 45 minutes, doing the most routine of exams. He had a biology roll-down chart, which had a sagittal section of the eye on it, and he would use a stick with a hook on the end of it to pull this chart down. At the end of each exam, he'd roll it back up just so he could dramatically pull the chart down for the next patient.

"This practice, you might assume, was where the patients were extremely satisfied," Mr. Pinto says. "In point of fact, his practice was shrinking due to his inefficiency. When we talked to some of his patients in a group, one patient said, 'He's okay, but when he pulls down that chart, I know I'm going to be in there for a while.' He was providing graduate level education for his patients, and they weren't satisfied. It wasn't belittling—he was just a pedant. We heard a lot of, 'I don't want to know that much about my eyes. I want to get in, get out and get on with my day.'

"Thankfully, the vast majority of ophthalmologists practice between the extremes of Doctors A and B," Mr. Pinto says.

Joseph Panarelli, MD, an ophthalmologist based in New York, discusses his experience with talking to patients in terms they'll understand. "There's definitely a learning curve when you start, because you've come out of school and residency and your instinct is to keep talking like you're being tested. It's a weird feeling because that language is a part of your life at that point. You need to be able to step back and realize that the vast majority of people won't understand what glaucoma is or what is medically happening to their eyes," he says. "It's an invaluable skill to be able explain, in layman's terms, what is happening. It's a tough instinct to shake. It just takes time and practice."

Staff and Patients

Because a great staff can enhance a patient's visit and make the doctor's life that much easier, proper communication with not only patients but also with your staff is essential for having a patient leave a practice satisfied with his visit. "There is nothing more frustrating than having a tech express one thing to a patient, and then a doctor expresses a different or contradictory opinion," Ms. Waddle claims. "That's a training issue with the staff. You have to get that under control. It does help the doctor to have the techs and scribes do some patient education, but there's definitely a line. It's critical, because if you have conflicting messages, that will break down the patient's confidence and trust in the doctor."

Mr. Pinto also says he's seen this happen. "I've seen examples where techs have overstepped their bounds and have begun telling patients what's wrong with them and what the next steps are. Then the doctor comes in and sees that the tech has it wrong. That has to be stopped," he states. "I've seen opposite far extreme of that too, where the staff has to memorize scripts with responses to questions that patients have. Like being on Broadway with no latitude. That's stiff and off-putting to the patients and the staff.

"It takes a couple years of decent training and exposure for a person who's never been a tech before to become an effective tech," he continues. "In practices that have great HR habits, technicians stick around long enough to learn all these things. But practices that are problematic have this adverse cycle they'll get into. The working conditions aren't great, so the tenure isn't long, so the staff don't hang in there long enough to learn how to do their jobs confidently. Then the doctors get frustrated, and the wheel keeps turning."

Mr. Pinto offers some solutions to this issue, seen in some of the most efficient practices. "The doctor has to be engaged in the process of staff education, to make sure that the patients feel cared for," he says. "Even at the front desk, patients will often have follow-up questions before they leave about how to use their new eye drops or something to that effect. If you don't know how to talk to them there, you could lose a valued patient."

Further emphasizing the importance of a well-trained staff, Mr. Pinto says, "It's not always about the face-to-face time with the doctor. I think it's about listening, ultimately. Not how much you can tell the patient, but how you can make sure they're heard. You can't view them as patients you've seen thousands of times before, even though you have. You have to give them time as individuals and make sure they feel their concerns and questions are heard. Doctors can have three- to four-minute encounter times when they're supported by a great staff that delight patients and are extremely efficient in how they run their practice," he continues. "On the flip side, you also see doctors with 10- to 15-minute times that have unsatisfied patients. Your staff can take a lot of the pressure off your hands if they're properly trained."

Putting the Patient at Ease

When practice-management experts sit down with patients and doctors, one of the most valuable attributes of the doctor is the ability to put the patient

at ease about whatever procedure the doctor is performing and to effectively explain a complex procedure in simple terms.

Mitchell Jackson, MD, an ophthalmologist from Lake Villa, Ill., says, "I think this is an area where there's a steep learning curve. It's valuable because this will be why patients come back, and what they'll talk about when people ask them how the procedure went," he says. "I take five to 10 minutes to explain to them what we're about to do and walk them through the procedure as best I can, in terms they're familiar with. Analogies help here, but if it gets into the real nitty-gritty technical stuff, I'll brush over that, and focus on the bigger picture and end results of the procedure."

Dr. Jackson notes the importance of the staff in his approach to putting the patient at ease. "There's only so much you can say," he points out. "If you have a trained staff behind you that the patient trusts, then their word supporting yours means a lot. That can be the difference between someone who's a nervous wreck and someone who's confident going into surgery. Even before surgery, the staff can be there to comfort patients and reassure them. If you have a competent and trustworthy staff behind you, it's much more comforting for the patient."

Ms. Waddle also gives some advice to doctors on how to put a patient at ease before a procedure. "When you're going into surgery, recommend that the patient bring someone with him. We all hear and perceive things differently, so to have at least one other person listening along with the patient who can help clarify is always helpful and reassuring," she says. "They might also ask a question that the patient didn't think of at the time, which can be valuable. So encourage patients to bring loved ones or family with them. It goes a long way. It also helps to have some simple instructions or common experiences for the patients in writing. A lot of practices use videos sometimes, too.

"Most importantly I think, is for doctors to learn from each other—take these pearls from your colleagues and figure out what works when communicating with patients," she continues. "Listen for the best analogies and descriptions that will resonate with your patients. I know a lot of doctors use the camera analogy to describe your eyes. It's great if you can find a few analogies that work and connect with the patients. That helps them be more confident in what they're facing."

"We are all patients of one doctor or another and we've all had the experience of being jabbed by a needle or poked at without any fair warning," Mr. Pinto adds. "There's a real call for some advanced notice and timing. I recently had a procedure and the doctor took me in and had his assistant in the room hold my hand. Now I don't necessarily need that, but it's a really nice touch, one that we could learn a lot from in eye care."

Legal Troubles

Not only can a lack of communication with patients lead to an inefficient and stunted practice, there are also some weighty legal pitfalls that could come attached. Anne Brendel, a health-care attorney in Los Angeles, claims, "Legal issues often make physicians pay more attention to their requirements. They're more likely to listen if they can be punished for it." With that in mind, here's a look at some legal troubles that could befall a practice as a result of inefficient communication with its patients.

"Initially, talking to the patients obviously helps strengthen that patient-doctor relationship. Good communication also helps practitioners obtain proper consent," Ms. Brendel says. "CMS has offered guidelines for informed consent as well. Communication can also decrease civil and criminal liability.

"Ultimately, and worst-case scenario, fraud can be an issue—even malpractice," she continues. "Having the appropriate conversation with the patient is important as a way to decrease liability for practitioners. Documenting this conversation is important too. Should an action arise later, it's not he-said, she-said, because the conversations were documented."

As for how to avoid these legal issues, she offers some advice. "Treatment information sheets are very helpful. You can attach those to the informed-consent forms. In addition to having a conversation with the patient, you should keep a document ultimately signed by the patient that lays everything out clearly," she says. "Something that says that you talked about the risk and the patient had an opportunity to ask questions. This can also protect physicians later, too, because there will be documentation that the patient had the opportunity to raise a question, even if he chose not to. When you have that, it protects the physicians since it puts the fault back on the patient for not raising a concern when he had an opportunity to."

With new technologies on the rise and increasingly strict regulatory measures, taking five minutes to talk and actively listen to patients is becoming a forgotten art. However, the best practices still know the intrinsic value of taking the time to talk with a patient. "Ultimately, in the best practice, where satisfaction is the highest, these things are seen as important from the top of the organization down," Mr. Pinto says. "These interactions are as much what patients are paying for as the surgery or treatment they may need. The best practices hone their communication craft just as they do their surgical craft." REVIEW

None of the contributors to this article have disclosed any financial interests.

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Disability Insurance: What You Need to Know

By Kristine Brennan, Senior Associate Editor

How to shop for something you hope you'll never need.

You've invested years of work, and often a mind-boggling sum of money, to be able to call yourself an ophthalmologist. Whether your highest earnings are still on the horizon or your hard work has transformed all that potential into tangible assets, insurance can help you avoid derailing your dreams for the future. Underlying any other type of coverage that you may need depending upon your practice setting—malpractice, premises liability, key-employee disability insurance, health insurance for any employees—personal disability insurance helps protect your ability to sustain your and your family's financial life.

Although the last thing many people think about is the prospect of disability, it may be more real to ophthalmologists, who routinely bear witness to ocular injuries and pathologies that lead to permanent vision loss. The Council for Disability Awareness estimates that one in four 20-year-olds can expect to experience an episode of disability before retirement. To make matters worse, the organization adds that most Americans lack disability coverage and enough emergency savings to weather 34.6 months—the average duration of a disability claim (www.disabilitycanhappen.org).

In this article, seasoned insurance brokers with expertise in helping physicians choose the right disability coverage offer advice on what to look for and what to avoid when it comes to protecting your livelihood.

Hedge Your Bets

"Insurance is really legalized gambling," acknowledges Lawrence B. Keller, CFP, founder of Physician Financial Services (http://www.physicianfinancialservices.com) headquartered in Woodbury, N.Y. But he stresses that it's a gamble that surgeons can't afford to forgo. "Disability insurance is something that anyone who's working but has not yet achieved financial independence needs. You might love what you do, but you're working because you need to generate an income. You need to protect that income, and the only effective way to do that is disability insurance," he says.

Richard Reich of Intramark Insurance Services in Glendale, Calif. (https://www.protectyourincome.com), is a life and disability insurance specialist with an emphasis on insurance for physicians. Intramark estimates that policyholders should expect to pay 2 to 5 percent of their income toward disability premiums. "Here's how I present it to people," says Mr. Reich, "Would you rather have 90 per-

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cent of your income and be insured against disability, or would you rather keep 100 percent of it and take your chances?"

To clarify, there are other kinds of disability insurance that practice owners can buy for themselves and for critical employees, such as key-employee disability insurance; that is paid for by the business owner, who receives a payout if the key employee becomes disabled. The payout replaces business expenses and lost income occasioned by that employee's absence from work. Our focus will be on personal disability insurance.

Because personal disability insurance is applicable to every practice setting and stage of life, our experts will explore its nuances and share the features they encourage their physician clients to look for.

Supplementing Group Coverage

Both experts note that as more young surgeons forgo solo practice, employer- and hospital-provided group disability plans have become prevalent. "Just 10 or 15 years ago there wasn't a lot of group coverage, but many doctors—not just ophthalmologists—are joining groups now," says Mr. Reich. "So we're losing clients for their initial disability insurance in many cases. But we often help them pick up supplemental coverage."

Personal disability coverage for doctors is a small market, Mr. Reich adds. "There are only a handful of companies that offer this coverage especially for physicians. There were a lot of companies that got burned in the past by writing very broad, very rich coverage and they lost a lot of money. So now you have a handful." He adds that although there are fewer carriers than in the past, pricing is competitive. "You might think that the rates would have gone up a lot, but that isn't the case. Rates have remained fairly consistent. There is stiff competition between the carriers, and some of them try to catch up with some of the others by increasing the coverage in some areas, improving benefits overall. We haven't really seen premiums go up, and we've actually seen policies improve," he says.

The relative stability of premium costs may mean little to cash-strapped residents and fellows. According to Mr. Reich, however, employer-provided group disability policies often have gaps that might need filling-in with more coverage. "In most cases, you cannot turn down group coverage. A major caveat in many group policies, however, is that the benefits are often taxable. If the group is paying the premiums, that is the key factor in the taxability of the benefits. If the employer pays the premium, then the benefit is taxable," Mr. Reich explains. "I always recommend supplemental coverage, at least to recover on the taxability of group coverage. Most benefits pay 60 percent of your income. Let's say you're making $100,000, just to make it easy. You're earning less than $10,000 a month and your benefit is 60 percent of that. You'll be receiving less than $6,000 per month and that is taxable. So now your monthly net might be less than $3,000 after taxes. That's probably not going to cut it, and that's why they need to supplement it."

Mr. Keller agrees, adding that you may need to supplement to make up for taxes and any earnings you have in excess of the "cap" on the group LTD

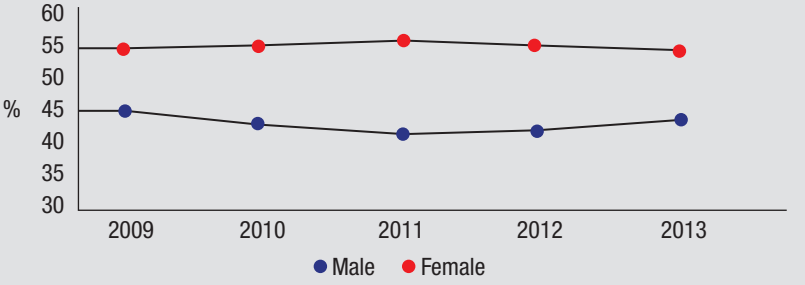
The "Pink Tax" for Women

Although women pay less than men for life insurance, they enjoy no such advantage when it comes to disability insurance. "The rate structure is based on claims experience," observes Richard Reich of Intramark Insurance Services in Glendale, Calif. "Illness is the major reason for disability, including breast cancer and pregnancy complications. Women pay less for life insurance because they live longer. But they make up for it in disability, unfortunately." The line graph below, based on data from the Council for Disability Awareness, illustrates the disparity between the sexes in claims filed.

"The cost of disability policies for females is substantially higher than for their male counterparts," adds Lawrence B. Keller, CFP, of Physician Financial Services in Woodbury, N.Y. "Female physicians should look for a unisex or gender-neutral rate structure, in addition to the other important riders. This could literally save them 40 to 50 percent off of the normal female premium rates. Certain companies like Mass Mutual and Principal still make unisex rates available, but you've got to do a little digging. It often ties in with hospital affiliations. For female surgeons, the Holy Grail is getting a unisex rate together with the own-occupation definition of total disability. This is hugely important," he says.

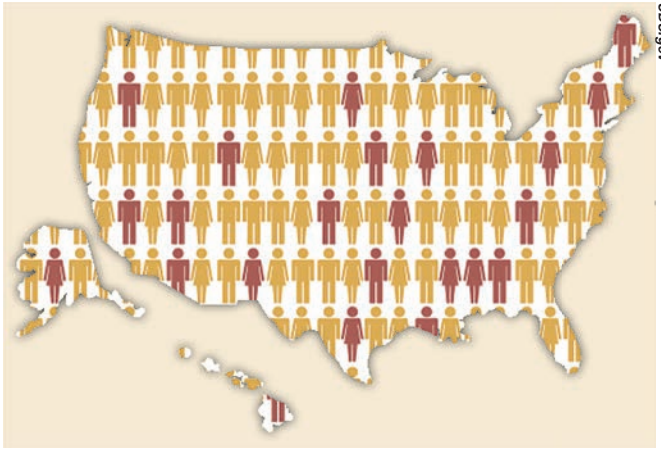
It may be important, but finding gender-neutral rates isn't easy. "For residents, medical students, interns and fellows, Principal just recently stopped offering it, so currently, the only place for a female resident or fellow to get unisex coverage would be Mass Mutual, provided that their hospital either has a discount plan established (which requires a total of three participants), or The Standard Insurance Company has what's called a GME plan (graduate medical education plan), but that's also only offered at a limited number of hospitals. Ameritas also has a few very old guaranteed standard-issue plans with unisex rates, but they're available mainly just through certain institutions in Texas," Mr. Keller notes.

Percent of New Long-Term Disability Claims by Gender



plan, and because you also need some portable disability coverage. "If you're working for a hospital and also doing some locum tenens work on the weekends, that work is self-employment income that has no coverage at all associated with it," he says. "You'll need to buy supplemental personal disability insurance."

Whether you're shopping for a disability policy that will supplement the policy your hospital or group offers, or you're looking for your main policy, Mr. Keller and Mr. Reich say that a good disability policy has a number of important features.



CDC.gov

The Centers for Disease Control has estimated that 22 percent of American adults have some type of disability. This estimate would subsume the number of workers suffering disabling illness or injury.

Own-Occupation Coverage

For physicians, the strongest possible definition of total disability comes from policy language that is specific to their own occupation or even specialty. Mr. Keller and Mr. Reich emphasize that it's well worth paying extra to get a more specific definition of disability than what's in a standard "any-occupation" policy, which requires you to be disabled from all work/employment before you can collect. An occupation-specific definition of total disability will help make sure you receive benefits when you need them to replace lost income. Total-disability language varies between carriers, but should resemble something to the effect of, "You are unable to perform the material and substantial duties of your occupation or profession," and not just employment in general.

"Make sure you get the own-occupation definition of disability, and make that specialty-specific," urges Mr. Reich. "Some companies have very strong language when it comes to making a policy specialty-specific. If you can't perform the duties of an ophthalmologist, because let's say you injure your hand and can't perform surgeries or do other specific duties, then you would be considered disabled even if you retrained, returned to work and earned income in some other career. You would still receive your full disability benefit," he says.

"You want to make sure you have the own-occupation definition of disability," Mr. Keller agrees. "At this point, there are only six companies that offer this to ophthalmologists, or any physicians: Berkshire Life (a Guardian company); Standard Insurance Company; Mass Mutual; Principal; Ameritas; and Ohio National—and the availability of this may vary by state and medical specialty."

And, when you begin shopping for a policy, make sure it's non-cancellable, experts say. "One of the first things to look for is a non-cancellable, guaranteed-renewal policy," Mr. Keller avers. "Once you're in, you're in; and the insurance company can't take it away or change the premium rates. You can get rid of them, but they can't get rid of you. That gives you the most protection as a consumer."

Association Policies

Mr. Keller notes that disability insurance provided through professional associations generally doesn't offer own-occupation coverage, and such plans typically have less-liberal contractual provisions compared to individual disability policies. "The organization gets the master policy contract, and the individual gets a certificate essentially saying they're part of this large group, but the individual members live and die by changes to the group. As with any policy you buy, make sure you do your research and understand what you're buying before actually purchasing it," he says.

Mr. Keller emphasizes that these association policies aren't the same as individual policies issued with an association discount, which he unreservedly urges physicians to seek whenever possible.

Residual and Recovery Riders

"Residual riders offer partial disability if you can't perform all of your duties, or if you can only work part time and have a loss of income as a result," Mr. Reich explains. "You would receive a partial benefit, and the percentage of that benefit would be based on the percentage of lost income."

