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June 2015

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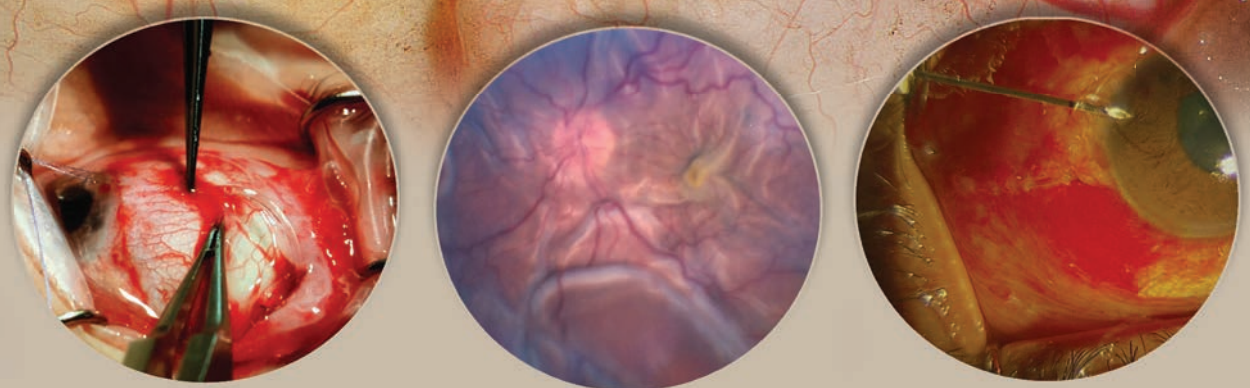
Glaucoma Issue:

Mastering TUBE Shunts

P. 20



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REVIEW NEWS
Volume XXII • No. 6 • June 2015

Benefits of Gene Therapy for Leber's Found to Be Transient

Gene therapy for Leber's congenital amaurosis, an inherited disorder that causes vision loss starting in childhood, has improved patients' eyesight and the sensitivity of the retina within weeks of treatment. Both of these benefits, however, peaked one to three years after treatment and then diminished, according to results from an ongoing clinical trial funded by the National Eye Institute.

The results, published online in the *New England Journal of Medicine*, focus on a subset of trial participants who routinely underwent extensive tests of their vision and imaging of the retina from baseline up to six years after treatment. These in-depth examinations revealed that the areas of treated retina rapidly gained visual sensitivity, expanded and then contracted.

"Gene therapy for LCA demonstrated we could improve vision in previously untreatable and incurable retinal conditions," said Samuel G. Jacobson, MD, PhD, who led the clinical trial at the University of Pennsylvania's Scheie Eye Institute, Philadelphia. "Even though the current version of the therapy doesn't appear to be the permanent treatment we were hoping for, the gain in knowledge about the time course of efficacy is an opportunity to improve the therapy so that the restored vision can be sustained for longer durations in patients."

The results, announced at the 2015 Association for Research in Vision and Ophthalmology annual meeting, contribute to the bigger picture of the potential benefits—and remaining problems to solve—in the field of gene therapy for LCA and other diseases that affect the retina.

About 10 percent of people with LCA carry a mutated form of the gene RPE65, which makes a key protein found in the retinal pigment epithelium, a layer of cells that nourish the light sensors or photoreceptor cells of the retina. The RPE65 protein is critical for vision. In the retina, millions of photoreceptors detect light and convert it into electrical signals that are ultimately sent to the brain. Photoreceptors rely on the RPE65-driven visual cycle to recharge their light sensitivity. They also need RPE65 for their long-term survival. In LCA, the cells eventually die, muting eye-to-brain communication.

Dr. Jacobson, along with Artur V. Cideciyan, PhD, University of Pennsylvania, and William W. Hauswirth, PhD, University of Florida, Gainesville, began the trial in 2007. Fifteen people with LCA received retinal injections of a harmless virus engineered to carry healthy RPE65 genes. This gene therapy relies on viral vectors as a means to deliver instructions for making the desired protein. In this case, the virus was designed to produce healthy RPE65. Dr. Hauswirth led the group that designed and produced the virus-gene material for testing in patients.

"Within days of the injections, some patients reported increases in their ability to see dim lights they had never seen before. It was remarkable for us to get this feedback that things were indeed changing positively," said Dr. Jacobson.

In addition to the rapid onset of greater light sensitivity, the researchers discovered changes to another component of vision that occurred slowly. Four of the 15 patients started relying on an area of the retina near the gene therapy injection site for seeing letters. Normally, the fovea with its high density of photoreceptors is responsible for seeing fine details.

"For some patients, preferential use of the treated area for seeing letters came about spontaneously about a year after the gene therapy and remained functional for up to six years," said Dr. Cideciyan, who reported these findings in *Investigative Ophthalmology & Visual Science* in January.

For the current study, Dr. Jacobson's team also examined the relationship between structure and function in the retina. Importantly, these results showed that photoreceptors continued to die at the same rate as they do in the natural course of the disease, regardless of treatment. The researchers concluded that gene therapy with RPE65 boosted the visual cycle, but did not delay photoreceptor cell death. Hence, the short-term gains in visual function.

"We now have six years of data showing that a gene therapy approach is safe and that it successfully improves vision in people with this blinding disease," said Paul A. Sieving, MD, PhD, director of NEI. "As with any application of a novel therapy, it now needs to be fine-tuned. More research is need-

ed to understand the underlying biology and how we can preserve or restore photoreceptors for a lifetime. Restoring vision is at the heart of the NEI's Audacious Goals Initiative, an effort to strategically fund research aimed at developing the knowledge and technology to make this goal a reality."