Residual disability riders should never limit your eligibility for benefits to a return to work after a total disability. Mr. Keller explains, "Suppose you have a condition that flares periodically, and you don't know what it is, but it forces you to miss work during flare-ups. You don't know what's going on, but you're forced to work sporadic hours and see fewer patients and do fewer surgeries," he says. "You might have a huge loss of income, but own-occupation coverage does not pay for loss of income alone, even in the best policies: After all, you're still working very spo-

radically as an ophthalmologist, and so you're not disabled from your specific occupation. You might have a huge loss of income, but your residual disability rider may stipulate that you can only get residual income upon a (restricted-duty or part-time) return to work after a period of total disability. Then suppose that three years later, your doctor says that it's MS, and now and you've got to stop working altogether. You get zero for the three years that you worked sporadic hours because you were never totally disabled, and so never returned to work after a total disability. Most disabilities are sicknesses, not trauma; they're gradual and might eventually become total. With the wrong residual-disability language in your plan, you can't get anything for lost income if your disability progresses gradually before becoming total. At that point, you'll only get your total, and then only after you meet your waiting period."

In terms of protection, a recovery rider takes it even one step further, says Mr. Reich. "You don't have to show a loss of time or a loss of duties," he says. "You just have to show a loss of income as a result of having had a disability. So you could be working full time and doing everything you'd been doing before. But suppose you were out on full disability previously, and you're just now returning to work. You'll need to build your practice back up in many cases, which means you'll still likely be suffering a loss of income during that time."

Elimination Periods

Even if your disability claim is approved, you're still on your own financially during the elimination or waiting period, which usually spans 90 or 180 days from date of onset. "Buying a rider that shortens your elimination period from 180 days to 90 days can make a huge difference by helping prevent you from selling off any of your assets to stay afloat," says Mr. Keller. Although electing a 180-day elimination period can cut 10 percent off your premium payment, Mr. Keller urges ophthalmologists to consider how close they are to financial independence when choosing their waiting period.

"There are a lot of things that will take someone out of work for more than 90 days that will never make it to 180," he cautions about the longer elimination period. "Later, from a risk-versus-reward standpoint, you may comfortably be able to extend the waiting period as you approach financial independence," he adds.

Duration of Benefits

Make sure your policy will pay benefits for as long as possible. Some policies limit receipt of benefits to as little as two years. "They'll usually last until at least 65 to 67 years of age," says Mr. Reich. "But there are some that have lifetime benefits."

If you have high earnings and are closing in on financial independence, both experts recommend keeping at least some coverage in place until age 65 or 67. "If you've already had good coverage and you're earning good money, keep some coverage in place, if only to protect your assets," advises Mr. Reich. If you want to save money on your premium, you can always modify the benefit amount, the elimination period, or some other feature of your policy to reduce your costs.

Future-Increase Option

Another key rider for younger, healthier surgeons is the future-increase option. "Ophthalmology residents and fellows at the very least should consider purchasing a tiny individual policy with a relatively small benefit now," says Mr. Keller. "If you still have group insurance from your program, the individual policy will at least make up for some of the taxes you'd lose on group-plan benefits. Then, if you select a future-increase option, you could potentially increase the individual plan from $1,000 per month to perhaps $17,000 or more as your career progresses—without ever undergoing a medical exam, blood test, urine test or answering any additional medical questions, as long as you're healthy at the time you purchase the policy."

"Future-increase options allow you to purchase additional coverage as your income increases without having to go through medical underwriting again," says Mr. Reich. "You just have to show proof of income."

One caveat is to make sure your policy is amended—not replaced—when you purchase more coverage. "Some policies are going to give you a new policy that might have different terms than the original one when the increase option is exercised," Mr. Keller cautions. "Others may just amend your existing policy. Clearly, an amendment to the existing policy is a safer bet than getting something new, because you just don't know what's going to change."

Grab a COLA

If you accept the Council of Disability Awareness' estimate that a disability claim lasts an average of 34.6 months, you'll need your benefits to increase with inflation should the unthinkable happen. That's where the cost-of-living adjustment (COLA) rider comes into play. "If you become disabled, the benefit will increase, typically between 3 or 6 percent annually for every year you're disabled to help you keep up with inflation," explains Mr. Reich.

Mr. Keller says that the COLA rider is well worth the extra premium costs for younger ophthalmologists. "This can be 10 to 15 percent of the cost of the policy," he acknowledges. "But if you buy it as a 29-year-old resident or fellow, and your plan is to practice

until 65, that rider's really important because you've got a lot of time ahead of you," he says.

Optional "Bells and Whistles"

"There are additional riders that I like, but these policies get very expensive when you start adding all the bells and whistles, so you balance what's affordable with what makes financial sense for you," says Mr. Reich. He adds that a personal disability policy with the riders enumerated thus far is very good. "If you want to make it even better, you can add a catastrophic rider, which would pay benefits if you have a catastrophic illness and then need assistance with daily living. You may also want an unemployment rider that will pay your premiums during your period of disability from work. There's also a student-loan payment rider that will cover your loan debt.

"There's another rider you can get that I like," Mr. Reich continues. "If somebody becomes disabled and can no longer pay into their retirement account, there's a rider that will contribute to retirement savings over the years."

Insurance as a Map

While newly minted ophthalmologists may wonder how to swing paying for even basic individual disability insurance, Mr. Keller says that as little as $20 to $30 per month for a very small benefit early can become very powerful over time. "Your money is what pays the premium, but your health is what buys the insurance," he notes.

"I don't think anybody should go bare at any point," says Mr. Reich. "Even if you've amassed a good amount of assets before you become disabled, you may need to dip into those assets and live off of them. I would rather somebody have some sort of policy in place so they won't have to reduce their assets significantly to get through a disability."

Both experts agree that you should re-evaluate your disability policy regularly, and consider making changes to move your coverage from earning-potential protection to asset protection over time. While something is always better than nothing where coverage is concerned, you can relax or eliminate some of your riders to reduce premium payments by getting rid of the COLA rider late in your career, for example. "If you bought your policy when you were young and healthy, and now you're older and your plan is to not work a tremendous number of additional years, you might consider getting rid of the COLA rider because your claim duration is going to be much shorter than it would have been when you bought the policy," Mr. Keller says. "If you're now 55, and your plan is to retire at 60, how much value does that COLA rider really provide?" he says. "You might find that as you're getting older, you can do a combination of things: remove the COLA rider; increase your elimination period; and potentially even reduce the monthly benefit. Your expenses are probably lower now; your kids' college educations are perhaps funded; you likely own your home so there's no mortgage. You simply don't need what you originally did," he says.

Mr. Keller says that it's helpful to view disability insurance as a map. "It's really just designed to protect you as you move from point A, where you have a lot of education, training and income potential, but no money, to point B, where you've converted all that into a high net worth. Do you really need it after many years? If you do, there's a very good chance that you don't need it in the same way that you did when you first started."

Mr. Reich emphasizes that you can adjust this disability-coverage map incrementally and move to a less aggressive, asset-protection approach. "You can make a lot of changes to your policy without underwriting," he says. "You can easily reduce the benefit, which I think is the most common way to reduce the cost among people I've worked with. You can lengthen the elimination period. Those are the two major steps, and you could also get rid of some of the riders that you don't need anymore. That leaves you with more of a bare bones or catastrophic-type coverage that will prevent you from having to dip into your assets should something happen. At that point, it becomes more about asset protection than income protection."

Something > Nothing

Mr. Keller and Mr. Reich emphasize the importance of getting disability insurance coverage in place as early as possible, ideally during residency or even at the tail end of your medical education. "Something is better than nothing, although many group plans are less than ideal," Mr. Keller observes. If you want advice without pressure, he suggests checking in with a fee-only certified financial planner. "They're not trying to sell you anything," he says. "You're just paying for their mind and whatever they tell you to do: Whether or not you choose to do it, their meter was running and they got paid for the ride.

"A good insurance rule of thumb is a corollary to 'Don't sweat the small stuff,'" he continues. "Don't insure things that are not going to be financially devastating to you. Insure against financial catastrophe."

When researched well and purchased wisely, disability insurance can protect your fundamental ability to keep your life moving forward if you're unable to work. "I've seen people receive claims. I love the product because of what it can do for people," Mr. Reich says. REVIEW

Mr. Reich is an independent broker. Mr. Keller has an affiliation with Guardian, but acts as a broker for all carriers without prejudice or bias.

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Using Tech to Track Glaucoma Progression

Christopher Kent, Senior Editor

Experts discuss the latest findings regarding how best to detect progression using visual fields and OCT.

Today, ophthalmologists have an extensive toolbox for managing glaucoma and preserving vision. However, clinical decisions about how and when to use those tools are made in large part based on whether or not the disease is progressing.

To monitor progression, doctors today primarily use visual fields and optical coherence tomography. In general, doctors are relying on OCT more than visual fields in early glaucoma, given that structural damage generally becomes evident earlier than the functional changes visual fields are designed to detect. Conversely, when disease is very advanced, many surgeons focus more on visual fields, since some (though not all) OCT tissue measurements stop changing—the "floor effect." Meanwhile, during the long stretch between early and advanced disease, most surgeons rely on both technologies.

Our understanding of how best to use these technologies continues to evolve. Here, four surgeons with expertise in both visual fields and OCT share pearls for making the most of these technologies when managing glaucoma patients. In the first half of the article they discuss the use of visual fields; in the second half, they share pearls for making the best use of OCT.

Visual Field Testing: Frequency

Most doctors perform an OCT and visual field on a patient diagnosed with glaucoma at least once a year. Current research, however, suggests that other frequencies might be more helpful.

Felipe A. Medeiros, MD, PhD, distinguished professor of ophthalmology, director of clinical research and vice chair for technology at Duke University School of Medicine in Durham, N.C., has participated in research regarding the benefit gained from different rates of visual field testing. "Some of the previous work in this area assumed that doubling the number of visual fields you perform would result in detecting progression twice as quickly," he says. "We decided to investigate that specific assumption with actual data, and it turns out it's not true. Frequency of testing is just one component of how quickly we can detect progression.

"In our study[1] we looked at more than 1,000 eyes that had undergone multiple visual fields over time in order to estimate the time it would take to detect progression given a particular rate of change and a specific frequency of testing—one, two or three tests per year," he continues. *(See table, facing page.)* For example, if you're performing one visual field per

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year and the patient is progressing at 0.5 dB per year, which is about average for glaucoma patients, it would take you 7.3 years to detect progression. Doing two tests a year helps you detect progression sooner, but it doesn't cut the time in half; it still takes 5.7 years. If you perform three visual fields per year, the time to detect progression drops again, to five years. Not surprisingly, the more tests you do, the faster you'll be able to detect progression. However, the time it takes to detect progression does not decrease proportionately.

Years Needed to Detect Progression with Visual Fields

Median Rate of Change	One Test per Year	Two Tests per Year	Three Tests per Year
-0.25 dB/year	11.4 years	9.2 years	8.0 years
-0.50 dB/year	7.3	5.7	5.0
-1.00 dB/year	4.8	3.6	3.2
-2.00 dB/year	3.3	2.4	2.1

A recent study found that doing visual fields more often did not proportionately reduce the time to detecting progression. Switching from one to two fields per year shortened the time to detection significantly, but did not cut it in half. Based on these results, the study authors recommend performing two tests per year rather than one, but note that moving to three or more fields per year produces diminishing returns. (Wu, Saunders et al. 2017.[1])

"Overall, what we've seen is that you make a significant gain moving from one visual field per year to two per year, but you get less of a benefit going from two to three tests per year," he says. "This suggests that a good overall strategy is to do two tests per year. Of course, depending on circumstances, you might want to do more or less. If your patient has more severe disease, you might want to do a visual field more frequently. You could also do more testing at the beginning of follow-up, because that helps you determine whether the patient is progressing unusually fast. After that, you could test twice a year."

Dr. Medeiros says that most clinicians don't do as many tests as this data suggests are needed. "Some studies have found that the average number of visual fields obtained in glaucoma patients is less than one per year—sometimes only one every couple of years," he notes. "That can be OK if the patient has very early glaucoma, or if the patient is a suspect. In that situation you could do more imaging instead, because imaging is more sensitive in the early stages, and just do a visual field once a year. For example, if the patient is an ocular hypertensive, you could do imaging more frequently and just do a visual field every two years. But if the patient has more advanced disease, he's at risk of losing his vision from glaucoma and having functional impairment. In that case, you need to do visual fields more often—maybe even more often than twice a year.

"Of course," he adds, "it's important to remember that having a patient come in to the clinic three or four times a year for testing might be a significant burden for the patient. That has to be balanced against the need to detect progression."

Donald Budenz, MD, MPH, chairman of the Department of Ophthalmology at the University of North Carolina, notes another factor that can influence how often visual fields are performed: concerns about reimbursement. "Many insurance companies limit the number of visual fields you can perform in the office each year," he notes. "That's a valid concern for the insurance companies because in decades past, eye-care providers would do a visual field every three months on glaucoma patients just so they could bill more often. As a result, the insurance companies put a limit on that. However, that doesn't mean you can't do more than one field per year."

Dr. Budenz points out that you still may be able to get paid when you perform extra visual fields. "You have to document the medical justification for doing it," he explains. "If you suspect progression but you need to confirm it before you adjust therapy, write that in your note. If the visual field has poor reliability and needs to be repeated for that reason, document that. Then, if you get a denial from the insurance company, have your people send it back in for review with your note. If the insurance company actually reviews the note they'll see the medical justification for it, and chances are you'll get paid. But if you don't get paid, don't worry about it. You're doing the best thing for the patient."

When to Repeat a Visual Field

Given the variability of visual field testing, knowing when to repeat a test is key.

• ***When first seeing a patient, get several visual fields in succession.*** "There's definitely a benefit to doing two or three baseline visual fields in short order, because of the learning effect," says Dr. Budenz. "Generally the visual fields will improve over the first few tests; if they're spread apart and the patient is progressing you won't realize it, because the test results are improving from the learning effect.

"You certainly don't want to judge whether progression has occurred based on a single baseline field and one follow-up test a year later, so having a minimum of two baseline visual fields—three, if the first two don't match—is really important," he adds. "This is less of an issue with OCT, because OCT tends to be very reproducible as long as you have a good-quality

Should You Use a 10-2 Visual Field Test?

Donald Budenz, MD, MPH, chairman of the Department of Ophthalmology at the University of North Carolina, notes that in some situations, adding a 10-2 visual field to an exam may be appropriate. "The 10-2 visual field tests 68 points within the central 10 degrees radius around fixation, rather than within the central 24 degrees of radius," he explains. "The density of test points is obviously much higher if you put all 68 of them in the central 10 degrees vs. spreading them out in the 24-2 test. That means the 10-2 visual field tests the macula specifically, and it can reveal small early defects that are missed by the 24-2.

"Some investigators, such as Don Hood, MD, in New York, are recommending doing a 10-2 visual field if nothing turns up on the 24-2 visual field," he continues. "I wouldn't normally get a 10-2 if someone has a normal 24-2. However, if I see a suspicious 24-2 test—maybe there's one or two reproducible spots that are abnormal but don't reach the threshold for the test to be considered abnormal, which is three abnormal points in a cluster—I'll get a 10-2 to look more closely at that central area. At this point, I don't think anyone has clearly demonstrated that patients benefit if we routinely do a 10-2 visual field."

Dr. Budenz says he's currently involved in a study looking at patients who have normal results with 24-2 white-on-white perimetry, but have an abnormality on the ganglion cell complex on OCT (despite a normal retinal nerve fiber layer elsewhere). "The hypothesis is that some people's glaucoma may begin near fixation," he explains. "In those patients the retinal nerve fiber layer, which has these arcuate bundles, isn't thin; instead, the early warning sign is a thin ganglion cell layer as measured by the Cirrus or RTVue. If I find an abnormality in the ganglion cell layer in the macula, it makes sense to do a 10-2 looking for early visual field defects that would perhaps not be detected by the 24-2 test. Our study will tell us if that's the correct approach, or if we're wasting our time and the insurance company's resources."

—CK

scan, since there's no OCT learning effect. That makes frequent early testing less important, although, ideally, you could get three scans at the same sitting when first seeing the patient to have more numbers to average. For most patients you can do an OCT every six months to a year, looking for change over time."

• ***If a visual field looks suspicious for progression, repeat it.*** In contrast to trend analysis, which generates a slope of change over numerous tests, event analysis involves looking at the change suggested by a single visual field in comparison to two baseline tests. "Trend analysis is very helpful, but you need years of testing to see a statistically significant slope over time," Dr. Budenz points out. "That's why we also like to look at event analysis. The Humphrey perimeter can do trend analysis, but it also can do event analysis using the test-retest variability data that's built into the machine. It takes your baseline data from two visual fields and compares the current test to that. If the change is more than the test-retest variability of the machine, it will indicate that there's been progression.

"When you do suspect progression, it's essential to repeat the visual field," he continues. "False positives are very common with visual fields, so there's a good chance that a visual field that seems to show progression will actually return to baseline upon repeat testing. The worst thing you can do is advance therapy with a laser or surgery based on a single visual field. Chances are, if you repeat it, the visual field will return to baseline. And if the repeat field still looks worse, do a third field, because the Normal-tension Glaucoma Study showed that even two seemingly worse fields in a row can go back to baseline if you retest the patient a third time. Besides, the Glaucoma Progression Analysis software won't give you a message of likely progression unless you've confirmed the worsening twice after the initial follow-up field suggests it's worse. So you really need three follow-up fields to confirm progression."

Dr. Medeiros agrees. "Every time you see a visual field that's suspicious of progression, you need to confirm it," he says. "In most cases, its not true progression; subsequent testing will revert back to what you had in previous tests. Even when the reliability indices are good, issues like patient fatigue or just test-retest variability can affect the result. Sometimes the patient is just having a bad day. Then the visual field may look worse, but it's not actually worse."

• ***If a visual field has a false-positive rate higher than 15 percent, repeat the test.*** "A false-positive rate higher than 15 percent indicates that it's not a reliable test and needs to be redone," notes Dr. Medeiros.

However….

• ***Don't do repeat visual fields on the same day.*** "Multiple fields can be done in close proximity, but not on the same day," says Dr. Budenz. "Patients become fatigued when they do even one visual field. Plus, there's a phenomenon called retinal fatigue, which is physiologic and something we all suffer from when faced with repeated stimuli. So if you're concerned about someone progressing, bring them back in in the future for repeat testing. How soon you bring them back depends on how concerned you are."