Dr. Jacobson's latest results are consistent with another independent investigation performed at Moorfields Eye Hospital and University College London. Those investigators found that retinal sensitivity improved in their LCA patients treated with gene therapy, but then it diminished after 12 months.

The current findings suggest a number of potential strategies for improving the outcome of gene therapy, Dr. Jacobson said. For example, the ability to stage the disease prior to gene therapy would help clarify the potential benefits for each individual. The treatment could then be guided to retinal areas that contain enough functional photoreceptors to respond. Select patients may benefit from a second round of gene therapy, or from having an adjacent area of the retina treated, or from combining gene therapy with medications designed to boost the visual cycle or to protect the retina from cell loss. "We've been able to positively alter and extend the visual life of patients with LCA, and we now have to develop workable strategies for extending it even further," Dr. Jacobson said.

Patients with AIDS at Increased Risk for AMD

Patients with acquired immunodeficiency syndrome have a fourfold increase in their risk of developing intermediate-stage age-related macular degeneration compared to people of the same age who are not infected with HIV, according to results from the Longitudinal Study of the Ocular Complications of AIDS (LSOCA). The results of the study, led by the National Eye Institute-funded Studies of the Ocu-

Wearable Device May Aid Visually Impaired

People who have lost some of their peripheral vision, such as those with retinitis pigmentosa, glaucoma or brain injury that causes half visual field loss, often face mobility challenges and increased likelihood of falls and collisions. As therapeutic vision restoration treatments are still in their infancy, rehabilitation approaches using assistive technologies are often times viable alternatives for addressing mobility challenges related to vision loss.

Researchers from Massachusetts Eye and Ear, Schepens Eye Research Institute used an obstacle course to evaluate a wearable collision warning device they developed for patients with peripheral vision loss. They found the device may help patients with a wide range of vision loss avoid collisions with high-level obstacles. Their findings are described online at iovs.arvojournals.org.

"We developed this pocket-sized collision warning device, which can predict impending collisions based on time to collision rather than proximity," said the senior author Gang Luo, PhD, an associate scientist at Mass Eye and Ear/Schepens, and assistant professor of ophthalmology at Harvard Medical School. "It gives warnings only when the users approach to obstacles, not when users stand close to objects and not when moving objects just pass by. So, the auditory collision warnings given by the device are simple and intuitively understandable.

"We tested the device in a density obstacle course to evaluate its effect on collision avoidance in people with peripheral vision loss. To show its beneficial effect, we compared the patients' mobility performance with the device and without it. Just demonstrating the device can give warning for obstacles in walking would not prove the device is useful. We have to compare with a baseline, which is walking without the device in this case."

Twenty five patients with tunnel vision or hemianopia completed the obstacle course study and the number of collisions and walking speed were measured. Compared to walking without the device, collisions were reduced significantly by about 37 percent with the device and walking speed barely changed. No patient had more collisions when using the device than when not using it. "We are excited about the device's potential value for helping visually impaired and completely blind people walk around safely. Our next job is to test its usefulness in patients' daily lives in a clinical trial study." Dr. Luo said.

lar Complications of AIDS Research Group, were published online in the *American Journal of Ophthalmology*.

"With HIV and AIDS patients living longer than ever before, they are at an increased risk of developing several age-related diseases at an earlier age than HIV-uninfected people including cardiovascular disease and diabetes," said Douglas A. Jabs, MD, MBA, professor of ophthalmology and medicine at the Icahn School of Medicine at Mount Sinai, and the lead author of the new study. "Their increased risk for age-related diseases in general led us to analyze how these patients are impacted by one of the most common age-related eye diseases, macular degeneration."

To determine how AIDS may contribute to AMD, Dr. Jabs and colleagues enrolled 1,825 patients ages 13 to 73 years with AIDS at 19 sites in United States between 1998 and 2011. The investigators graded retinal photographs for AMD and compared participants in the LSOCA cohort to published data on an HIV-uninfected, age-matched population from the Beaver Dam Offspring Study, which also graded retinal photographs for AMD features. The results showed that the prevalence of intermediate-stage AMD in patients with AIDS was nearly 10 percent and, when adjusted for any age differences, was approximately fourfold greater than that in the Beaver Dam Study.

The researchers also determined that the increased prevalence of AMD in the LSOCA cohort was not related to any drug or class of drugs used to treat HIV infection. Rather they point out that antiretroviral-treated, immune-restored, HIV-infected patients do not have normal immune systems; instead and on average they have immunologic changes similar to those seen in patients who are not infected who are older than 70 years of age, a phenomenon termed "immunosenescence."

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REVIEW News

"Although the underlying mechanism leading to this increase in AMD in persons with AIDS is not yet known, it may relate to the state of chronic immune activation and systemic inflammation seen in these patients," said Dr. Jabs. Dr. Jabs and colleagues note that further exploration of these findings may provide the opportunity to better understand the roles of immunosenescence and systemic inflammation in the development of AMD, which in turn could lead to new treatments. The results also add to the growing body of research suggesting that antiretroviral therapy-treated, immunorestored, HIV-infected persons may experience accelerated and accentuated aging.

Ebola Virus Persists in the Eye

Live Ebola virus can persist within the eyes for months after a patient recovers from acute Ebola viral disease (EVD), according to a case report published in the *New England Journal of Medicine* and presented at the ARVO 2015 annual meeting.

Despite the presence of Ebola virus within one patient's eye, samples from his tears and conjunctiva tested negative for virus, indicating that casual contact with Ebola survivors carries no risk. The finding points to a need for infection control precautions when Ebola virus disease survivors undergo invasive procedures involving the eyes. It also highlights the need for follow-up care for patients who have recovered from Ebola virus disease.

The case report describes a 43-year-old physician who was working in an Ebola treatment unit in Sierra Leone who became infected with Ebola virus. He was transported to the United States and treated at Emory University Hospital's Serious Communicable Disease Unit for 40 days, including 12 days of mechanical ventilation and 24 days of renal replacement therapy.

Two months after his discharge from the hospital, the patient was evaluated at the Emory Eye Center following the development of acute anterior uveitis and severe hypertension in one eye.

"The current outbreak has resulted in the largest number of EVD survivors in history. EVD survivors require ongoing medical care to manage complications from the infection that may develop during recovery," says Jay Varkey, MD, assistant professor of medicine in Emory University School of Medicine.

"Following recovery from Ebola virus disease, patients should be followed for the development of eye symptoms including pain, redness, light sensitivity and blurred vision, which may be signs of uveitis," says Steven Yeh, MD, associate professor of ophthalmology at Emory.

The patient was treated with topical corticosteroids and medications to decrease the elevated pressure within the eye. Removal of fluid by an anterior chamber paracentesis demonstrated live Ebola virus.

"To safely evaluate and treat EVD survivors who develop complications in the eye and other immune-privileged sites of the body, health-care providers who perform invasive procedures should develop standard operating protocols for: safely donning and doffing personal protective equipment; handling laboratory specimens; and managing medical waste," said Dr. Varkey.

The patient has experienced visual recovery following therapy for the uveitis and has ongoing ophthalmic follow-up. These findings have implications for the thousands of Ebola virus disease survivors in West Africa and also for health-care providers who have been evacuated to their home countries for ongoing care. Surveillance for the development of eye disease in the post-Ebola period is needed. REVIEW

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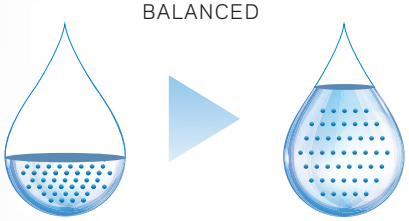

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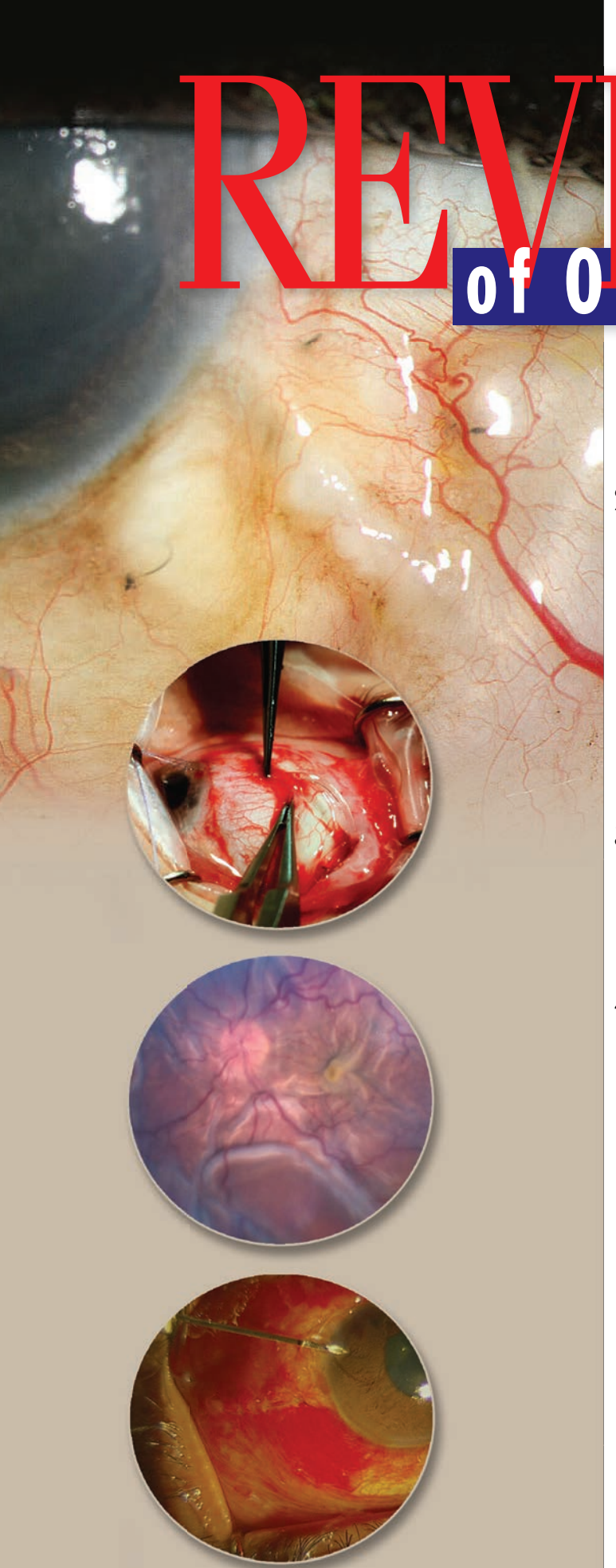