Event vs. Trend Analysis

Dr. Budenz points out that progression can be identified in visual field data using either trend or event analysis. "Trend analysis is just plotting a parameter like average retinal nerve fiber layer thickness or mean

deviation for the visual field index over time and seeing if there's a downward trend that exceeds the normal downward trend associated with aging," he says. "Change associated with aging is exceedingly slow, taking place over decades. In comparison, glaucomatous change generally takes place over years. There is some interest in a subgroup of glaucoma patients who have been labeled 'fast progressors' by Joseph Caprioli, MD, and the folks at UCLA. In those patients progression might be measured more in terms of months. But in general, clinical trials have found that the average glaucoma patient takes five to seven years to demonstrate progression."

Despite the relative reliability of trend analysis, given that it incorporates many data points, Dr. Budenz points out that if you rely solely on trend analysis it can take a long time to detect progression. "Event analysis potentially can identify progression sooner because it focuses on a localized area," he says. "Trend analysis uses what we call global indices, so the entire field has to be deteriorating for the visual field index or mean deviation to have a significant slope. In reality, we know that most patients progress focally; existing defects get deeper or bigger, and that kind of change can be picked up by event analysis. So it's likely a more sensitive early indicator of progression. Trend analysis is important because you wouldn't want to miss the whole field getting worse—but you wouldn't want to miss localized change, either."

However, Dr. Medeiros warns that you're not likely to detect progression if you're only comparing one test to another. "If you're just doing visual fields every couple of years and looking at one printout and comparing it to the previous printout, you won't be able to reliably detect progression," he says. "There's too much variability. You need to get a series of tests and look at the trend over time. Generally, that means two tests per year for patients who have glaucoma."

Using OCT

Nathan M. Radcliffe, MD, clinical associate professor at the New York Eye and Ear Infirmary, observes that one of the best things about today's OCT is that the platforms have generally been stable for the past five to seven years, resulting in comparable data over a significant period of time. "There have been software enhancements, but the way we're measuring the retinal nerve fiber layer has been stable," he says. "As such, all the data collected five years ago is still valuable. In fact, it becomes more valuable as time passes, because the older OCT data is, the more likely it is to help you prove that a given patient is either stable or has progressed. When spectral-domain OCT technology was new, we struggled to figure out if someone was stable or had gotten worse. But once you have five years of data, you can tell if the patient is stable. The OCT manufacturers did us a favor by creating stable acquisition platforms that don't need to be changed every year."

As with visual fields, an important question for a doctor monitoring glaucoma patients with OCT is how often to perform a scan. Dr. Medeiros notes that the nature of the technology may cause doctors to believe less testing is OK. "Many doctors think that because OCT is an objective test, OCT data is more reproducible than visual field data," says Dr. Medeiros. "That may be true comparatively speaking, but OCT tests still have a lot of variability. If you don't do enough of them, you won't be able to reliably detect change over time. Generally, you need to do an OCT two times a year to get a good sense of whether the patient is getting worse."

Sanjay Asrani, MD, professor of ophthalmology at Duke University School of Medicine, director of the

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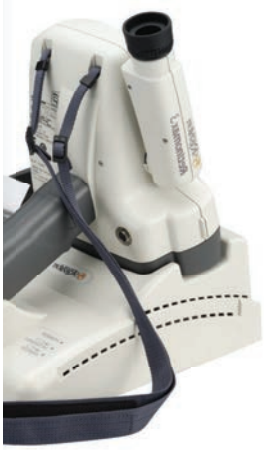
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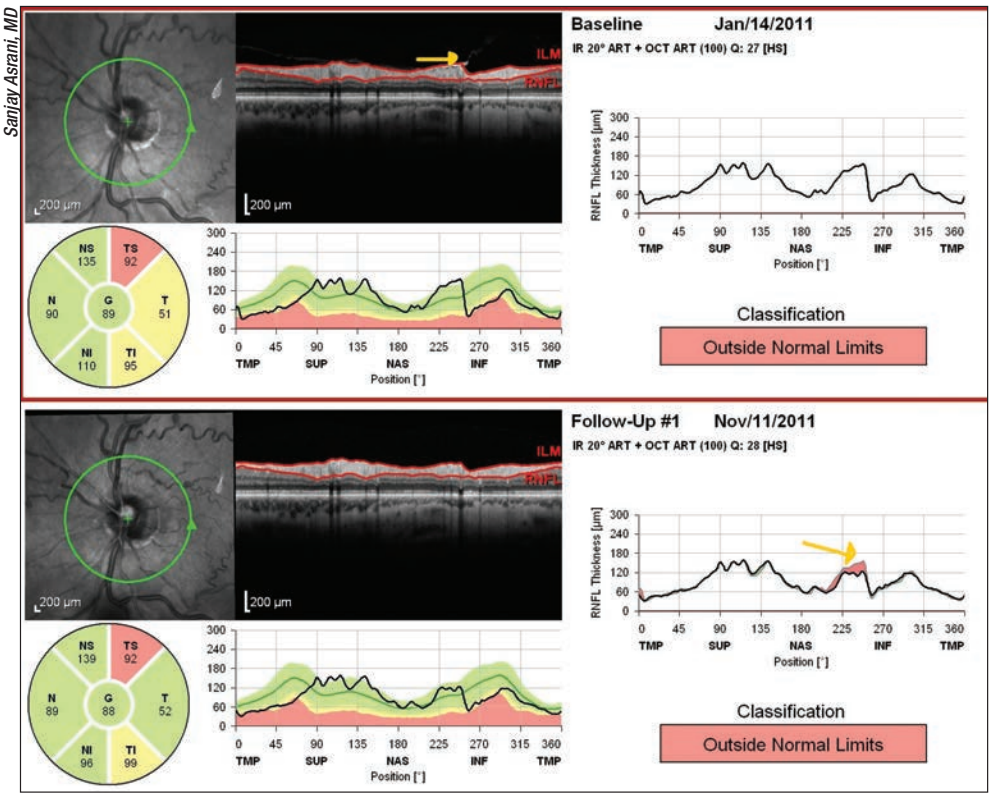

Examining the raw images in OCT reports is a key way to avoid being fooled by something that appears to be progression but is not. In the example above, an epiretinal membrane was tugging on the retinal nerve fiber layer (top image, yellow arrow); a posterior vitreous detachment released the tissue (bottom image, yellow arrow in graph), making the RNFL appear thinner. That, in turn, triggered an erroneous warning that progression had occured at that location.

Duke Eye Center of Cary and head of the Duke Glaucoma OCT Reading Center in Durham, N.C., notes that doing an OCT more often than twice a year may not be helpful, except in specific circumstances. He says he typically does not perform an OCT more often than every five to six months. "I haven't seen an OCT detect change if less than five months has passed," he says. "Therefore, if I have to repeat an OCT, I wait at least five months. However, if I'm not sure whether I'm seeing progression and I'm concerned about that patient, I might have him repeat the OCT in three months to see if the change is real and reproducible. If it's reproducible, then it's most likely real, and I might step up treatment. But when patients are stable or have mild glaucoma, I won't do an OCT more than once a year."

Dr. Radcliffe urges doctors not to base OCT frequency on reimbursement. "Let what's best for the patient be your guide," he says. "Patients who are at low risk, whose pressure is controlled and who have mild or moderate disease can safely be checked once a year using OCT, although I wouldn't scan less frequently than that. But when a patient has some other feature that puts him at higher risk, he can be checked more frequently. Don't base this decision on reimbursement.

"For example, consider a patient who always produces a lot of false positives when he takes a visual field test," he continues. "Why not get an OCT twice a year? That will cut your time to detect progression significantly, because the more data you have, the better you're able to determine the slope of a line. Ultimately, it's our confidence in the slope—meaning how quickly the patient is getting worse—that helps us determine the rate of progression, or whether progression has occurred. Or you may have someone whose pressure is wildly out of control, who also doesn't do well with visual field tests. I might get an OCT on this patient every three months because there's a high risk of progression. Knowing whether the patient is stable or progressing will immediately impact clinical decision-making. I don't want to wait a year or six months for that."

Acquiring the Data

These strategies can help ensure that the OCT data you capture is maximally useful:

• ***Scan the macula, not just the optic nerve.*** Dr. Radcliffe notes that over the past five years surgeons have begun looking for progression in the macula. "We've developed a good appreciation that glaucoma often affects central vision, even early in the disease," he says. "If central vision is affected by glaucoma, that nerve damage—ganglion cell or retinal nerve fiber layer damage—will show up in the macula. So not only can we detect glaucomatous damage in the macula, we can now trace the progression of glaucoma damage in the macula.

"There are two ways to do that," he continues. "One is by checking total retinal thickness, which incorporates the retina and the retinal nerve fiber layer. The other is by segmenting out the retinal nerve fiber layer, or the ganglion cell layer, at the macula. Our Zeiss OCT now has software for guid-

ed progression analysis of the macular retinal thickness or ganglion cell layer."

• ***Get a baseline macula and optic nerve scan, together, at the patient's first visit.*** "That first baseline is going to be very valuable," notes Dr. Radcliffe. "It's particularly important to do this if you think the patient is a glaucoma suspect, and it's essential if the patient already has a glaucoma diagnosis and takes a drop."

• ***Work continuously with your technicians and reinforce the importance of getting good scans.*** "I talk to my imaging techs every day," says Dr. Radcliffe. "I remind them to scan the nerve and macula on every patient and make sure the patient is dilated. When a bad scan does come through, take the time to go and talk to the technician; re-educate him so you get the best scans. Don't let it slide, because if you wait a month to fix the problem you'll have a month of bad scans. That's going to interfere with your ability to detect progression."

Interpreting the Data

Once you've obtained good-quality data, it's crucial to know how to interpret it. These strategies can help:

• ***When looking for change, focus on the supero- and inferotemporal quadrants.*** "Some doctors look for global thickness change, the overall average of the nerve fiber layer," notes Dr. Asrani. "However, it makes more sense to look at the average thickness of the supero- and inferotemporal quadrants to see if there's any change, because in the early to moderate stages of glaucoma the change is usually in those two quadrants. The average total thickness will include the nasal area, which typically does not change over time. That can hide change that's occurring in the supero- and inferotemporal quadrants."

• ***Look for change greater than 10 µm***. Dr. Asrani says that a change smaller than 10 µm in the supero- and inferotemporal quadrants may not be real. "That's because 5 µm is the intervisit variability of the machine's measurements of the average thickness of the quadrant," he explains. "One has to see greater than two standard deviations of that, a 10-µm difference, to be sure you're seeing real change. Less than that could just be a variation falling within the machine's accuracy limit."

• ***Take into account the loss of tissue caused by aging—because OCT machines don't.*** Dr. Medeiros points out that, unlike visual field instruments, OCT machines don't account for potential loss of tissue caused by aging. "We know that people can lose nerve tissue as they age," he says. "That's particularly concerning with OCT, because you're getting measurements such as the thickness of the nerve fiber layer. As you age, those measurements are likely to go down, giving you a false impression that glaucoma is progressing."

Dr. Medeiros says his group decided to follow a group of healthy subjects over time, ranging from 30 to 90 years old, to find out how much change in nerve fiber layer thickness could be attributed to aging alone.[2] "We found that the mean rate of tissue loss with aging was about 0.5 µm per year," he says. "However, because that's an average, it means that about 50 percent of normal people will progress faster than that. So, we calculated the confidence limits for a rate that would subsume 95 percent of healthy people. We found that 95 percent of healthy people lose nerve fiber layer thickness on OCT at a rate slower than about 1 µm per year. The bottom line is, if you're losing *more* than 1 µm per year of nerve fiber layer thickness on OCT, chances are it's caused by glaucoma, not by aging."

Dr. Medeiros points out that visual field machines have taken aging into account for decades. "We still don't

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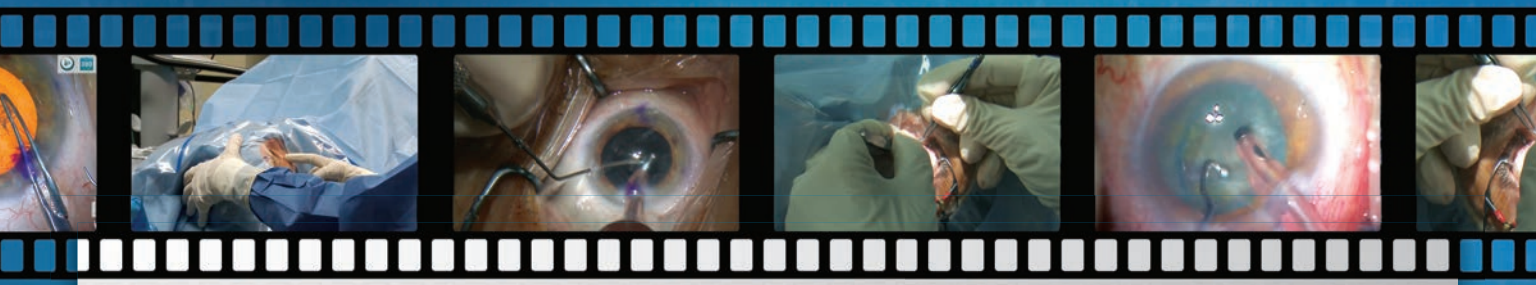

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Episode 24:
"Shallow Chamber and Convex Anterior Lens Capsule"

Surgical Video by:
Richard J. Mackool, MD

Video Overview:
An eye with a shallow anterior chamber is at increased risk for endothelial cell loss during phacoemulsification. A convex anterior capsule increases the risk of anterior capsulotomy "runout". In this case, I discuss and demonstrate techniques that protect the endothelium and prevent capsulorhexis problems in these eyes.

MackoolOnlineCME.com MONTHLY Video Series

Richard J. Mackool, MD

Welcome to the second year of Mackool Online CME! With the generous support of several ophthalmic companies, I am honored to have our viewers join me in the operating room as I demonstrate the technology and techniques that I have found to be most valuable, and that I hope are helpful to many of my colleagues. We continue to edit the videos only to either change camera perspective or to reduce down time – allowing you to observe every step of the procedure.

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

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

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

- Present strategies that reduce corneal endothelial cell loss and successful capsulorhexis creation in an eye with a shallow anterior chamber and convex anterior lens capsule.

Accreditation Statement
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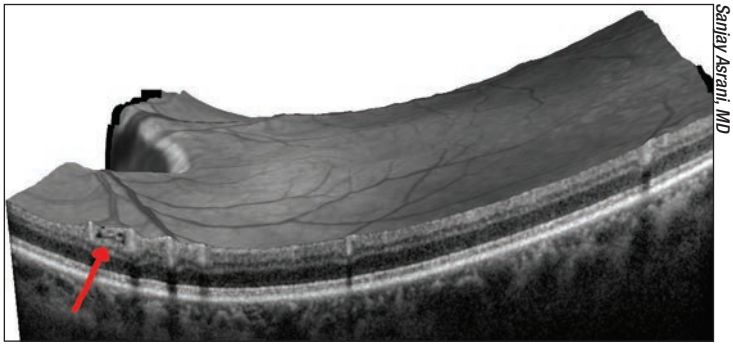
have that for imaging technology, but we need it," he says. "Doctors are being misled into thinking that if they see progression on the OCT, it must be caused by glaucoma when it could be from aging. It's an important point."



Sanjay Asrani, MD

In early glaucoma "schisis cavities" may form in the nerve fiber layer as axons disappear. These can create a "Swiss cheese" appearance on the scan *(example above)*. If the internal limiting membrane suddenly collapses at that location because of the hollow NFL beneath, the drop in thickness may trigger a warning of significant progression. Looking carefully at the previous scan may reveal evidence of a schisis cavity, indicating that only a small physical change has actually taken place, not significant worsening.

• ***Look for arcuate-shaped changes in macular thickness to confirm progression.*** Dr. Asrani notes that there are plenty of artifacts that can cause the illusion of progression. "For example, the release of an epiretinal membrane might appear to be progression," he says. "That can make it appear that the retinal nerve fiber layer area has thinned out at that location. But typically, if the progression is real, you'll also be able to see it in the form of an arcuate-shaped loss in the macula thickness maps. If you just find a generalized thinning of the macula, that's not caused by glaucoma."

• ***If you see a sudden change in the thickness of the RNFL, go back and look for signs of schisis cavities in the nerve fiber layer.*** "One thing that can appear as a change in thickness on OCT is the collapse of the nerve fiber layer bundle," Dr. Asrani explains. "This is something you may see in early glaucoma; the internal limiting membrane collapses because the nerve fiber layer was hollow. Sometimes that collapse has been evolving over time. When the collapse happens it will appear to be significant progression, but the collapse is actually a very small physical change.

"We call these hollow areas 'schisis cavities' in the nerve fiber layer, because the nerve fiber layer is thinning out as a result of those bundles of axons disappearing," he continues. "It turns out that in many cases, you can see the hollow structures before they disappear; they have a 'Swiss cheese' appearance. So if one has the time and inclination, one can look at the raw images and at the nerve fiber layer itself to see if they have this appearance. If you look at the previous OCT scan, you might find that this type of nerve fiber layer change was in the area in which the roof collapsed.

"I typically look for this in all of my patients," he adds. "I realize that not every clinician will have the time to look at each scan in such detail, but if I know that the nerve fiber layer is hollow, then I won't be that concerned if the nerve fiber layer thickness suddenly changes dramatically at the next visit. Put another way, if you see a sudden change in thickness, it's worth going back to the previous scan to see whether there was evidence of hollow tubes that were ready to collapse. If you find this, then what you're seeing is probably not a significant worsening of the disease."

OCT: Event vs. Trend Analysis

As with visual fields, OCT data can theoretically be interpreted by comparing tests or by looking at data trends over time. Dr. Budenz notes that although today's OCT instruments provide trend analysis, they don't do event analysis, although it should be possible. "If you know the precise test-retest variability of each clock hour or quadrant, then it should be possible to compare today's value to a baseline value," he says. "If the change is beyond the test-retest variability at that location, it could be flagged, and if the data is repeatable, you could diagnose changes focally, as we do with visual fields.

"We know that the smaller the measured area, the higher the variability," he continues. "For instance, the variability at a single point would be very high since you can't sample that exact same point each time. The least-variable parameter is average retinal nerve fiber layer thickness, due to signal averaging. The test-retest variability for average retinal nerve fiber layer thickness with the Cirrus OCT is between 4 and 5 µm, which is very good. So, any change greater than that is suspicious for progression, as long as you have good baseline and follow-up data.

"Of course, we may want to look at the quadrants or clock hours, because glaucoma can progress focally," he notes. "However, the variability increases as the area in question gets smaller and the number of data points shrinks. There's also the problem of imperfect registration between scans. For clock hours, the variability might be as great as 8 to 12 µm. As a result, most doctors who attempt to use event-based progression analysis rely on average retinal nerve fiber layer thickness.

"In reality," he adds, "I suspect most doctors don't even attempt this. But I think we'll eventually move toward automated event analysis for diagnosing focal change on OCT."

Making the Most of OCT Technology

Sanjay Asrani, MD, professor of ophthalmology at Duke University School of Medicine and director of the Duke Eye Center of Cary in Durham, N.C., and Donald Budenz, MD, MPH, chairman of the Department of Ophthalmology at the University of North Carolina, offer two suggestions for getting better data with OCT, strategies that many surgeons haven't yet adopted:

• ***Use OCT serial analysis to detect progression before the machine labels it.*** "There's a lot of interest in diagnosing glaucoma earlier, and I think we're missing an opportunity by just relying on the OCT color charts," says Dr. Budenz. "Doctors are waiting until they see yellow or red to decide that a patient has glaucoma, whereas the OCT serial analysis can reveal this long before the machine shows yellow or red on the chart. There's a lot of genetic variability in normal retinal nerve fiber layer thickness, so the machine may take a while to show yellow or red; but if you look at serial overlays of the retinal nerve fiber layer plot, you can see if the line that represents retinal nerve fiber layer thickness is actually declining over time inside the normal range.

"This is information the manufacturers are already providing that most of us are not looking at," he points out. "You have to print out the serial analysis and take the time to look at it. If we believe that the earliest opportunities to detect glaucoma are in changes in structure, then we need to look at comparative structural measures from the first time the patient had an OCT until today. It's very easy to do, and I teach this in all of my OCT courses. I call it 'change in the green' to highlight that thinning within the normal range can occur, and it's also glaucoma. Doctors get it once they see it, but in general they're not doing this. It's a missed opportunity for diagnosing early glaucoma from OCT."

• ***Consider routine scanning of the macula in glaucoma patients.*** "It's about time that doctors add the macula to what they check," says Dr. Asrani. "All OCT machines have the capability of looking at macular thickness. If a change appears only in the retinal nerve fiber layer and not in the macular thickness, it could be an artifact—not a real change. Furthermore, in advanced disease, OCT may not show any changes in the retinal nerve fiber layer because it's reached the floor effect. Macular thickness, on the other hand, can show OCT changes even in the late stages. So, looking at macular thickness is very valuable in late-stage disease. Ideally, everyone should be checking both the RNFL and the macula to detect change."

—CK

Dr. Medeiros notes that relying on an OCT test-to-test comparison to detect change is fraught with pitfalls. He points out that although his recent study found that a change of more than 1 µm per year suggests a loss beyond that caused by aging, that rate of loss can't be determined by simply comparing two OCT scans taken at different points in time. "When I talk about 1 µm of change per year, I'm not saying that the change from one test to the next test a year later is 1 µm," he explains. "This rate refers to a trend of loss collected from a series of tests over time, not just from comparing one printout with another. It's important to make sure the rate can be estimated with precision, and that requires multiple tests.

"Some people have suggested that a test-retest change of 5 µm in the average RNFL thickness on OCT is indicative of true progression," he continues. "However, we need to keep in mind that 5 µm is actually about 10 percent of the dynamic range of the instrument. The average OCT nerve fiber layer thickness measurement in a patient who is 60 years old is about 90 to 100 µm. In very advanced disease, such as in someone who's gone blind from glaucoma, the measurements never fall below 40 to 50 µm. That's the floor effect. Therefore, the dynamic range of measurements is about 50 µm. When you take these numbers into account, you start to realize that a change of 5 µm is not that small—it's actually 10 percent of the range of measurements. In order to detect smaller changes over time, you'll need to look at the slope of change, obtained from a series of tests. And many tests are needed if one wants to obtain a precise estimate of the slope and detect small changes."

OCT: Pitfalls to Avoid

As with most high-tech instruments, there are a host of ways your OCT data can be thrown off, leading to poor treatment decisions. To make sure your data is sound:

• ***Make sure all of your scans are of similar quality.*** "What this means, for example, is that if you dilate on that first exam, dilate at every exam when you see that patient," explains Dr. Radcliffe. "Try to scan the eye in the same state, and get the same quality images you got at the first visit. Bad image quality or having the eye in different condition will end up hampering your ability to detect progression."

• ***Beware of false positives.*** "Most doctors know how to manage false positives with visual fields, but false positives on OCT are more problematic because OCT is very reproducible and not subject to long-term fluctuation like visual fields," says Dr. Budenz. "OCT can definitely produce false positives, so before you conclude that glaucoma is progressing, check for other things that might explain the positive result you're seeing. It could be the result of poor signal strength, a change in positioning between scans, or some other cause. And of course, compare this result to what you're finding on the visual fields."

• ***To avoid being fooled by artifacts, always look at the raw OCT images.*** "You may find a pathol-

(continued on page 40)

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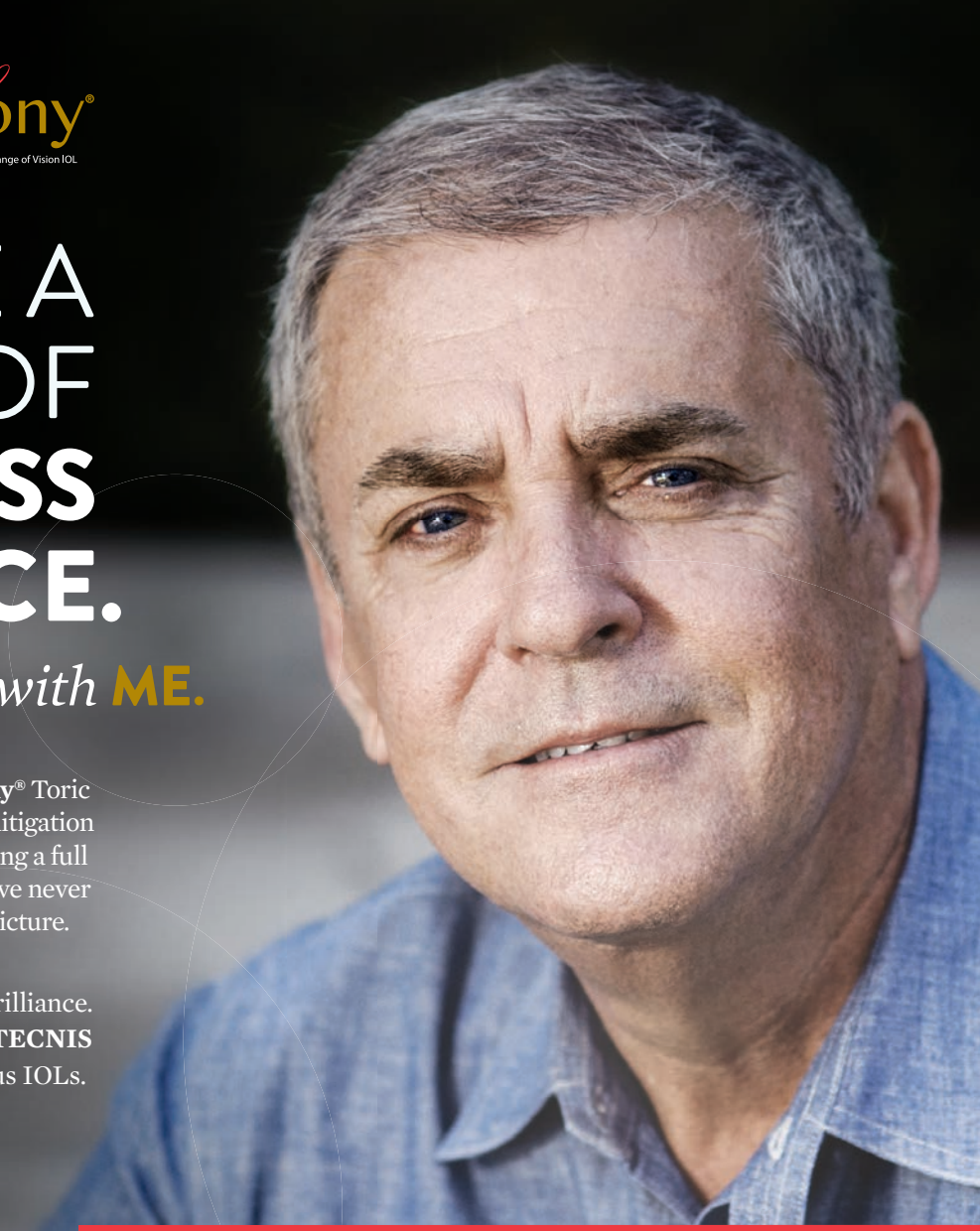

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(continued from page 38)

ogy such as an epiretinal membrane," notes Dr. Asrani. "Sometimes a measurement will be altered by something like a posterior vitreous detachment, or PVD. If the vitreous was tugging on the retinal nerve fiber layer and now has been released because a PVD occurred, the retinal nerve fiber layer will appear thinner. *(See example on page 34.)* It will look like progression, but it's not.

"That's something that can be detected by examining the raw image," he adds. "The raw image will also let you confirm that the software has correctly identified the edges of the RNFL. Sometimes those thumbnail-sized images don't clearly show the details, and if you can't see the details, you can't say for sure whether there has been progression." *(For more about how to avoid being fooled by OCT artifacts, see the article on page 48.)*

• ***Beware of thickness changes caused by uveitis.*** "One of our biggest discoveries in the past two years has been that when a patient has uveitis, the nerve fiber layer swells," says Dr. Asrani.[3,4] "If there's any uveitis activity—either idiopathic uveitis or secondary uveitis post-surgery—the nerve fiber layer may appear thicker than it actually is. Swelling in the nerve fiber layer may lull the clinician into a sense of security that the glaucoma is not getting worse because the swelling keeps the nerve fiber layer thickness intact. In fact, the glaucoma may actually be getting worse.

"Then, if the uveitis is subsequently treated with steroids and controlled, the nerve fiber layer swelling will gradually disappear," he continues. "That can dramatically reduce the nerve fiber layer measurement, making it appear that progression has occurred. It's very confusing because the swelling happens in both the nerve fiber layer and the rim of the optic nerve, so even the optic nerve cupping appears to get bigger as the uveitis gets controlled. And it's possible that at the same time prednisolone is causing the pressure to be borderline because it's treating the uveitis. All of this makes it look like the glaucoma is rapidly getting out of control, and may lead the clinician to undertake aggressive treatment. In fact, all that's happening is resolution of the nerve fiber layer edema.

"The ultimate message of the papers we published on this topic was that in patients with inflammation, retinal nerve fiber layer and macular thickness should be used with extreme caution for any baseline measurements or management of progression," he says. "One needs to use visual fields in those cases."

• ***Don't be fooled if the visual field changes but the OCT does not.*** Dr. Asrani notes that when changes in visual fields and OCT don't happen at the same time, clinicians may misinterpret what this means. "One must be aware that visual field changes in the early-to-moderate glaucomas will take place after the change has occurred in the OCT," he says.

"What often happens is, we see a change on OCT, and when we're sure that it's a real change, we step up treatment," he continues. "Then, a year and a half later, the visual field changes but the OCT doesn't. That's because the lost structure takes a long time to appear as a loss in function. At this point, many clinicians become confused; they may think the OCT is not working right, and given the change in the visual field, they may increase treatment even more. But all that they're seeing is the natural progression of structure changing before function."

Dr. Asrani notes that one reason many clinicians find this confusing is that not many have had the luxury of following patients with both OCT and visual fields for multiple years. "Some of us who have had both capabilities for a number of years have experienced this conundrum," he explains. "I've been using the same OCT machine for eight years, so I can now share my experience. When the visual field changes but the OCT doesn't, we start doubting the capability of our OCT. In that situation you have to be cautious about stepping up treatment if you've already stepped it up previously.

"Of course," he adds, "if you haven't stepped it up previously, this is a good time to do so."

Coming: Structure & Function

Dr. Budenz sees help coming in the years ahead. "Some time soon we should have computers that can integrate information on progression from OCT and visual fields, using Bayesian analysis to come up with a probability score that someone with glaucoma has progressed," he says. "It's possible to do this today with either visual fields or OCT technology, but it will be great when the two sets of data can be integrated.

"There's a lot of work still to be done," he adds, "but I think that's the direction in which we're moving." REVIEW

Dr. Budenz has no financial ties to any product discussed. Dr. Radcliffe has previously consulted with Carl Zeiss Meditec. Dr. Asrani receives lecture honoraria from Heidelberg Engineering. Dr. Medeiros has received consulting fees from Carl Zeiss Meditec and Heidelberg Engineering.

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Edited by


Taliva D. Martin, MD


Sara J. Haug, MD

Mastering LASIK and PRK

Edward Manche, MD
Stanford, Calif.

An experienced refractive surgeon shares his top surgical pearls.

As anyone who's ever done any house painting knows, preparation is about 80 percent of the work—get the prep right, and the actual painting is (almost) a breeze. Likewise, a lot of the work of refractive surgery is front-loaded: managing patient expectations; choosing the refractive target; ruling out suspicious corneas, etc. These all take time and expertise to evaluate properly. Here, I'll share a variety of tips based on my experience with thousands of corneal refractive surgeries.

LASIK

Minimal pain and quick recovery have made LASIK the most popular laser refractive surgery in the United States. Taking the time to go through key aspects of the operation will ensure it's a successful procedure with your patients, as well.

• ***Preop exam.*** A thorough physical exam of the eye, including a dilated exam, imaging, pachymetry, topography and wavefront aberrometry will help you determine if the patient is a potential candidate for refractive surgery. We like to use an imaging system that includes the posterior cornea. I use the Pentacam, but other systems, such as the Galilei, can also give you data on the posterior corneal shape. This aspect of the exam is important because imaging the posterior cornea may allow you to pick up cases of early keratoconus that you might not detect on placido disk-based topography. Another emerging technology that may prove helpful is epithelial mapping using anterior-segment optical coherence tomography. This can be helpful in patients who have slightly irregular topography but normal corneal thickness. An OCT epithelial map can give you information on whether that patient has subclinical keratoconus. If a patient is otherwise a candidate for refractive surgery, but his corneal thickness is less than 500 µm and/or there are any subtle changes on corneal topography, we discuss considering PRK over LASIK.

• ***Motivations and expectations.*** Though the results of the physical exam can put a hard stop to any refractive surgery, your discussion with the patient regarding his motivations for the surgery is equally important. Someone can be a good candidate on paper but then, when you have a conversation and find out what he's looking for, you might discover he doesn't have realistic expectations.

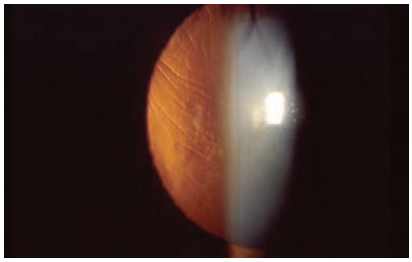
A common example is the 45-year-old who wears -1 D glasses but doesn't wear reading glasses and has never worn contact lenses. She wants crystal-clear distance vision and doesn't understand the concept of presbyopia. In cases like this, I'll demonstrate presbyopia in the office, or fit

her with contact lenses to demonstrate it. When I do this, in many cases these patients decide not to have the surgery, since it would result in them constantly having to wear glasses for reading and near tasks. I see a fair number of referrals who were -1 D or -1.25 D, who had beautifully performed surgery and are now in their 40s or early 50s, and are unhappy because they lost their ability to see at intermediate and near.

Unfortunately, many patients who are interested in refractive surgery think that it's a panacea that's going to correct their vision at all distances, and are surprised when you explain that it won't. These are good cases in which to try monovision if they haven't already. These concepts are less of an issue when you are dealing with a patient who wears contact lenses on a regular basis, because he understands what life after refractive surgery will be like.

Another patient to be somewhat cautious of is someone who's unhappy with her glasses, doesn't like soft lenses, and feels that the only corrective lens remotely adequate for her is a rigid gas permeable contact lens. She'll often bring in several pairs of glasses with small, 0.25-D differences in sphere or cylinder and declare that none of them work for her. This is another type of patient who's likely to be unhappy with the results of laser vision correction, and you probably won't be able to satisfy her.

• ***Prep the surface.*** If the patient has significant dry eye, you have to address it. This can take the form of more frequent lubrication, Restasis or Xiidra, or a short course of topical steroids. Also, be sure to treat any external disease like meibomian gland dysfunction and blepharitis with lid hygiene, warm compresses and/or a brief course of steroids, as these conditions can lead to a sterile inflammatory response at the edge of the flap if they're not addressed prior to refractive surgery.



Flap wrinkles are most effectively treated when addressed early in the postop course.

• ***Femtosecond flap issues.*** Though there are several systems with which to make flaps, I routinely use the IntraLase and the Visumax. Each system has its own strengths and weaknesses.

When performing a treatment with the IntraLase, a suction break is very uncommon due to its very strong suction. However, you can still take some extra precautions to ensure this doesn't occur. First, make sure the patient is relaxed and knows what to expect before you activate the suction. Before you activate it, explain that he'll feel pressure and the lights will dim or brown out. Have him avoid clenching his facial muscles and/or trying to squeeze out the ring. It often helps to tell patients to keep their shoulders relaxed and to not clench their teeth. Also, explain how long the process will take.

When using the IntraLase, if the patient has a small cornea or a cornea with neovascularization, intracameral bubbles can occur if the photodisruption is very near the limbus. Because of this, you may want to consider creating a smaller-diameter flap, trying to avoid the limbal blood vessels, because the gas can tract back through Schlemm's canal, go inside the eye, and make eye-tracking with the laser challenging.

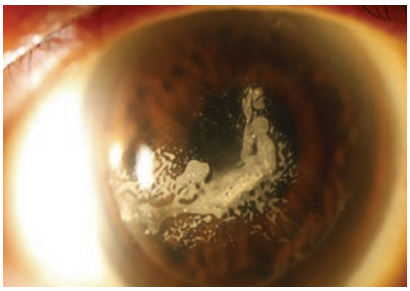
With the Visumax laser, instead of suction being applied to the sclera, it gets affixed to the cornea. It's a very light suction, so it's more prone to suction breaks. The benefit, however, is that patients get no postop subconjunctival hemorrhage, no discomfort during the treatment and their vision doesn't go dark during the procedure as it does during IntraLase flap creation. The disadvantage is, if the patient has a strong Bell's phenomenon or squeezes his eye, he can break suction during the actual treatment.