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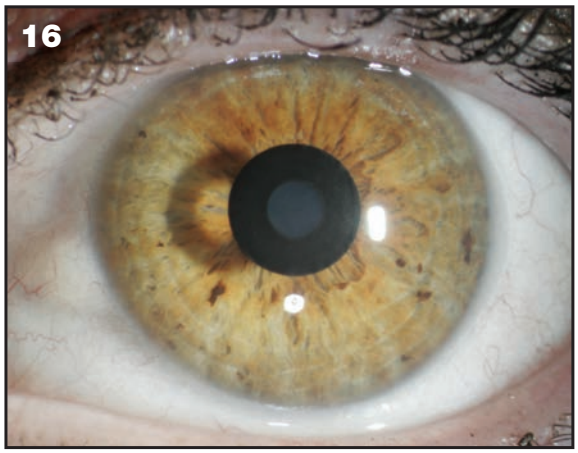

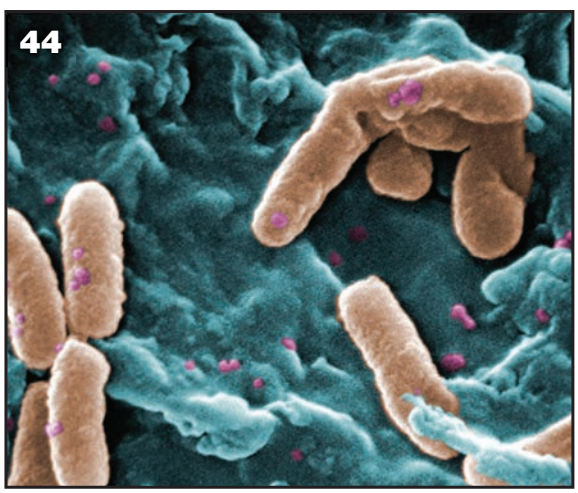

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The concomitant use of two topical beta-adrenergic blocking agents is not recommended[4,5]

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- Both ISTALOL® (timolol maleate ophthalmic solution) and TIMOPTIC® (timolol maleate ophthalmic solution) in OCUDOSE® (dispenser) are contraindicated in patients with: bronchial asthma; a history of bronchial asthma; severe chronic obstructive pulmonary disease; sinus bradycardia; second or third degree atrioventricular block; overt cardiac failure; cardiogenic shock; hypersensitivity to any component of the product.
- **The same adverse reactions found with systemic administration of beta-adrenergic blocking agents may occur with topical administration. Severe respiratory reactions and cardiac reaction, including death due to bronchospasm in patients with asthma, and rarely death in association with cardiac failure, have been reported following systemic or ophthalmic administration of timolol maleate.**
- Patients with a history of atopy or severe anaphylactic reactions to a variety of allergens may be unresponsive to the usual doses of epinephrine used to treat anaphylactic reactions.
- Timolol has been reported rarely to increase muscle weakness in some patients with myasthenia gravis or myasthenic symptoms.
- Beta-adrenergic blocking agents may mask signs and symptoms of acute hypoglycemia or certain clinical signs of hyperthyroidism. Patients subject to spontaneous hypoglycemia, or diabetic patients receiving either insulin or oral hypoglycemic agents, or patients suspected of developing thyrotoxicosis, should be managed carefully, with caution.
- In patients undergoing elective surgery, some authorities recommend gradual withdrawal of beta adrenergic receptor blocking agents because these agents impair the ability of the heart to respond to beta-adrenergically mediated reflex stimuli.
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Please see Brief Summary of Prescribing Information for ISTALOL and TIMOPTIC in OCUDOSE on the following pages.

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This Brief Summary does not include all the information needed to use TIMOPTIC® 0.25% AND 0.5% (timolol maleate ophthalmic solution) in OCUDOSE® (DISPENSER) safely and effectively. See full prescribing information for TIMOPTIC in OCUDOSE.

PRESERVATIVE-FREE STERILE OPHTHALMIC SOLUTION
in a Sterile Ophthalmic Unit Dose Dispenser

TIMOPTIC® 0.25% AND 0.5% (TIMOLOL MALEATE OPHTHALMIC SOLUTION)

in OCUDOSE® (DISPENSER)

INDICATIONS AND USAGE

Preservative-free TIMOPTIC in OCUDOSE is indicated in the treatment of elevated intraocular pressure in patients with ocular hypertension or open-angle glaucoma.

Preservative-free TIMOPTIC in OCUDOSE may be used when a patient is sensitive to the preservative in TIMOPTIC (timolol maleate ophthalmic solution), benzalkonium chloride, or when use of a preservative-free topical medication is advisable.

CONTRAINDICATIONS

Preservative-free TIMOPTIC in OCUDOSE is contraindicated in patients with (1) bronchial asthma; (2) a history of bronchial asthma; (3) severe chronic obstructive pulmonary disease (see WARNINGS); (4) sinus bradycardia; (5) second or third degree atrioventricular block; (6) overt cardiac failure (see WARNINGS); (7) cardiogenic shock; or (8) hypersensitivity to any component of this product.

WARNINGS

As with many topically applied ophthalmic drugs, this drug is absorbed systemically.

The same adverse reactions found with systemic administration of beta-adrenergic blocking agents may occur with topical administration. For example, severe respiratory reactions and cardiac reactions, including death due to bronchospasm in patients with asthma, and rarely death in association with cardiac failure, have been reported following systemic or ophthalmic administration of timolol maleate (see CONTRAINDICATIONS).

Cardiac Failure: Sympathetic stimulation may be essential for support of the circulation in individuals with diminished myocardial contractility, and its inhibition by beta-adrenergic receptor blockade may precipitate more severe failure.

In Patients Without a History of Cardiac Failure continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of cardiac failure, Preservative-free TIMOPTIC in OCUDOSE should be discontinued.