Because of the different kind of suction, the Visumax calls for a different technique. Once the suction ring is applied to the patient's eye, he is instructed to look at a green light, which will remain in view throughout the treatment. When the applanation cone is brought down onto the cornea, that green light becomes very clear. At that point, you want to make sure the light is properly centered and then engage suction. When you engage the suction, be sure to tell the patient that it's all locked in place and that, after about 14 seconds, the green light will get fuzzy, so he should avoid the impulse to chase it—it's best to look beyond it at that point. A 9-mm flap takes about 18 seconds to create, with the treatment starting in the periphery and then moving to the center. As this occurs, we'll do a treatment countdown, so the patient can focus on staying still, secure in the knowledge that it will be over at the end of the countdown. We also tell patients that, once the treatment starts, they shouldn't try to talk, because it can cause their head to move and break suction with a device with relatively light suction like the Visumax.

One tactic I use to try to avoid intraoperative suction breaks is to put my hand on the patient's head, with my finger on the upper lid to try and detect any attempt at squeezing the eye. The touch of my hand helps calm the patient, but the finger also alerts me if she is squeezing too hard.

If a suction break occurs with the Visumax, the company recommends you re-engage with the same patient interface. Basically, Zeiss says you don't have to abort the procedure, and you can re-cut at any point. However, if you've performed the complete lamellar cut but not the side cut, you have to use a workaround: You need to program the laser to perform another flap. Then, pinch the suction tube with your fingers to simulate suction without the suction ring on the eye. Depress the foot pedal for 13 seconds to discharge the lamellar cut while pinching the tube–essentially wasting the lamellar cut portion of the procedure. After the 13 seconds, you release suction. The system will then detect a suction break. You then apply the suction ring to the eye and complete the treatment with the remaining five seconds. The last five seconds is the side-cutting portion of the treatment. (If you have a suction break after the lamellar cut has been made during LASIK with the IntraLase, you can program the laser to perform a side cut only.)

Tissue bridges can be somewhat challenging to break when you try to lift a Visumax flap in the presence of an opaque bubble layer, which is a film composed of bubbles in the intrastromal interface that can block laser pulses and result in hard-to-lift flaps. The best approach is to try and avoid OBL to begin with. One way to do this is to have Zeiss' corporate field representatives slightly lower the power so as to not get too much OBL. If the treatment does result in OBL, gently work at the OBL with the instrument when you go to lift the flap, taking great care not to perforate or tear the flap. Additionally, with the Visumax, I'll typically score the 270-degree side cut first, because occasionally there are tissue bridges not completely cut by the laser. However, if you trace around 270 degrees first, it makes lifting the flap easier because there won't be tags at the flap edge. Overall, I've performed a couple thousand LASIK procedures using the Visumax, and have had only one suction break during flap creation. I re-did it without a problem. I've performed more than 20,000 LASIK surgeries with the IntraLase, and have had only one, maybe two, suction breaks. I re-engaged it without a problem in those instances.



Once ingrowth is removed, recurrence can be prevented by sealing down the flap.

On the IntraLase, if you do encounter intracameral bubbles—and there aren't a lot of them—you can turn down the light source on the excimer to help it track the pupil more accurately. As long as the excimer is capturing the pupil's edge, you can safely perform the treatment. If, for some reason, the tracker on the Visx excimer laser won't engage, you can turn it off and do the procedure. Alternatively, you can wait, have the patient come back the following day, and complete the treatment at that time.

If there's scarring present, such as from an old pterygium that you don't want to cut through when you're making the flap, you can program the femtosecond laser to put the hinge in a better place. For instance, if the pterygium scar is nasally located, you can place the hinge nasally. Or, if there's significant pannus superiorly, make a superior hinge.

Be sure to use surgical drapes that cover the patient's lashes. If you don't, the oil from the meibomian glands and debris from the lid margin start to float around the cornea during LASIK, potentially flowing beneath the flap and leading to diffuse lamellar keratitis or, rarely, an infection. Also, if there are a lot of secretions, irrigate them away before you lift the flap, and make sure the fornices are dry while you do the treatment. Otherwise, all that debris has the potential to get under the flap when you reposition it in place. A clean interface not only looks good, but it also lowers the risk of inflammation and infection.

LASIK Complications

Unfortunately, any patient can develop a complication. Though you can't reduce the rate of complications to zero, you can minimize it.

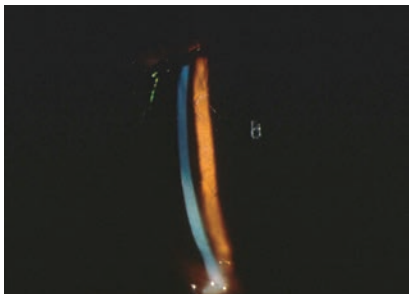
• ***Buttonhole flaps.*** If you're doing thin-flap LASIK with a femtosecond laser in a patient with a previous scar and you get vertical gas breakthrough, or you get a buttonhole while using a microkeratome, don't lift the flap and ablate. Instead, stop and replace the flap. Then, let it heal and, two to three months later, perform a surface ablation. It may take a little extra time, and a different procedure, but patients will see well in the end. However, if you lift the buttonholed flap and ablate the cornea during the initial

flap creation, the patient will almost certainly get epithelial ingrowth due to the potential mismatch between the flap and the underlying surface, which is more difficult to deal with. Also, epithelial ingrowth in the setting of a buttonhole is a common occurrence and can be difficult to manage.

• ***Epithelial ingrowth.*** By way of a quick review, epithelial ingrowth is as its name implies, epithelial cells that grow into the LASIK interface rather than just healing over on the surface of the cornea. There are a couple courses of action you can take in these cases.

We've had success with cleaning out the ingrowth and then applying a tissue adhesive to seal down the flap: We published a case series of this approach using Tisseal glue, which we found works well. We've also just submitted a case report on a patient in whom we used ReSure sealant on a very large buttonhole that had massive epithelial ingrowth. In some cases, we would be forced to amputate the flap and the patient would develop corneal scarring. Now, however, with the advent of tissue glue and sealant, we can more readily manage these cases.

For cases of LASIK enhancements, we're beginning to study the prophylactic use of tissue sealant. For instance, if a patient who had LASIK three to five years ago comes in for a touch-up, we'll perform the ablation and then apply sealant prophylactically on the edge of the flap. In a study of this technique that we're conducting, in the small number of patients on whom we've done this procedure so far, none have had developed epithelial ingrowth. However, it's worth noting that many surgeons have switched over to surface ablation for these late LASIK enhancements. The problem with that approach, however, is that the patients have a long recovery time and often have a significant hyperopic shift over the first couple of months postoperatively. They're also a little less satisfied with PRK after having experienced the "wow" factor of LASIK.



Diffuse lamellar keratitis, if caught early, can be treated with increased steroids.

• ***Corneal striae and folds.*** Due to the more-frequent use of femtosecond lasers, which results in more-uniform flaps than those we used to make mechanically, we don't encounter striae and flap folds as much as we used to. You can run into this complication, however.

If you do see striae, either micro or macro, it's important to address them early. If you leave them in place, they become fixed folds that are very difficult to remove. For micro-folds, you can often just smooth them out and eliminate them that way. If you wait weeks or months, however, the fixed folds will probably require a flap lift and a suture to remove.

To smooth out a cornea with a fold, if it's the first day postop, I'll take two Weck-Cel sponges and, starting in the center of the cornea, move them in opposite directions across the cornea to stretch it out. This will flatten many small striae.

For fixed folds that have been present for weeks or months, I'll take the patient back to the LASIK suite and remove the epithelium under topical anesthesia in order to see where the folds are in Descemet's. This step is necessary because the epithelium can mask the extent of striae. Then, I'll smooth out the cornea and place sutures that will leave the flap on-stretch. I typically leave the sutures in for three to six weeks depending on the severity of the striae and the length of time the striae have been present.

• ***Diffuse lamellar keratitis.*** DLK isn't that common, but early recognition is still imperative. If you find DLK early on, you can just increase the steroid drops. For example, if I diagnose DLK on postoperative day one, I'll use Durezol as often as six to eight times per day for a few days and it will effectively resolve it. Using this regimen, I haven't had anyone go on to stage-IV DLK.

• ***Interface fluid.*** This is a rare postop presentation that can occur if a patient is treated with an aggressive course of topical steroids for too long a duration, which can occur if a surgeon believes he's treating DLK. DLK isn't chronic, and if a patient has been treated for two weeks with aggressive steroids for DLK, it probably isn't actually DLK. What can occur instead, however, is a pressure rise from the steroids, causing fluid to accumulate in the interface and creating a "false" anterior chamber effect. Because of this, applanation tonometry in the central cornea will read normal or low, but a device such as the Tonopen, when used in the periphery, will read the actual pressure—often as high as 40 to 80 mmHg. The upshot is that you shouldn't be using aggressive steroids for more than seven to 10 days for DLK management. A slit lamp exam or anterior segment OCT can reveal this condition or rule it out.

PRK

Once thought to be a phased-out procedure whose time had passed, the advent of LASIK-induced ectasia several years ago brought surgeons back around to the understanding that there are some patients for whom surface ablation is the better choice. Here's what I've learned about it over the years.

• ***Prep the surface.*** As with LASIK, you want to make sure that the corneal surface is optimized preop. If the patient has dry eye, be proactive in fitting punctal plugs, either permanent or dissolvable collagen varieties. I've found that, if the eye is well lubricated ahead of time, it heals much faster than if it's a chronic dry eye. Along these lines, if the patient is a smoker, have him stop beforehand, since I feel it can slow epithelial recovery and increase the risk of scarring and haze.

• ***Epithelial debridement.*** Though there are several different ways to debride the epithelium, I've come to prefer the use of a rotating brush. The brush is very fast, leaves smooth edges and, with practice, you can remove just the right amount of tissue with it. The rotating brush also takes only a few seconds to use, and the debridement is very consistent from eye to eye.

I've never been a fan of alcohol-assisted removal because alcohol is a desiccant, and if it's left on the epithelium too long or spills onto the limbus, it's very irritating and can delay re-epithelialization. If it finds its way into the stroma and causes desiccation, it can potentially result in non-uniform flattening.

• ***Mitomycin C.*** Besides postop pain, haze and regression are the next serious concerns. To help stave them off, I use MMC in virtually all cases. I'll vary the exposure time of the 0.02% MMC based on the amount of tissue removal. If it's more than 90 to 100 µm, I'll use it for 40 seconds. For 45 to 89 µm, I'll apply it for 25 seconds, and if the correction is under 45 µm, I'll use it for 15 seconds. When we use it in this way, the risk of developing scarring or haze is significantly less than 1 percent and, if the patients do develop scarring or haze, it tends to be relatively mild and treatable.

• ***Pain management/postop surface issues.*** As alluded to above, postop pain is a consideration with PRK. Though we can't eliminate it, we can

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take some steps to minimize it. We use chilled BSS during the procedure, and have patients put their lubricant drops in the fridge at home when they're not using them. My postop regimen consists of the following:

- one NSAID drop after the bandage contact lens is in place (I prefer an 8.4 base-curve Acuvue);
- a fourth-generation fluoroquinolone and Pred Forte until the epithelium heals;
- following re-epithelialization, Pred Forte q.i.d. for two weeks, then b.i.d. for two weeks (for lower corrections, possibly q.i.d. for 10 days and b.i.d. for 10);
- avoid postop topical NSAIDs, which I feel don't offer a lot of comfort and can slow down re-epithelialization.

Also, before surgery, we'll have patients begin taking ibuprofen to try to get ahead of the pain cycle and circumvent the inflammation cycle. We'll also occasionally give Tylenol with codeine or Vicodin for breakthrough pain.

In cases of lid swelling postop (the eye itself doesn't discriminate between the eye and lid in cases of inflammation), we'll recommend an ice pack.

With regard to the ocular surface, some patients will develop transient dry eye postop. In such cases, we're aggressive with lubricants. If that's not enough, we're quick to use Restasis or Xiidra. If those aren't effective enough, we have a low threshold for going to plugs because we've found that patients with symptomatic dryness preop really respond well to plugs postop.

Though refractive surgery has been around a while and it may seem that some surgeons have gotten it down to a science, a tough case will surprise you sooner or later. I hope that these tips and strategies for lamellar and surface procedures will help make it much later. REVIEW

Dr. Manche is the director of cornea and refractive surgery at the Stanford University Eye Laser Center, and a professor of ophthalmology at the university. He is a consultant for Allergan, Avedro, Shire, J & J Vision, Carl Zeiss Meditec, Ocular Therapeutix and Avellino Labs.

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Don't Be Fooled: Spotting OCT Artifacts

Numerous factors can cause your machine to produce a misleading result. Here's how to identify bogus data.

Teresa C. Chen, MD, Boston

When it comes to diagnosing and monitoring our patients, technology is a big part of the equation. However, technology comes with a caveat: All of the devices we rely upon —including optical coherence tomography—are imperfect, and the data they present us with sometimes contain artifacts. Since it's our responsibility to interpret that data and make accurate clinical decisions, it's crucial that we recognize these artifacts and either interpret them accordingly or repeat the scan. If we fail to recognize testing artifacts, we can make incorrect treatment decisions that adversely affect our patients.

Here, I'd like to discuss 10 of the most common artifacts associated with using OCT to diagnose and monitor glaucoma patients.[1] Then, I'll describe how any of these 10 artifacts can contribute to the phenomenon of "OCT diseases," which can only occur if you have an OCT machine. These "diseases" occur when the OCT printout presents us with an incorrect color classification of green, yellow or red, which can lead us to believe that the patient is doing well or poorly when the opposite is actually true. Lastly, I'll talk about the pitfalls of OCT data when the same patient is tested using different OCT instruments or technologies.

The Top 10 Artifacts

There are probably dozens of ways in which OCT measurements can be distorted, given the complexity of the technology. However, some artifacts occur more often than others. Let's look at the top 10 OCT artifacts you're most likely to encounter, going from least common to most common. (Although OCT can scan the retinal nerve fiber layer, the macula or the disc, the retinal nerve fiber layer is the most commonly used OCT parameter when following glaucoma patients. Therefore, this article will focus on the 10 most frequently encountered retinal nerve fiber layer artifacts.)

10 ***The edge of the scan is cut off.*** In this situation the data is incomplete because the scan is incomplete, most likely because the patient moved during the scan. The problem is that the machine will give you a measurement for the rest of the scan anyway. If the technician doesn't realize that the patient has moved or notice that the scan is incomplete at the edge, the data may be saved and given to the doctor. This is one of many reasons that it's important for your technicians to be educated about OCT artifacts; they're often easy to detect. (If the technician does realize that this artifact has occurred, the scan should ideally be repeated.)

9 ***Motion artifacts.*** This is data distortion that results from the patient moving during the scan. In this particular artifact, the patient moves so much that parts of the scan may fall outside of the rectangular display box on the printout. The resulting data is generally not usable.

An error of this kind should also be easy to spot if the technician knows to look for it. Consider how a typical OCT scan of the nerve fiber layer appears. A typical OCT scan is black at the top and the bottom of the printout, with horizontal white segments running across the middle of the page from side to side representing the many layers of the retina. The top-most layer of the retina is the retinal nerve fiber layer, which is usually represented by a white horizontal linear segment;

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two colored lines depict the front and back borders of the retinal nerve fiber layer. The computer then calculates the retinal nerve fiber layer thickness, delimited by the two colored lines.

If there's a motion artifact, the retinal nerve fiber layer may appear to zigzag. *(See examples on page 48.)* One or both of the colored lines may also look out of place. If the patient moved a lot, parts of the scan may simply be missing.

If the technician knows to look for this type of artifact and sees that it has happened, the technician should instruct the patient to hold still and repeat the scan.

8 ***Incomplete segmentation.*** Segmentation refers to the computer deciding where the borders of the retinal nerve fiber layer tissue lie, which it displays visually as two colored lines. If you don't see the two colored lines going all the way from the left to the right of the printout, you have incomplete segmentation, which means the machine was unable to completely draw the colored lines and unable to determine the complete borders of the retinal nerve fiber layer. *(See example on page 48.)* In this situation, the machine may not be able to calculate a retinal nerve fiber layer thickness value where there are no colored lines.

If neither the technician nor the busy ophthalmologist notices that the colored lines are incomplete, the doctor won't realize that the data is garbage and should be discounted. The doctor may not be able to make clinical decisions based on this incomplete information.

7 ***Peripapillary-atrophy-associated error.*** Peripapillary atrophy is a common abnormality that can occur in the vicinity of the optic nerve; it's often seen in older patients and patients who have glaucoma. Usually the OCT scan circle is larger than most PPA, so most scans are not affected by it. However, in patients who have really large areas of PPA, the OCT machine will scan over it. Because certain layers of the retina are missing in an area of PPA, the machine will give a funny retinal nerve fiber layer thickness value.

If this happens, the overlap will be visible on the printout. If you see that the OCT scan circle extends over the area of PPA, you should know that the retinal nerve fiber layer thickness value will not be accurate. In some cases, when you look at the printout, the colored lines will zigzag around, indicating that the computer wasn't able to accurately determine the borders of the retinal nerve fiber layer.

Only a very experienced technician would be likely to catch this problem and realize that the scan needs to be redone, offsetting the green circle to avoid the PPA (if possible). In most cases, the physician will have to be the one to catch this.

6 ***Missing sections of the scan.*** Middle parts of a scan may be missing because something inside the eye, such as a floater, prevents data from being collected in one or more areas. As a result, the printout won't show any retinal nerve fiber layer in that area, and there will be a black space (or spaces) instead. In those areas the data is missing, and the retinal nerve fiber layer values in those regions—if any values are even generated—should be disregarded.

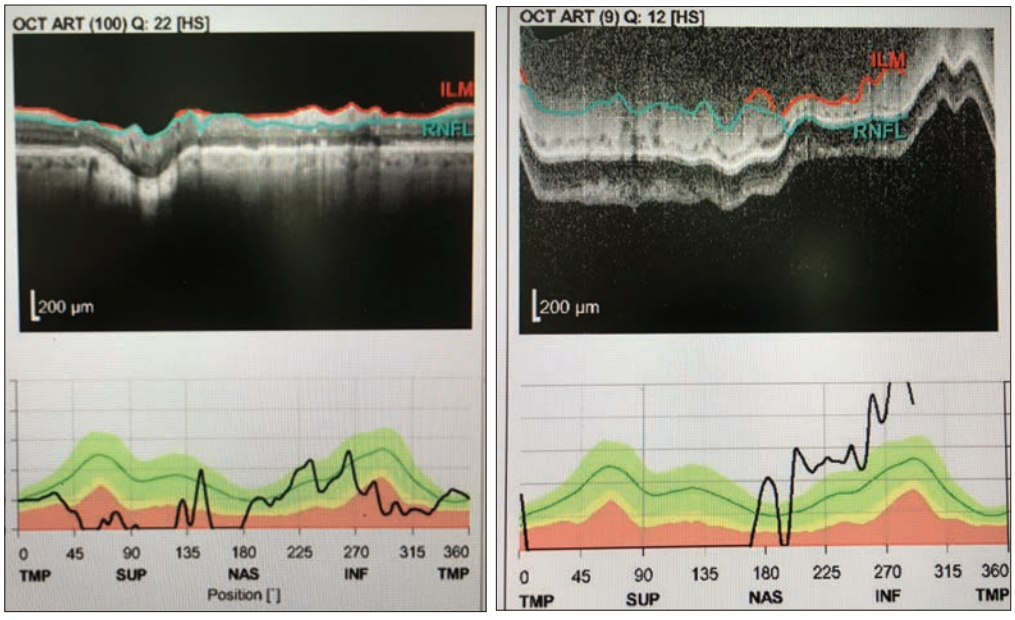
This type of error is obvious if you look at the scan. However, the doctor may not take the time to stop and look, or may not realize the significance of the gaps.

5 ***Misidentification of the anterior boundary of the retinal nerve fiber layer.*** In this situation the machine has made a mistake when drawing the top colored line representing the top border of the retinal nerve fiber layer. The resulting measurements can be either too large or too small. Common ocular issues that could cause this kind of error include an epiretinal membrane or a posterior vitreous detachment. It should be fairly easy to see that this has occurred if you look at the scan;

Prevalence of 12 Types of RNFL Artifacts on OCT*

Relative Frequency	Artifact	Number of Scans	Percentage of Scans (%)
1	Decentration	644	27.8
2	PVD-associated Error	332	14.4
3	Posterior RNFL Boundary Misidentification	177	7.7
4	Poor Signal	118	5.1
5	Anterior RNFL Boundary Misidentification	73	3.16
6	Missing Sections of Scan	35	1.51
7	PPA-associated Error	27	1.2
8	Incomplete Segmentation	14	0.6
9	Motion Artifact	5	0.22
10	Cut Edge	4	0.17
11	Staphyloma-associated Error	1	0.04
12	MNFL-associated Error	1	0.04

* Based on 2,313 scans from 1,188 patients scanned with the Spectralis OCT.
PVD=posterior vitreous detachment; PPA=peripapillary atrophy; MNFL=myelinated nerve fiber layer. Based on Liu et al, 2015.[1]



Multiple artifacts can occur in the same scan. A motion artifact caused by patient movement affected the data in the left-hand scan above, making the retinal nerve fiber layer appear to zigzag. The scan on the right shows both a movement artifact and incomplete segmentation; the colored lines don't reach from side to side.

instead of the top colored line hugging the top of the white retinal nerve fiber layer, it's pulled up into the middle of the page. Since the distance between the colored lines determines the RNFL measurement, the numbers will be inaccurate and will sometimes give an artifactually thick retinal nerve fiber layer measurement.

4 ***Poor signal.*** Common causes of this artifact are dry eyes and cataracts. If there is a cataract, the OCT beam is partly blocked from reaching the nerve tissue it's trying to measure. It's like looking through frosted glass instead of a clear windowpane. The resulting picture will look grainy or blurry, and the contrast between the gray retinal layers and the white retinal layers will be indistinct. You should be able to see this when looking at the scan. If the borders of the retinal nerve fiber layer are blurry, the machine will have a hard time figuring out where to draw the colored lines or retinal nerve fiber layer borders.

If the poor signal is caused by dry eyes, putting a drop of artificial tears on the eye before retaking the scan will help—assuming the technician recognizes the problem. Of course, this won't help if the problem is an early cataract, but I tell my staff to have the patient blink or try artificial tears if the scan is blurry, to see if it solves the problem.

3 ***Misidentification of the posterior retinal nerve fiber layer boundary.*** In this case, the bottom colored line is incorrectly delineated. Interestingly, this is usually due to glaucoma, because glaucoma not only causes retinal nerve fiber layer thinning but also causes the retinal nerve fiber layer to become less reflective. That's a problem because OCT technology creates a cross-sectional picture of the eye based on differences in tissue reflectivity. So instead of getting a normally bright, highly reflective, white retinal nerve fiber layer, that tissue becomes kind of grayish and less differentiated from the background noise and the underlying retinal layers. This glaucomatous change makes it harder for the machine to identify the back boundary of the retinal nerve fiber layer. It's easy to understand why this artifact is a common problem in glaucoma patients.

If you encounter this artifact, the machine's resulting measurements can be either too big or too small—or even zero. When a doctor sees a retinal nerve fiber layer thickness value of zero on the printout, the doctor can immediately tell that this is an artifactually low and incorrect measurement. A retinal nerve fiber layer value of zero is physiologically impossible even in the most advanced stages of glaucoma, because even after complete loss of nerve tissue, at least 50 µm of non-neuronal tissue, such as glial tissue and blood vessels, will remain. (This is called the "floor effect.") Therefore, a retinal nerve fiber layer thickness value of zero is always an artifact; real measurements can never fall below 50 µm.

On the other hand, if the data indicate that the retinal nerve fiber layer is very thick, that's harder to notice and identify as an artifact. All the technician and doctor may see is that the tissue is labeled as being normal—an example of "green disease," where the machine erroneously says the patient is healthy when he may actually have advanced glaucoma.

You should be able to see that misidentification of the posterior retinal nerve fiber layer boundary has occurred if you look at the scan; the location of the lines will show that the machine has incorporated layers below the retinal nerve fiber layer into its measurements. (It might be a

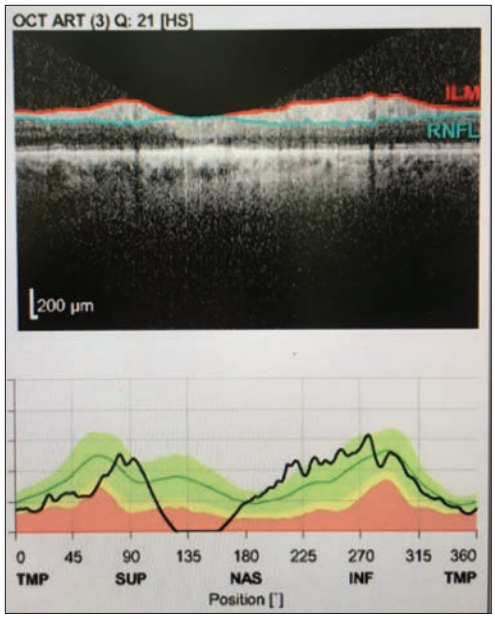
bit much to expect a technician to catch this.)

2 ***Posterior vitreous detachment-associated error.*** A posterior vitreous detachment is a normal degeneration of the eye associated with aging; it results in floaters. Most people develop this problem eventually. In the normal evolution of the PVD, the PVD may pull on the surface of the retina, causing the OCT's measurements to be artifactually thick. On the other hand, when a PVD releases, one may find artifactual *thinning* of the nerve fiber layer. In still other cases, if the PVD is floating freely in the vitreous and is not adherent to the retina, it may not affect the measurement at all.

This is another phenomenon that should be easy to spot if you look at the scan. If you do see a PVD in the scan, you have to look at it carefully and consider the possibility that it may be affecting the measurements.

1 ***Decentration.*** This is the most common OCT artifact in certain OCT machines. In a good scan, the OCT scan circle is nicely centered around the optic nerve. However, because the retinal nerve fiber layer is normally thicker as you get closer to the optic nerve and thinner as you move farther away from the optic nerve, unintentional decentration of the OCT scan circle can lead to erroneous thickness values. For example, the part of the scan that ends up farther from the nerve will erroneously give artifactually thinner values, creating the impression that the disease has worsened in that area. Meanwhile, the part of the scan circle that's closer to the nerve will give erroneously thicker tissue values than expected.

Like many of the other artifacts we've discussed, this should be easy to see if you take the time to look at the scan to make sure that it's properly centered.



In this scan the OCT machine has misidentified the posterior retinal nerve fiber layer boundary, leading to erroneous thickness measurements.

Red, Yellow & Green Disease

One reason it's easy to miss artifacts when they occur is that OCT machines are designed to make things easier by telling us if the patient's measurements are normal or not in comparison to a normative database; they can tell us if our patient's retinal nerve fiber layer thickness value is thicker, thinner or similar to what is expected for a normal patient without glaucoma.

If your patient's measured values fall within what's normal for most healthy people, the machine will label that section of the tissue green, or normal. Conversely, if the value is thinner than what's been measured in normal eyes, the machine will show a red color to indicate that the patient probably has glaucoma. If the value is borderline, the machine will show yellow. When the colors are wrong due to one of the top 10 artifacts (or because of a nonglaucomatous disease), we refer to this problem as green, red or yellow disease. This means that the OCT machine gave the wrong diagnosis and incorrectly labeled the patient as either normal (green disease), having glaucoma (red disease) or having borderline measurements (yellow disease).

A lot of busy doctors in the clinic just look at the colors on the printout; if all the colors on the printout are red, they may assume the patient has glaucoma. But if you don't take the time to look at the rest of the printout, you risk running into trouble. Some of the time, the machine is correct. If you see green all over the printout, the patient is probably normal and doesn't have glaucoma; if the machine shows red, the tissue may in fact be thinner as a result of glaucoma. However, some of the time the machine will be wrong because of these artifacts. As already noted, most artifacts are easy to spot—if you take the time to look at the printout, not just at the colors the machine is using to label each segment of tissue.

How often do these "OCT diseases" actually occur? One study found that a quarter of the time when the machine showed yellow, the patient was actually normal, after the segmentation errors were manually corrected.[2] Therefore, the incidence of yellow disease could be as high as 25 percent.

Strategies for Success

To avoid being fooled by an OCT artifact:

• ***Always look at the entire printout.*** When an OCT artifact goes unnoticed, the reason is almost always the same: The doctor failed to look at the entire printout. In a busy clinic, pressed for time, the easy thing to do is just look at the colors on the chart. If everything's green, the patient is fine. On to the next patient!

Most of the time, the machine's analysis is probably trustworthy. But

Different Machines, Different Measurements

OCT technology has a reputation for making highly reproducible measurements. Nevertheless, different OCT instruments may produce different measurements for the same patient on the same day. If you're using the same machine that you've used for many years, this isn't a problem. However, there are at least a half-dozen OCT machines that can be used to diagnose and monitor glaucoma patients, and each one has different software.

For example, different machines may have different algorithms for drawing the two colored lines that delineate the boundaries of the retinal nerve fiber layer. Some of the time this won't make much difference—but sometimes it does, and subtle OCT measurement differences due to different OCT machines should be factored into one's clinical decision-making. If you take the same patient on the same day and scan that patient on four different machines, you'll get four different values that could disagree by as much as 14 µm.[3] So if you see a new patient in clinic whose chart says the retinal nerve fiber layer thickness was 100 µm at his previous doctor's office, but your machine says 95 µm, is that difference because the patient has lost tissue, or because you're using a different machine?

For example, in our glaucoma service, we originally had a time-domain OCT machine. When we upgraded to a new spectral-domain OCT, one patient's retinal nerve fiber layer measurements were slightly lower. Then, when that patient's doctor left our group practice and I inherited the patient, I started scanning the patient on another spectral-domain OCT machine made by a different company. The patient's retinal nerve fiber layer values increased again with this third machine. When all the clinical data was interpreted together, it was clear that the patient was stable the whole time, but the use of three different OCT machines produced three different retinal nerve fiber layer thickness values.

There's nothing wrong with favoring one instrument over another; doctors are often convinced the machine they're using is the best. However, if we're forced to compare measurements made by different machines, we need to understand that the values are not interchangeable, and be very careful how we interpret the results. If possible, it makes sense to use the same machine every time; then we can more easily tell if the values are getting higher, lower or are stable. And if you need to replace your machine, it's good to consider these factors when deciding whether you're going to buy an OCT machine from the same manufacturer.

—T.C.

now and then, artifacts occur. If you take a moment to look over the entire printout for signs of an artifact, you'll catch them when they do occur. If you don't, sooner or later you'll make an important clinical decision based on inaccurate data.

When you spot an artifact, you'll have to decide whether to toss out the data completely or use whatever part of the test is accurate (if any). If a bad test result isn't discovered until the scan is reviewed by the doctor, going back to redo the test in a busy clinic may not be practical. Also, depending on the cause of the artifact—a cataract, for example—redoing the test might not correct the problem. However, you can make that call based on the individual situation. The main issue is to always look over the entire printout, so you don't fail to notice when part or all of the data is bad.

• ***Be on the alert for a discrepancy between the patient's condition and what the machine says.*** Sometimes your knowledge of the patient's condition may reveal the problem. For example, you may know the patient has advanced disease, but the machine shows all green, indicating healthy tissue. You should be doubly suspicious of an error in a situation like this. If the patient can't even see the eye chart, but the scan says the tissue is thick and healthy, that's a clear warning sign. If you look at the actual scan, you'll almost certainly find the reason the value doesn't make sense.

• ***Train your technicians to look for major artifacts.*** All of these artifacts are things the doctor should know about and be looking for, but some of them—as noted earlier—can also be spotted by a well-trained technician, increasing the odds that bad data won't fall through the cracks. Catching a problem when the test is being conducted will save time and possibly prevent the doctor from making a bad treatment decision later. Even if the artifact is the result of technician error, the doctor is still ultimately responsible for making the right treatment decisions.

• ***Never make a diagnosis based on a single test.*** Given the reality that any test can have artifacts, it's never a good idea to base your clinical choices on the results of a single test. Instead, perform multiple tests and consider their results as a whole. All of the tests should generally point in the same direction; if there's an outlier in one of the tests, that test may have an artifact. REVIEW

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How to Manage Steroid-Refractory Uveitic CME

These cases can be challenging, but there are systemic therapies that have the potential to make them easier to treat.

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The burden of cystoid macular edema among those with uveitis is considerable, affecting more than 30 percent of all patients and remaining a leading cause of visual morbidity.[1-3] In the setting of uncontrolled inflammation, an escalation of immunosuppressive therapy usually will control both the uveitis and associated edema, and partial or complete visual recovery can be anticipated.[4] Indeed, looking at their two-year uveitic macular edema outcomes, the Multicenter Uveitis Steroid Treatment Trial found that edema improved in 71 percent and completely resolved in 60 percent of all patients, with no difference between those treated with systemic immunosuppression versus intravitreal fluocinolone implant.[5] But a substantial minority of patients will develop chronic CME, unresponsive to multiple therapies.

Without question, corticosteroids—parenteral, regional or topical—are the mainstay of therapy for uveitic CME. But when disease remains refractory to these standard therapies, or they're contraindicated (e.g., in advanced glaucoma or in patients known to develop ocular hypertension in response to corticosteroids), finding effective alternatives can be challenging. Intravitreal anti-VEGF agents, though temporarily effective in some cases,[6,7] aren't a practical option for chronic cases, especially in the setting of bilateral disease, given the rapid recrudescence of fluid and need for frequent, and perhaps indefinite, injections.[8-10] The following brief review discusses some of the more promising systemic therapies for precisely this indication: chronic, inflammatory CME for which conventional therapy has failed or carries excessive risk.

Systemic Interferons

Given its rapidity of effect and near complete response rate, subcutaneously (SC) injected interferon alpha should be considered early in the treatment algorithm for chronic, uveitic CME once it's been determined that corticosteroids are contraindicated or ineffective. This is especially true for bilateral and severe disease, as the benefits must significantly offset the numerous risks and adverse events associated with this therapy. While the precise mechanism of action regarding its efficacy for CME remains elusive, investigators have demonstrated that interferon alpha-2b decreases the permeability of bovine retinal microvasculature.[11]

The use of interferon for ocular inflammation began with Behçet's disease patients;[12] indeed, Behçet himself had suspected a viral etiology for this disease as early as 1937.[13] In 2003, Germany's Ina Kötter, MD, and colleagues[14] prospectively enrolled 50 Behçet's disease patients with refractory uveitis and demonstrated a 92-percent response rate to SC injected interferon alpha-2a. Incidentally, in 58 eyes with angiographic CME, they noted 100-percent resolution. Separately, in a small trial of 12 patients with intractable posterior or panuveitis, only two of whom had Behçet's disease, uveitis significantly improved in 10 patients with subcutaneous interferon alpha-2b, and in the 14 eyes with CME the authors noted rapid resolution in all cases.[15]

Encouraged by the prompt and complete resolution of CME seen in their prior trial of 50 Behçet's disease patients, the same investigators

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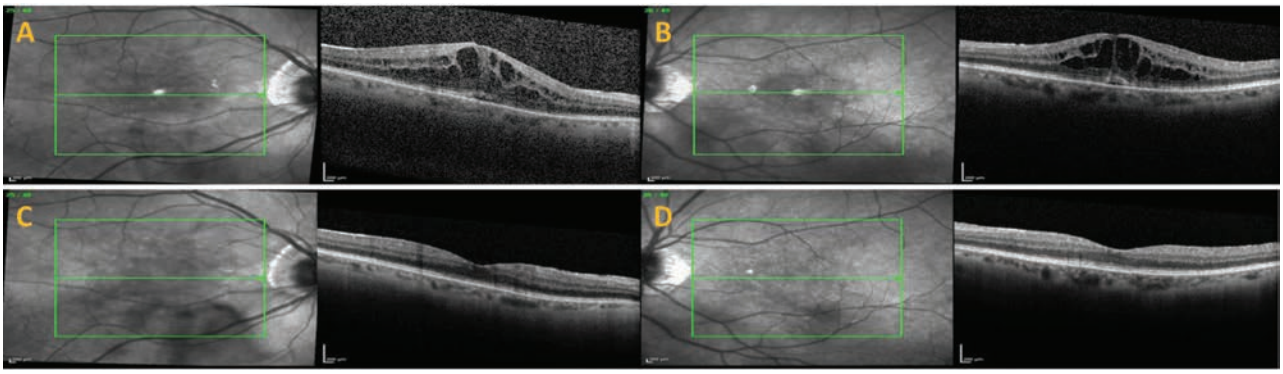

Figure. A 60-year-old white female with quiescent anterior and intermediate uveitis with retinal vasculitis, complicated by chronic CME. Panels A and B represent the right and left eyes, respectively, prior to interferon therapy. Panels C and D represent the response in each eye after two weeks of interferon alpha-2b, 3 million units daily administered subcutaneously.

designed a pilot study to assess the efficacy of systemic interferon alpha for uveitic CME in patients without associated Behçet's disease.[16] In all 15 eyes (of eight patients), the uveitis was quiescent and the CME remained refractory and long-standing (mean duration: 52 months). Thirteen of 15 eyes demonstrated 100-percent resolution of CME within two to four weeks of starting interferon alpha-2a, 3 or 6 million units SC daily (mean foveal thickness change: 551 to 143 µm; mean best-corrected visual acuity gain: +0.80 to +0.42 logMAR). Later, they expanded this consecutive, interventional case series to 24 patients (40 eyes) and reported on them retrospectively, finding interferon "effective" in 62.5 percent of patients and partly effective in 25 percent.[17] Underscoring the stringency of their outcome measure definitions, "partly effective" eyes still experienced more than a 300-µm reduction in mean foveal thickness by the end of follow-up (587 to 285 µm), and roughly half of the eyes in each group—"effective" and "partly effective"—gained three or more lines during follow-up.