Obstructive Pulmonary Disease: Patients with chronic obstructive pulmonary disease (e.g., chronic bronchitis, emphysema) of mild or moderate severity, bronchospastic disease, or a history of bronchospastic disease (other than bronchial asthma or a history of bronchial asthma, in which TIMOPTIC in OCUDOSE is contraindicated [see CONTRAINDICATIONS]) should, in general, not receive beta-blockers, including Preservativefree TIMOPTIC in OCUDOSE.

Major Surgery: The necessity or desirability of withdrawal of beta-adrenergic blocking agents prior to major surgery is controversial. Beta-adrenergic receptor blockade impairs the ability of the heart to respond to beta-adrenergically mediated reflex stimuli. This may augment the risk of general anesthesia in surgical procedures. Some patients receiving beta-adrenergic receptor blocking agents have experienced protracted severe hypotension during anesthesia. Difficulty in restarting and maintaining the heartbeat has also been reported. For these reasons, in patients undergoing elective surgery, some authorities recommend gradual withdrawal of beta-adrenergic receptor blocking agents.

If necessary during surgery, the effects of beta-adrenergic blocking agents may be reversed by sufficient doses of adrenergic agonists.

Diabetes Mellitus: Beta-adrenergic blocking agents should be administered with caution in patients subject to spontaneous hypoglycemia or to diabetic patients (especially those with labile diabetes) who are receiving insulin or oral hypoglycemic agents. Beta-adrenergic receptor blocking agents may mask the signs and symptoms of acute hypoglycemia.

Thyrotoxicosis: Beta-adrenergic blocking agents may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta-adrenergic blocking agents that might precipitate a thyroid storm.

PRECAUTIONS

General: Because of potential effects of beta-adrenergic blocking agents on blood pressure and pulse, these agents should be used with caution in patients with cerebrovascular insufficiency. If signs or symptoms suggesting reduced cerebral blood flow develop following initiation of therapy with Preservative-free TIMOPTIC in OCUDOSE, alternative therapy should be considered.

Choroidal detachment after filtration procedures has been reported with the administration of aqueous suppressant therapy (e.g. timolol).

Angle-closure glaucoma: In patients with angle-closure glaucoma, the immediate objective of treatment is to reopen the angle. This requires constricting the pupil. Timolol maleate has little or no effect on the pupil. TIMOPTIC in OCUDOSE should not be used alone in the treatment of angle-closure glaucoma.

Anaphylaxis: While taking beta-blockers, patients with a history of atopy or a history of severe anaphylactic reactions to a variety of allergens may be more reactive to repeated accidental, diagnostic, or therapeutic challenge with such allergens. Such patients may be unresponsive to the usual doses of epinephrine used to treat anaphylactic reactions.

Muscle Weakness: Beta-adrenergic blockade has been reported to potentiate muscle weakness consistent with certain myasthenic symptoms (e.g., diplopia, ptosis, and generalized weakness). Timolol has been reported rarely to increase muscle weakness in some patients with myasthenia gravis or myasthenic symptoms.

Information for Patients: Patients should be instructed about the use of Preservative-free TIMOPTIC in OCUDOSE.

Since sterility cannot be maintained after the individual unit is opened, patients should be instructed to use the product immediately after opening, and to discard the individual unit and any remaining contents immediately after use.

Patients with bronchial asthma, a history of bronchial asthma, severe chronic obstructive pulmonary disease, sinus bradycardia, second or third degree atrioventricular block, or cardiac failure should be advised not to take this product. (See CONTRAINDICATIONS.)

Drug Interactions: Although TIMOPTIC (timolol maleate ophthalmic solution) used alone has little or no effect on pupil size, mydriasis resulting from concomitant therapy with TIMOPTIC (timolol maleate ophthalmic solution) and epinephrine has been reported occasionally.

Beta-adrenergic blocking agents: Patients who are receiving a beta-adrenergic blocking agent orally and Preservative-free TIMOPTIC in OCUDOSE should be observed for potential additive effects of beta-blockade, both systemic and on intraocular pressure. The concomitant use of two topical beta-adrenergic blocking agents is not recommended.

Calcium antagonists: Caution should be used in the coadministration of beta-adrenergic blocking agents, such as Preservative-free TIMOPTIC in OCUDOSE, and oral or intravenous calcium antagonists, because of possible atrioventricular conduction disturbances, left ventricular failure, and hypotension. In patients with impaired cardiac function, coadministration should be avoided.

Catecholamine-depleting drugs: Close observation of the patient is recommended when a beta blocker is administered to patients receiving catecholamine-depleting drugs such as reserpine, because of possible additive effects and the production of hypotension and/or marked bradycardia, which may result in vertigo, syncope, or postural hypotension.

Digitalis and calcium antagonists: The concomitant use of beta-adrenergic blocking agents with digitalis and calcium antagonists may have additive effects in prolonging atrioventricular conduction time.

CYP2D6 inhibitors: Potentiated systemic beta-blockade (e.g., decreased heart rate, depression) has been reported during combined treatment with CYP2D6 inhibitors (e.g., quinidine, SSRIs) and timolol.

Clonidine: Oral beta-adrenergic blocking agents may exacerbate the rebound hypertension which can follow the withdrawal of clonidine. There have been no reports of exacerbation of rebound hypertension with ophthalmic timolol maleate.

Injectable epinephrine: (See PRECAUTIONS, *General, Anaphylaxis*)

Carcinogenesis, Mutagenesis, Impairment of Fertility: In a two-year oral study of timolol maleate administered orally to rats, there was a statistically significant increase in the incidence of adrenal pheochromocytomas in male rats administered 300 mg/kg/day (approximately 42,000 times the systemic exposure following the maximum recommended human ophthalmic dose). Similar differences were not observed in rats administered oral doses equivalent to approximately 14,000 times the maximum recommended human ophthalmic dose.