In close agreement with these findings, a study in which I took part demonstrated 100-percent resolution of uveitic CME in eight eyes (four patients).[18] In all cases, the CME was long-standing (mean duration: 31 months) and refractory to numerous other therapies, and the response to interferon alpha-2b SC was rapid and clinically meaningful (mean BCVA gain: 20/129 to 20/56, p=0.0004; mean central macular thickness change: 563 to 267 µm, p=0.002). Most recently, in a randomized controlled trial of 48 patients, interferon alpha, comparable to the systemic corticosteroid arm, effected a significant reduction in CMT relative to an untreated control group.[19] These differences between treated and untreated groups didn't meet statistical significance criteria in the intention-to-treat analysis—only in the per-protocol analysis—likely because the study failed to complete its projected enrollment.

Aside from the clear indication for Behçet's disease-associated uveitis and CME, systemic interferon may be a particularly apt therapy in several other clinical situations. For patients with multiple sclerosis, in addition to treating the underlying disease, interferon beta has demonstrated efficacy for MS-associated uveitis and uveitic CME.[20] An additional case scenario involves the treatment of chronic, inflammatory CME in the setting of prior intraocular infection, in which intravitreal or systemic corticosteroid may put the patient at risk of relapse.[21,22] Systemic interferon carries no such risk; in fact, in the setting of quiescent viral infections (e.g., cytomegalovirus retinitis or acute retinal necrosis), interferon offers a protective antiviral effect. Lastly, interferons don't carry a risk of malignancy; on the contrary, they have antiproliferative effects, and therefore may be particularly suitable for chronic CME in the setting of autoimmune or cancer-associated retinopathy.

Exogenous interferon therapy has numerous side effects and associated adverse events, but they are rarely fatal or life-threatening.[23] Virtually all patients will develop a flu-like illness. Other important adverse events include neutropenia, thrombocytopenia, liver transaminase elevations, suicidality and exacerbation of underlying autoimmunity.[24] With careful monitoring, however, cessation of therapy is rarely required.

Tocilizumab

More recently, the interleukin-6 (IL-6) receptor blocker tocilizumab has been gaining traction as a niche therapy for uveitic CME, based initially on rather modest results from a small case series.[25] The rationale for this approach stems from our understanding of the pro-inflammatory nature of IL-6 and its increased expression in the ocular fluid of patients with uveitis[26] and macular edema

from various causes.[27,28] Following the initial report, separate investigators demonstrated dramatic improvement in CMT (896 to 182 µm) in a single patient with panuveitis refractory to multiple therapies, including tumor necrosis factor alpha (TNF-α) blockade, after commencing monthly infusions of tocilizumab.[29] Bolstered by the results of their test case, the same group continued to employ anti-IL-6 therapy in the setting of recalcitrant inflammatory CME and retrospectively reported their experience with five consecutive patients.[30] Prior to tocilizumab, the uveitis was quiescent in all cases but the CME persisted, despite therapy with multiple immunosuppressive and biologic agents. Mean CMT improved with anti-IL-6 therapy by more than 200 µm from baseline to month one (p=0.006). By six months of follow-up, mean CMT had reduced by more than 300 µm from baseline and half of eyes (p=0.028) had gained ≥ 2 lines of BCVA. The same investigators next demonstrated that the beneficial effects of tocilizumab for uveitic CME extend out to 12 months in a retrospective cohort study of seven patients; though they also discovered that CME rapidly recurred in the two patients in whom they attempted to discontinue therapy.[31] Recently, the 24-month results for this same cohort of patients, expanded to 12 (16 eyes), have been published, confirming that uveitic CME remains controlled out to two years, but rapidly recrudesces with suspension of therapy. Five out of five patients relapsed within one to three months of stopping tocilizumab.[32]

Others have repeated these results, finding similar efficacy for IL-6 blockade with inflammatory macular thickening in the setting of specific uveitic disease entities, such as juvenile idiopathic arthritis (JIA)[33,34] and birdshot chorioretinititis.[35] All of the enrolled patients in these studies had intractable disease, having failed multiple prior therapies, including at least one TNF-α inhibitor, suggesting that tocilizumab may be even more effective in selected patients. In assessing five patients (eight eyes) with similarly severe uveitis, the German group responsible for much of the work regarding type-I interferons for uveitic CME found at least a 25-percent reduction in CMT with tocilizumab in 75 percent of eyes.[36] The systemic disease associations, though not uniform, were more homogenous (JIA (in two patients), rheumatoid arthritis (2), ankylosing spondylitis (1) and all had active inflammatory arthritis, which was the main reason the investigators avoided recombinant interferon alpha.

Overall, tocilizumab, in comparison with systemic interferon, appears to clear inflammatory CME less rapidly but with significantly fewer side effects and adverse events. Importantly, whereas exogenous interferons may be associated with triggering or exacerbating underlying autoimmunity, IL-6 blockade in many cases may be an effective treatment for uncontrolled inflammation (in the eye or elsewhere in the body). Thus, the patient's systemic disease activity should be taken into account when considering this therapy for uveitic CME.

Octreotide

Much less evidence exists in support of octreotide, a somatostatin analog, for chronic, uveitic CME. The available literature, however, does suggest efficacy. In 1998, a single case report linked octreotide therapy with resolution of long-standing, refractory, idiopathic CME and suggested that this treatment might have benefit for macular edema from other causes.[37] In 2005, Greece's Thekla Papadaki, MD, and her colleagues provided the first evidence that octreotide may have potential for treating uveitic CME.[38] After failing standard therapy (oral acetazolamide, topical and systemic non-steroidal anti-inflammatory drugs, and regional steroid injections), the patient's bilateral CME responded completely to octreotide 100 µg SC t.i.d. Notably, her uveitis, prior to initiation of octreotide, had been under complete control with methotrexate. Following this report, the same group published results of five patients (nine eyes) with uveitic macular edema resistant to standard therapy, finding "marked improvement or complete resolution" of fluid in seven of nine eyes.[39] One patient with bilateral edema had no response in either eye. For the entire cohort, the mean foveal thickness improved from 496 to 241 µm over a range of eight to 24 months of treatment. In the largest study to date, analyzing 20 patients with quiescent uveitis, investigators found that monthly intramuscular injection of a long-acting formulation of octreotide decreased CME significantly in 70 percent of episodes.[40]

The mechanism of action for octreotide's effect on CME is poorly understood. Somatostatin and its analogs inhibit insulin-like growth factor 1, a potent promoter of blood-retina barrier breakdown.[41] Further, somatostatin appears to act directly at the level of the retinal pigment epithelium, enhancing its apical-basal fluid transport function.[40] Investigators have determined that vitreous concentrations of somatostatin are significantly reduced in quiescent uveitis patients with chronic macular edema as compared to controls (39 pg/ml vs. 487 pg/ml; p<0.0001),[42] suggesting a role for octreotide as replacement therapy in this setting. With regard to side effects, octreotide is very well tolerated, though clinicians should screen patients for symptoms of gastrointestinal distress and cholelithiasis.

ICAM Inhibitors

The anti-CD11a antibody efalizumab interferes with intercellular adhesion molecule-1 functionality. In patients with uveitis, ICAM-1 is significantly upregulated and increases vascular permeability.[43,44] A single case report[45] and a small case series[46] suggest that efalizumab may have efficacy for patients with chronic CME. The drug was voluntarily withdrawn from the market by the manufacturer in 2009, however, due to concerns of a possible association with progressive multifocal leukoencephalopathy (PML).

Natalizumab, another adhesion molecule inhibitor, has been approved for relapsing MS and, more recently, moderate to severe Crohn's disease. Despite also carrying an increased risk for PML, natalizumab remains available on a restricted basis when the clinical benefits outweigh the risks of therapy. As such, natalizumab may be considered in the setting of MS or Crohn's disease with associated uveitis and sight-threatening macular edema refractory to other therapies.

In Conclusion

Unlike other complications of uveitis such as cataracts, the vision loss of uveitic CME may not be recoverable once the disease has persisted long enough to damage photoreceptors. Most patients will respond to standard therapy consisting of the escalation of immunosuppression, the possible addition of acetazolamide, and/or supplemental corticosteroid therapy. However, in some patients, the uveitis is already quiescent and corticosteroids fail (or they are contraindicated), and inflammatory CME may become chronic and persist for years, if not indefinitely. These patients gradually lose vision, and some of this vision loss may be attributable to ophthalmologists' lack of awareness of effective alternatives. Hopefully, with increasing knowledge of the high efficacy of available treatments such as systemic interferon alpha, tocilizumab and octreotide, clinicians will be better able to control chronic, uveitic CME far earlier in the disease process, long before permanent damage occurs. REVIEW

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Ocular Effects of Zolmitriptan

In a unique case of drug-induced transient myopia, researchers from Sydney, Australia, sought to describe the case of a patient being treated with zolmitriptan for migraines.

A 42-year-old woman who had been using increasing amounts of zolmitriptan over the previous 12 months presented with an acute myopic shift and increased intraocular pressures with anterior chamber shallowing. The researchers reviewed clinical examination findings at presentation and at follow-up visits.

Initial examination revealed unaided visual acuities of 20/100 in the right eye and 20/125 in the left, with IOPs of 34 mmHg bilaterally. Zolmitriptan was ceased and the patient was started on glaucoma drops. Within two weeks, IOP had normalized, with deepening of the anterior chamber and complete resolution of her myopia. Her final recorded unaided visual acuities were 20/12.5 in the right eye and 20/16 in the left. When the glaucoma medication was ceased the patient developed pressure-related headaches and surgeons performed selective laser trabeculoplasty to minimize the need for long-term topical medication use.

The researchers say that idiosyncratic drug reactions resulting in ciliochoroidal effusion, secondary angle closure and transient myopia are well described, but haven't been previously reported with zolmitriptan use. They add that awareness of the various potential causative agents is important, as findings are generally reversible if recognized early and if the offending drug is discontinued.

J Glaucoma 2017;26:954-956

Lee JTL, Skalicky SE, Lin ML.

Optimized Keratometry for Toric IOL Calculation

Researchers at the G. B. Bietti Foundation IRCCS in Rome conducted a prospective case series to compare keratometric astigmatism and different modalities of measuring total corneal astigmatism for toric intraocular lens calculation, and to optimize corneal measurements in order to eliminate residual refractive astigmatism after cataract surgery.

The researchers enrolled 62 patients (64 eyes) who had a toric IOL. Preoperatively, the study measured TCA through ray tracing. They compared different combinations of measurements at a 3-mm diameter, centered on the pupil or the corneal vertex and performed along a ring or within it. Keratometric astigmatism was measured using the same Scheimpflug camera and a corneal topographer. Astigmatism was analyzed with Næser's polar value method. The optimized preoperative corneal astigmatism was back-calculated from the postoperative refractive astigmatism.

With both devices, KA produced an overcorrection of with-the-rule astigmatism by 0.6 D and an undercorrection of against-the-rule astigmatism by 0.3 D. The lowest meridional error in refractive astigmatism was achieved by the TCA pupil/zone measurement in WTR eyes (0.27-D overcorrection) and the TCA apex/zone measurement in ATR eyes (0.07-D undercorrection). In the whole sample, no measurement allowed more than 43.75 percent of eyes to yield an absolute error in astigmatism magnitude lower than 0.5 D. Optimized astigmatism values increased the percentage of eyes with this error up to 57.81 percent, with no difference compared with the Barrett calculator and the Abulafia-Koch calculator. Compared with KA, TCA improved calculations for toric IOLs; however, optimization of corneal astigmatism measurements led to more accurate results.

J Cataract Refract Surg 2017;43:1140-1148

Savini G, Næser K, Schiano-Lomoriello D, Ducoli P.

Learning Curve of SMILE

In an effort to evaluate the surgically challenging learning curve of small incision lenticule extraction, researchers from India described the intraoperative complications observed during the initial learning curve of SMILE and their management.

The surgeons performed a prospec-

This article has no commercial sponsorship.

tive evaluation of 100 consecutive eyes (50 patients) undergoing SMILE at an apex tertiary-care ophthalmic center. Patients older than 18 years with a stable refractive error ranging from -1 to -10 D myopia and up to 3 D astigmatism were included. Any intraoperative complications and their management were noted. Postoperative examination including visual acuity was performed on day one, one week and one month.

Intraoperative difficulties observed in the initial 100 eyes included suction loss (2 percent), black spots (11 percent), opaque bubble layer (19 percent), epithelial defect (2 percent) and difficult lenticule extraction (9 percent). Lenticule dissection and extraction was the most surgically challenging step and resulted in posterior stromal damage, as well as anterior cap tear (1 percent), side-cut tears (4 percent), a partially retained lenticule (1 percent) and completely retained lenticules (2 percent). Difficulties with dissection/extraction incidence decreased from 16 percent (8/50) in the initial 50 cases to 2 percent (1/50) in the next 50. Two eyes with completely retained lenticules were retreated with flap-based excimer laser ablation after three months. Optimal visual and anatomical outcomes could be achieved, the surgeons say, and no sight-threatening complication was observed in any case.

According to these results, lenticule dissection and extraction is the most difficult step, leading to a multitude of SMILE complications. However, most complications that result in delayed visual recovery are observed in the initial 50 cases.

Cornea 2017;36:1377-1382
Titiyal J, Kaur M, Rathi A, et al.

Optimizing the Number of Postop Visits

In a prospective case series conducted at the Eye Clinic of Sweden's Sunderby Hospital, researchers sought to evaluate safety issues that might arise if there were no planned postoperative visits after cataract surgery.

Composed of 1,249 patients (1,115 in the study group and 134 in the control group), the study examined all cataract surgery cases during a one-year period. The study group had the standard routine at the clinic, that is, no planned postoperative visit for patients without comorbidity and uneventful surgery. For the control group, patients who had surgery during one month of the one-year period were chosen. All these patients had a planned postoperative visit. The outcome measures were any planned postoperative visit, any complication and/or adverse event, postoperative corrected distance visual acuity and any postoperative control/contact initiated by the patient.

No significant differences in demographics, postoperative CDVA, frequency of planned visits because of ocular comorbidity or postoperative patient-initiated contacts were found between the two groups. Of the 1,249 patients, 9 percent (117 patients) initiated a postoperative contact, of whom 26 percent (30 patients) also had a scheduled visit. The reasons for the patient-initiated contacts were visual disturbance, redness and/or chafing, pain and anxiety. An evaluation of all medical records two years postoperatively found no reports of missed adverse events.

Based on these results, the researchers concluded it is possible to refrain from planned postoperative visits for patients having uncomplicated cataract surgery. However, they say, preoperatively, patients with comorbidities should be provided with individual planning of their postoperative follow-up. They note that preoperative counseling is important, and the clinic must have resources to answer questions from patients and be prepared for additional unplanned postoperative visits.

J Cataract Refract Surg 2017;43:1184-1189
Westborg I, Monestam E.

IOP Responses: Influence of Fitness Level

Researchers from the University of Granada, Spain, conducted a study to investigate the acute effect of different levels of resistance on intraocular pressure depending on participants' fitness level when performing cycling sprints.

In total, 26 physically active collegiate men performed five cycling sprints against different resistances in a randomized order, and IOP was measured immediately before and after each sprint. Participants were divided into two subgroups (low- and high-fitness) according to their maximum power output relative to body weight to assess the influence of fitness level. Two identical testing sessions were performed to assess the repeatability of IOP values.

Researchers found that IOP decreases with the lightest resistance ($p<0.01$), whereas IOP increases with heavier resistances ($p<0.01$), and it showed a positive linear tendency (r=0.99). They say that their results suggest that participants' fitness level seems to influence IOP responses, with a more stable response in the high-fitness group. A strong intersession repeatability of IOP values was observed (intraclass correlation coefficient range: 0.82 to 0.98; coefficients of variations range: 1.76 percent to 6.23 percent).

Based on the study, the researchers drew three conclusions: IOP is sensitive to cycling resistance in all-out sprints, with a lowering effect on the lightest resistance and an increasing effect with medium and heavy resistances; high fitness level is beneficial for avoiding IOP fluctuations during sprints; and these changes are comparable when measured on two different days under the same experimental conditions. Future studies are needed to clarify the consequences of exercise in glaucoma patients, the researchers say.

J Glaucoma 2017;26:881-887
Vera J, Redondo B, Garcia-Ramos A, et al.

B+L and Nicox's Vyzulta Approved

In early November, Baush + Lomb, with Nicox, announced it received FDA approval for Vyzulta, the first prostaglandin analog with one of its metabolites being nitric oxide. Vyzulta is indicated for the reduction of intraocular pressure in patients with open-angle glaucoma or ocular hypertension.

Topically administered once a day, Vyzulta is a monotherapy with a dual mechanism of action, working by metabolizing into two moieties: latanoprost acid, which works within the uveoscleral pathway to increase aqueous humor outflow; and butanediol mononitrate, which releases NO to increase outflow through the trabecular meshwork and Schlemm's canal. Common ocular adverse events include conjunctival hyperemia, eye irritation, eye pain and instillation site pain. Increased pigmentation of the iris and periorbital tissue and growth of eyelashes can also occur.

Bausch+Lomb says that for glaucoma patients, damage to the trabecular meshwork, through which the majority of the aqueous humor passes, can lead to reduced drainage, resulting in elevated IOP. Lowering IOP can delay, or even prevent damage to the optic nerve, helping to reduce the risk of glaucomatous visual field loss, Bausch + Lomb adds.

For information on Vyzulta, visit Bausch.com/vyzulta.

Topcon's Aladdin HW 3.0

Topcon recently announced that its Aladdin biometer now features the Olsen formula, a ray-tracing method of calculating the IOL power with the concept of the C-constant to predict implant location.

The measure parameters used in the calculation are:

- axial length;
- K-values;
- anterior chamber depth; and
- lens thickness.

The lens position is well-predicted, and the calculation of the IOL power leads to better refractive outcomes in patients, Topcon says.