In a lifetime oral study in mice, there were statistically significant increases in the incidence of benign and malignant pulmonary tumors, benign uterine polyps and mammary adenocarcinomas in female mice at 500 mg/kg/day (approximately 71,000 times the systemic exposure following the maximum recommended human ophthalmic dose), but not at 5 or 50 mg/kg/day (approximately 700 or 7,000 times, respectively, the systemic exposure following the maximum recommended human ophthalmic dose). In a subsequent study in female mice, in which post-mortem examinations were limited to the uterus and the lungs, a statistically significant increase in the incidence of pulmonary tumors was again observed at 500 mg/kg/day.

The increased occurrence of mammary adenocarcinomas was associated with elevations in serum prolactin which occurred in female mice administered oral timolol at 500 mg/kg/day, but not at doses of 5 or 50 mg/kg/day. An increased incidence of mammary adenocarcinomas in rodents has been associated with administration of several other therapeutic agents that elevate serum prolactin, but no correlation between serum prolactin levels and mammary tumors has been established in humans. Furthermore, in adult human female subjects who received oral dosages of up to 60 mg of timolol maleate (the maximum recommended human oral dosage), there were no clinically meaningful changes in serum prolactin.

Timolol maleate was devoid of mutagenic potential when tested *in vivo* (mouse) in the micronucleus test and cytogenetic assay (doses up to 800 mg/kg) and *in vitro* in a neoplastic cell transformation assay (up to 100 mcg/mL). In Ames tests the highest concentrations of timolol employed, 5,000 or 10,000 mcg/plate, were associated with statistically significant elevations of revertants observed with tester strain TA100 (in seven replicate assays), but not in the remaining three strains. In the assays with tester strain TA100, no consistent dose response relationship was observed, and the ratio of test to control revertants did not reach 2. A ratio of 2 is usually considered the criterion for a positive Ames test.

Reproduction and fertility studies in rats demonstrated no adverse effect on male or female fertility at doses up to 21,000 times the systemic exposure following the maximum recommended human ophthalmic dose.

Pregnancy: *Teratogenic Effects* — Pregnancy Category C. Teratogenicity studies with timolol in mice, rats and rabbits at oral doses up to 50 mg/kg/day (7,000 times the systemic exposure following the maximum recommended human ophthalmic dose) demonstrated no evidence of fetal malformations. Although delayed fetal ossification was observed at this dose in rats, there were no adverse effects on postnatal development of offspring. Doses of 1000 mg/kg/day (142,000 times the systemic exposure following the maximum recommended human ophthalmic dose) were maternotoxic in mice and resulted in an increased number of fetal resorptions. Increased fetal resorptions were also seen in rabbits at doses of 14,000 times the systemic exposure following the maximum recommended human ophthalmic dose, in this case without apparent maternotoxicity.

There are no adequate and well-controlled studies in pregnant women. Preservative-free TIMOPTIC in OCUDOSE should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: Timolol maleate has been detected in human milk following oral and ophthalmic drug administration. Because of the potential for serious adverse reactions from timolol in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

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

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

ADVERSE REACTIONS

The most frequently reported adverse experiences have been burning and stinging upon instillation (approximately one in eight patients).

The following additional adverse experiences have been reported less frequently with ocular administration of this or other timolol maleate formulations:

BODY AS A WHOLE: Headache, asthenia/fatigue, and chest pain.
CARDIOVASCULAR: Bradycardia, arrhythmia, hypotension, hypertension, syncope, heart block, cerebral vascular accident, cerebral ischemia, cardiac failure, worsening of angina pectoris, palpitation, cardiac arrest, pulmonary edema, edema, claudication, Raynaud's phenomenon, and cold hands and feet.
DIGESTIVE: Nausea, diarrhea, dyspepsia, anorexia, and dry mouth.
IMMUNOLOGIC: Systemic lupus erythematosus.
NERVOUS SYSTEM/PSYCHIATRIC: Dizziness, increase in signs and symptoms of myasthenia gravis, paresthesia, somnolence, insomnia, nightmares, behavioral changes and psychic disturbances including depression, confusion, hallucinations, anxiety, disorientation, nervousness, and memory loss.
SKIN: Alopecia and psoriasiform rash or exacerbation of psoriasis.
HYPERSENSITIVITY: Signs and symptoms of systemic allergic reactions including anaphylaxis, angioedema, urticaria, and localized and generalized rash.
RESPIRATORY: Bronchospasm (predominantly in patients with pre-existing bronchospastic disease), respiratory failure, dyspnea, nasal congestion, cough and upper respiratory infections.
ENDOCRINE: Masked symptoms of hypoglycemia in diabetic patients (see WARNINGS).
SPECIAL SENSES: Signs and symptoms of ocular irritation including conjunctivitis, blepharitis, keratitis, ocular pain, discharge (e.g., crusting), foreign body sensation, itching and tearing, and dry eyes; ptosis; decreased corneal sensitivity; cystoid macular edema; visual disturbances including refractive changes and diplopia; pseudopemphigoid; choroidal detachment following filtration surgery (see PRECAUTIONS, *General*); and tinnitus.
UROGENITAL: Retroperitoneal fibrosis, decreased libido, impotence, and Peyronie's disease.