Some of the key features that Topcon highlights are:

- point-and-shoot acquisition (all measurements are taken in less than five seconds);
- accurate measurement of axial length, lens thickness and central corneal thickness;
- nine measurements in one instrument;
- the ability to print the IOL report;
- precise IOL power calculation formulae and a generic toric IOL calculator (including the Abulafia-Koch astigmatic regression formula);
- onboard Olsen formula with C-constant;
- onboard Barrett IOL Calculation Suite, which includes the Barrett Rx, The Barrett Toric IOL Calculator, the Barrett True K and the Barrett Universal II formulae; and
- a built-in Placido topography system, which offers all the additional diagnostic capabilities of any stand-alone topographer.

For more information on Topcon's Aladdin HW3.0 Biometer, visit topconmedical.com.

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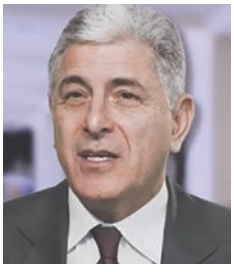

Graham Barrett, MD
Lions Eye Institute

Dr. Barrett explains how the Barrett Universal II IOL power calculation formula has improved on the conventional formulas used in the ‘80s and ‘90s. He also explains the advantages that physicians experience when using a biometer combined with a corneal topographer.

Ike Ahmed, MD
University of Toronto

Dr. Ahmed outlines his experience with the Aladdin. He explains why the incorporation of pupillometry analysis into a measuring device is a benefit for surgeons. He also describes how the Barrett Universal II IOL power calculation formula helps obtain more accurate outcomes.

John Sheppard, MD
Virginia Eye Consultants

Dr. Sheppard describes a recent study completed at his practice which evaluates the benefits of the Aladdin. He outlines results of the study and comments on how the efficiency of the Aladdin has improved patient flow and outcomes in his practice.

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A middle-aged man with a unique condition presents at Wills Eye Hospital's Ocular Oncology Service.

Michael Abendroth, MD, MBA, and Carol L. Shields, MD

Presentation

A 62-year-old Caucasian man was referred to the Wills Eye Hospital Ocular Oncology Service for evaluation of a pigmented choroidal lesion in the left eye that was suspicious for melanoma. He reported sporadic episodes of painless blurred vision OS over the preceding two months.

Medical History

Ocular history included uncomplicated LASIK in both eyes 14 years prior. Medical history included cranial migraines and depression. He denied smoking and reported minimal alcohol intake. Family history was negative for cutaneous or ocular melanoma. Review of systems was unremarkable.

Examination

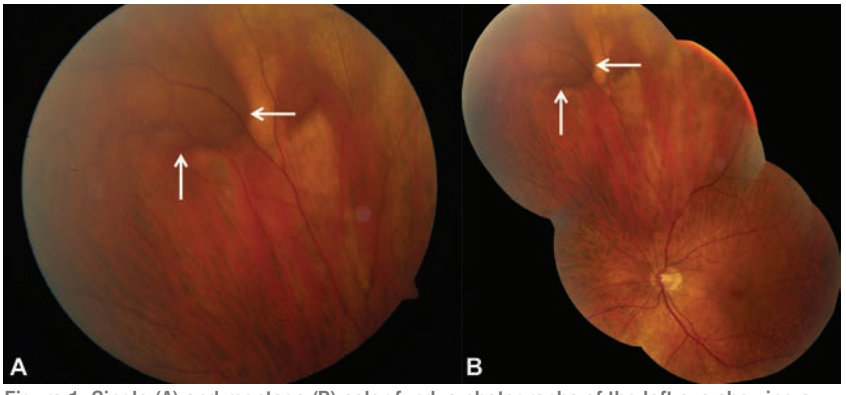

Figure 1. Single (A) and montage (B) color fundus photographs of the left eye showing a round, hyperpigmented choroidal lesion (arrows) in the superonasal equatorial region.

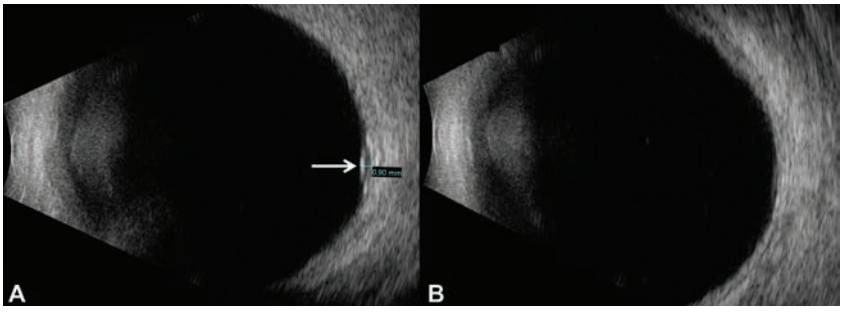

Figure 2. Ultrasonography of the left eye depicting an echolucent, dome-shaped lesion (arrow) with no extrascleral extension. The lesion inflated to 0.90 mm thickness in superonasal gaze (A) and deflated in primary gaze or with digital pressure on the globe (B).

Visual acuity was 20/25 OU. Pupillary response, extraocular movements and confrontation visual fields were normal OU. Intraocular pressures were 10 mmHg OD and 8 mmHg OS. The anterior segment was quiet with mild nuclear sclerosis OU. There was no evidence of ocular melanocytosis.

Fundus examination OD showed normal findings. Fundus examination OS revealed a clear vitreous cavity and normal macula without subretinal fluid. In the superonasal equatorial region there was a round, hyperpigmented choroidal lesion causing elevation of the retina *(Figure 1, arrows)*. The lesion measured 6 x 5 mm in basal dimension and 0.9 mm in ultrasonographic thickness *(Figure 2A)*. Curiously, the lesion waxed and waned with ocular movements, inflating in fixed superonasal gaze and deflating in primary gaze. There was no hemorrhage, subretinal fluid, orange pigment or related drusen.

What is your diagnosis? What further workup would you pursue? The diagnosis appears on the next page.

Workup, Diagnosis and Treatment

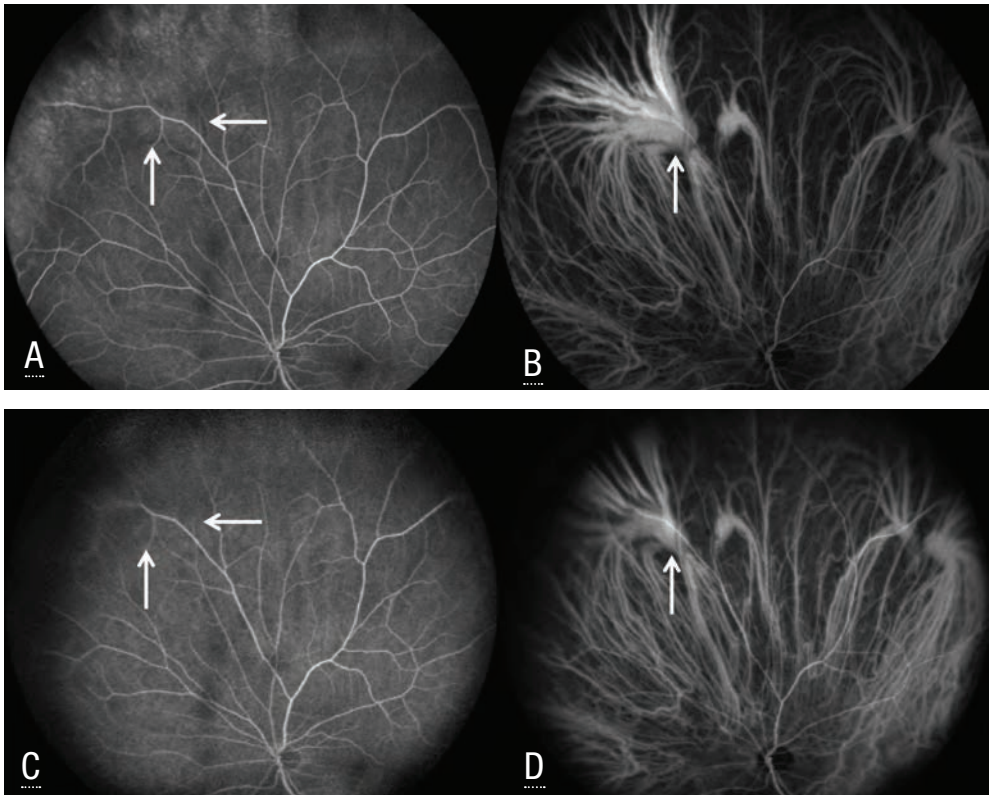

Figure 3. Fluorescein angiography showing a patchy area of mild hyperfluorescence with a hypofluorescent rim (arrows) that corresponds to the lesion (A). Simultaneous indocyanine green angiography demonstrating early homogenous filling of the lesion superonasally (arrow) without leakage or staining (B). Gaze repositioning or digital pressure caused the lesion (arrows) to decrease in fluorescence on FA (C) and cyanescence on ICGA (D).

Ocular ultrasonography depicted an echolucent, dome-shaped lesion with no extrascleral extension. The lesion was maximally visible (inflated) in superonasal gaze and not visible (deflated) in primary gaze or with digital pressure on the globe *(Figure 2B)*. Video-capture fluorescein angiography revealed a patchy area of mild hyperfluorescence with a hypofluorescent rim that corresponded to the lesion *(Figure 3A, arrows)*. Simultaneous video-capture indocyanine green angiography demonstrated more revealing features of early homogenous filling of the lesion superonasally without leakage or staining *(Figure 3B, arrow)*. Gaze repositioning or digital pressure caused the lesion to gradually decrease in fluorescence on FA and cyanescence on ICGA *(Figures 3C and D, arrows)*. Optical coherence tomography documented a smooth, dome-shaped elevation of the choroid and retinal pigment epithelium-Bruch's membrane complex without subretinal fluid or retinal edema *(Figure 4, asterisk)*. Similar to the prior studies, the OCT showed disappearance of the lesion with digital pressure. These findings supported a diagnosis of vortex vein varix, a benign vascular ectasia than can simulate small choroidal melanoma.

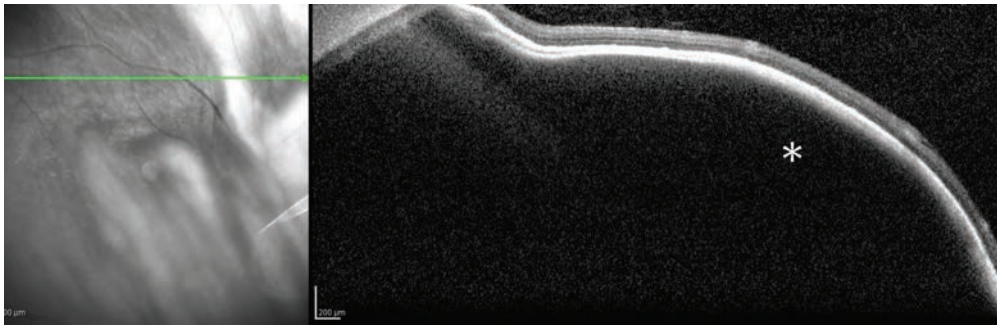

Figure 4. Optical coherence tomography documenting a smooth, dome-shaped elevation of the choroid and retinal pigment epithelium-Bruch's membrane complex (asterisk) without subretinal fluid or retinal edema.

Discussion

Uveal melanoma is the most common primary intraocular tumor in adults. One study estimated the worldwide incidence to be 7,095 cases annually, with 4,747 in Caucasian, 1,286 in Asian, 738 in Hispanic, and 316 in African patients.[1] This malignancy is slightly more common in males (4.9 per million) than in females (3.7 per million).[2] In an analysis of 8,033 patients with uveal melanoma over a 40-year period, Wills Eye's Carol Shields, MD, and her colleagues reported that the mean patient age at diagnosis was 58 years, with a range of 3 to 99 years. In that series, uveal melanoma primarily involved the choroid (90 percent), compared to the ciliary body (6 percent) and iris (4 percent).[3] Treatment options for uveal melanoma include enucleation, radiotherapy, local resection, transpupillary thermotherapy, photodynamic therapy and some emerging methods with nanoparticle-labeled photodynamic therapy. Each of these interventions can potentially impact visual acuity, so accurate diagnosis is critical.

Several conditions can clinically simulate uveal melanoma, leading to diagnostic ambiguity.[4] In an analysis of 12,000 patients referred for uveal melanoma over a 25-year period at Wills Eye Hospital, Drs. Jerry and Carol Shields' group found that 1,739 (14 percent) had a simulating condition, namely pseudomelanoma.[5] The most frequent pseudomelanomas included choroidal nevus (49 percent), peripheral exudative hemorrhagic chorioretinopathy (8 percent), congenital hypertrophy of the retinal pigment epithelium (6 percent), idiopathic hemorrhagic detachment of the retina or retinal pigment epithelium (5 percent), circumscribed choroidal hemangioma (5 percent), and age-related macular degeneration (4 percent).[5] Vortex vein varix comprised only 0.4 percent of cases, likely due in part to its relatively rare recognition.[5] Though this condition is benign and asymptomatic, its potential confusion for small choroidal melanoma makes the varix clinically important.

The diagnosis of vortex vein varix is facilitated by an understanding of the choroidal venous system. The choroidal blood drains from the eye through large venous tributaries that coalesce into an average of eight vortex veins, with at least one vortex vein per quadrant of the eye.[6,7] These vortex veins exit the globe through scleral canals and typically merge with other vortex veins in the orbit before draining into the ophthalmic vein.[6] Prior to entering the scleral canal, about half of the vortex veins have an aneurysmal dilatation of varying sizes and shapes, termed a vortex vein ampulla.[7] These ampullae generally are visible anterior to the equator of the globe. In rare cases, an ampulla bulges large enough to resemble a choroidal neoplasm. In this case, the dilatation is termed a varix of the vortex vein ampulla.[6]

The vortex vein varix is most common in middle-aged or older patients but has been reported in patients as young as 23 years.[8] This lesion is typically single and unilateral but can be multifocal or bilateral.[6,8] The varix appears as a smooth, reddish-brown, subretinal elevation along the equator, usually in the superonasal or inferonasal quadrants.[6,9]

The vortex vein varix characteristically inflates with gaze toward the lesion, achieving a basal diameter of up to 6 mm and a thickness up to 2.5 mm.[6] The enlarging varix can compress the surrounding choroid and display a brownish-red color that raises concern for choroidal melanoma.[6] However, the varix deflates and the hyperpigmentation disappears with return to primary gaze or pressure on the globe. The etiology of this fluctuation is unclear, but likely involves gaze-evoked narrowing of the scleral canals or kinking of the episcleral vortex veins, leading to stagnation of venous outflow and inflation of the varix.[6] A Valsalva maneuver, prone positioning and other factors that increase intraocular venous pressure have also been implicated.[6,9]

The dynamic nature of the varix's size distinguishes it from choroidal melanoma, which doesn't diminish with gaze or pressure.[6] Ancillary testing can help demonstrate this distinction. Ultrasonography of the varix reveals inflation with gaze toward the lesion and deflation with primary gaze or pressure with the probe.[10] OCT shows an ectatic choroidal vessel with an internal low optical signal, corresponding to the dilated ampulla.[11] ICGA is particularly useful because it delineates the surrounding choroidal vasculature from the gaze- and pressure-dependent vascular tree of the varix.[9] Together, these tools help distinguish the benign vortex vein varix from choroidal melanoma and prevent unnecessary medical treatment. REVIEW

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REVIEW Medicare Q&A

(Continued from page 18)
low error rates or sufficient improvement in error rates, as determined by CMS." In other words, providers and suppliers who have moderate and high error rates after round one continue to a second round. Those with high error rates in round two move to round three. The definition of what constitutes "low," "moderate" and "high" is determined by CMS.

Medicare also notes that "MACs also educate providers throughout the probe-review process, when easily resolved errors are identified, helping the provider to avoid additional similar errors later in the process."

Q What sort of education gets provided if I don't do well after a round?

A CMS does this in a "one-on-one education session (usually held via teleconference or webinar), [where] the MAC provider outreach and education staff will walk through any errors in the provider/supplier's 20 to 40 reviewed claims. Providers/suppliers will have the opportunity to ask questions regarding their claims and the CMS policies that apply to the item/service that was reviewed." Generally, it would take six to eight weeks for changes to be implemented and claims filed and processed before the next round begins.

Q What happens if I don't do well on round three of TPE?

A Medicare says those providers and suppliers can be referred for additional actions (which are more serious). They note "continued high error rates after three rounds of TPE may be referred to CMS for additional action, which may include 100 percent prepay review, extrapolation, referral to a Recovery Auditor, or other action."

For instance, 100 percent pre-payment review means that all services will require records submission, review by the MAC, and a determination of correctness before any payment is forthcoming. This could have a significant financial impact on those practices and providers in terms of cash-flow management.

Extrapolation means your error rate on the small number of claims is applied to all your submitted claims for a payer. Defending this could become extremely burdensome and expensive.

Q How do I protect myself from a TPE review?

A If you provide a high number of a particular service to Medicare beneficiaries compared to your peers, you might be selected for TPE "round one." As CMS moves to more robust data analysis, they are focusing their reviews far more specifically. It's likely that private payers will use your claims data in the same way, if they aren't already. Your documentation and support for medical necessity in your charts for the services you deliver is likely to be the determining factor on how well you do. Careful attention to any and all payer policies and standard of care are a key factor.

Q What resources does CMS provide to help me?

A CMS has a "TPE Q&A" that was produced on October 25, 2017. It is available on the TPE webpage in the "Downloads" area. REVIEW

Mr. Larson is a senior consultant at the Corcoran Consulting Group. Contact him at plarson@corcoranccg.com.

1. https://www.cms.gov/Research-Statistics-Data-and-Systems/Monitoring-Programs/Medicare-FFS-Compliance-Programs/Medical-Review/Targeted-Probe-and-EducateTPE.html accessed 26 October 2017.

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xiidra® (lifitegrast ophthalmic solution) 5%

Rx Only

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

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

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

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

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

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

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

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

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

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

Shire

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

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

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US Patents: 8367701; 9353088; 7314938; 7745460; 7790743; 7928122; 9216174; 8168655; 8084047; 8592450; 9085553; 8927574; 9447077; 9353088 and pending patent applications.
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SIGN & SYMPTOM IMPROVEMENT

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

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

Check it out at Xiidra-ECP.com

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

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

Indication

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

Important Safety Information

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

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

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

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

Please see the adjacent page for Brief Summary of Safety Information and visit Xiidra-ECP.com for Full Prescribing Information.

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