The following additional adverse effects have been reported in clinical experience with ORAL timolol maleate or other ORAL beta blocking agents, and may be considered potential effects of ophthalmic timolol maleate: *Allergic:* Erythematous rash, fever combined with aching and sore throat, laryngospasm with respiratory distress; *Body as a Whole:* Extremity pain, decreased exercise tolerance, weight loss; *Cardiovascular:* Worsening of arterial insufficiency, vasodilatation; *Digestive:* Gastrointestinal pain, hepatomegaly, vomiting, mesenteric arterial thrombosis, ischemic colitis; *Hematologic:* Nonthrombocytopenic purpura; thrombocytopenic purpura; agranulocytosis; *Endocrine:* Hyperglycemia, hypoglycemia; *Skin:* Pruritus, skin irritation, increased pigmentation, sweating; *Musculoskeletal:* Arthralgia; *Nervous System/Psychiatric:* Vertigo, local weakness, diminished concentration, reversible mental depression progressing to catatonia, an acute reversible syndrome characterized by disorientation for time and place, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics; *Respiratory:* Rales, bronchial obstruction; *Urogenital:* Urination difficulties.

OVERDOSAGE

There have been reports of inadvertent overdosage with Ophthalmic Solution TIMOPTIC (timolol maleate ophthalmic solution) resulting in systemic effects similar to those seen with systemic beta-adrenergic blocking agents such as dizziness, headache, shortness of breath, bradycardia, bronchospasm, and cardiac arrest (see also ADVERSE REACTIONS).

Overdosage has been reported with Tablets BLOCADREN* (timolol maleate tablets). A 30 year old female ingested 650 mg of BLOCADREN (maximum recommended oral daily dose is 60 mg) and experienced second and third degree heart block. She recovered without treatment but approximately two months later developed irregular heartbeat, hypertension, dizziness, tinnitus, faintness, increased pulse rate, and borderline first degree heart block.

An *in vitro* hemodialysis study, using ^{14}C timolol added to human plasma or whole blood, showed that timolol was readily dialyzed from these fluids; however, a study of patients with renal failure showed that timolol did not dialyze readily.

DOSAGE AND ADMINISTRATION

Preservative-free TIMOPTIC in OCUDOSE is a sterile solution that does not contain a preservative. The solution from one individual unit is to be used immediately after opening for administration to one or both eyes. Since sterility cannot be guaranteed after the individual unit is opened, the remaining contents should be discarded immediately after administration.

Preservative-free TIMOPTIC in OCUDOSE is available in concentrations of 0.25 and 0.5 percent. The usual starting dose is one drop of 0.25 percent Preservative-free TIMOPTIC in OCUDOSE in the affected eye(s) administered twice a day. Apply enough gentle pressure on the individual container to obtain a single drop of solution. If the clinical response is not adequate, the dosage may be changed to one drop of 0.5 percent solution in the affected eye(s) administered twice a day.

Since in some patients the pressure-lowering response to Preservative-free TIMOPTIC in OCUDOSE may require a few weeks to stabilize, evaluation should include a determination of intraocular pressure after approximately 4 weeks of treatment with Preservative-free TIMOPTIC in OCUDOSE.

If the intraocular pressure is maintained at satisfactory levels, the dosage schedule may be changed to one drop once a day in the affected eye(s). Because of diurnal variations in intraocular pressure, satisfactory response to the once-a-day dose is best determined by measuring the intraocular pressure at different times during the day.

Dosages above one drop of 0.5 percent TIMOPTIC (timolol maleate ophthalmic solution) twice a day generally have not been shown to produce further reduction in intraocular pressure. If the patient's intraocular pressure is still not at a satisfactory level on this regimen, concomitant therapy with other agent(s) for lowering intraocular pressure can be instituted taking into consideration that the preparation(s) used concomitantly may contain one or more preservatives. The concomitant use of two topical beta-adrenergic blocking agents is not recommended. (See PRECAUTIONS, *Drug Interactions, Beta-adrenergic blocking agents.*)

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BRIEF SUMMARY OF PRESCRIBING INFORMATION

This Brief Summary does not include all the information needed to use ISTALOL® (timolol maleate ophthalmic solution) 0.5% safely and effectively. See full prescribing information for ISTALOL.

Istalol® (timolol maleate ophthalmic solution) 0.5%

Initial U.S. Approval: 1978

STERILE

INDICATIONS AND USAGE

Istalol (timolol maleate ophthalmic solution) 0.5% is a non-selective beta-adrenergic receptor blocking agent indicated in the treatment of elevated intraocular pressure (IOP) in patients with ocular hypertension or open-angle glaucoma.

CONTRAINDICATIONS

4.1 Asthma, COPD: Istalol is contraindicated in patients with bronchial asthma; a history of bronchial asthma; severe chronic obstructive pulmonary disease (see **WARNINGS AND PRECAUTIONS, 5.1, 5.3**).

4.2 Sinus Bradycardia, AV Block, Cardiac Failure, Cardiogenic Shock: Istalol is contraindicated in patients with sinus bradycardia; second or third degree atrioventricular block; overt cardiac failure (see **WARNINGS AND PRECAUTIONS, 5.2**); cardiogenic shock.

4.3 Hypersensitivity Reactions: Istalol is contraindicated in patients who have exhibited a hypersensitivity reaction to any component of this product in the past.

WARNINGS AND PRECAUTIONS

5.1 Potentiation of Respiratory Reactions Including Asthma: Istalol contains timolol maleate; and although administered topically, it can be absorbed systemically. Therefore, the same adverse reactions found with systemic administration of beta-adrenergic blocking agents may occur with topical administration. For example, severe respiratory reactions and cardiac reactions including death due to bronchospasm in patients with asthma, and rarely death in association with cardiac failure, have been reported following systemic or ophthalmic administration of timolol maleate (see **CONTRAINDICATIONS, 4.1**).

5.2 Cardiac Failure: Sympathetic stimulation may be essential for support of the circulation in individuals with diminished myocardial contractility, and its inhibition of beta-adrenergic receptor blockade may precipitate more severe failure. In patients without a history of cardiac failure, continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of cardiac failure, Istalol should be discontinued (see also **CONTRAINDICATIONS, 4.2**).

5.3 Obstructive Pulmonary Disease: Patients with chronic obstructive pulmonary disease (e.g., chronic bronchitis, emphysema) of mild or moderate severity, bronchospastic disease, or a history of bronchospastic disease [other than bronchial asthma or a history of bronchial asthma in which Istalol is contraindicated (see **CONTRAINDICATIONS, 4.2**)] should, in general, not receive beta-blocking agents, including Istalol.

5.4 Increased Reactivity to Allergens: While taking beta-blockers, patients with a history of atopy or a history of severe anaphylactic reactions to a variety of allergens may be more reactive to repeated accidental, diagnostic, or therapeutic challenge with such allergens. Such patients may be unresponsive to the usual doses of epinephrine used to treat anaphylactic reactions.

5.5 Potentiation of Muscle Weakness: Beta-adrenergic blockade has been reported to potentiate muscle weakness consistent with certain myasthenic symptoms (e.g., diplopia, ptosis, and generalized weakness). Timolol has been reported rarely to increase muscle weakness in some patients with myasthenia gravis or myasthenic symptoms.

5.6 Masking of Hypoglycemic Symptoms in Patients with Diabetes Mellitus: Beta-adrenergic blocking agents should be administered with caution in patients subject to spontaneous hypoglycemia or to diabetic patients (especially those with labile diabetes) who are receiving insulin or oral hypoglycemic agents. Beta-adrenergic receptor blocking agents may mask the signs and symptoms of acute hypoglycemia.

5.7 Masking of Thyrotoxicosis: Beta-adrenergic blocking agents may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta-adrenergic blocking agents that might precipitate a thyroid storm.

5.8 Contamination of Topical Ophthalmic Products After Use: 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 (see **PATIENT COUNSELING INFORMATION, 17**).

5.9 Impairment of Beta-adrenergically Mediated Reflexes During Surgery: The necessity or desirability of withdrawal of beta-adrenergic blocking agents prior to major surgery is controversial. Beta-adrenergic receptor blockade impairs the ability of the heart to respond to beta-adrenergically mediated reflex stimuli. This may augment the risk of general anesthesia in surgical procedures. Some patients receiving beta-adrenergic receptor blocking agents have experienced protracted severe hypotension during anesthesia. Difficulty in restarting and maintaining the heartbeat has also been reported. For these reasons, in patients undergoing elective surgery, some authorities recommend gradual withdrawal of beta-adrenergic receptor blocking agents. If necessary during surgery, the effects of beta-adrenergic blocking agents may be reversed by sufficient doses of adrenergic agonists.

5.10 Angle-Closure Glaucoma: In patients with angle-closure glaucoma, the immediate objective of treatment is to reopen the angle. This may require constricting the pupil. Timolol maleate has little or no effect on the pupil. Istalol should not be used alone in the treatment of angle-closure glaucoma.

5.11 Cerebrovascular Insufficiency: Because of potential effects of beta-adrenergic blocking agents on blood pressure and pulse, these agents should be used with caution in patients with cerebrovascular insufficiency. If signs or symptoms suggesting reduced cerebral blood flow develop following initiation of therapy with Istalol, alternative therapy should be considered.

5.12 Choroidal Detachment: Choroidal detachment after filtration procedures has been reported with the administration of aqueous suppressant therapy (e.g. timolol).

ADVERSE REACTIONS

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.

The most frequently reported adverse reactions have been burning and stinging upon instillation in 38% of patients treated with Istalol. Additional reactions reported with Istalol at a frequency of 4 to 10% include: blurred vision, cataract, conjunctival injection, headache, hypertension, infection, itching and decreased visual acuity. The following additional adverse reactions have been reported less frequently with ocular administration of this or other timolol maleate formulations.

Timolol (Ocular Administration): *Body as a whole:* Asthenia/fatigue and chest pain; *Cardiovascular:* Bradycardia, arrhythmia, hypotension, syncope, heart block, cerebral vascular accident, cerebral ischemia, cardiac failure, worsening of angina pectoris, palpitation, cardiac arrest, pulmonary edema, edema, claudication, Raynaud's phenomenon and cold hands and feet; *Digestive:* Nausea, diarrhea, dyspepsia, anorexia, and dry mouth; *Immunologic:* Systemic lupus erythematosus; *Nervous System/Psychiatric:* Dizziness, increase in signs and symptoms of myasthenia gravis, paresthesia, somnolence, insomnia, nightmares, behavioral changes and psychic disturbances including depression, confusion, hallucinations, anxiety, disorientation, nervousness and memory loss; *Skin:* Alopecia and psoriasiform rash or exacerbation of psoriasis; *Hypersensitivity:* Signs and symptoms of systemic allergic reactions, including angioedema, urticaria, and localized and generalized rash; *Respiratory:* Bronchospasm (predominantly in patients with pre-existing bronchospastic disease), respiratory failure, dyspnea, nasal congestion, cough and upper respiratory infections; *Endocrine:* Masked symptoms of hypoglycemia in diabetic patients (see **WARNINGS AND PRECAUTIONS, 5.6**); *Special Senses:* Signs and symptoms of ocular irritation including conjunctivitis, blepharitis, keratitis, ocular pain, discharge (e.g., crusting), foreign body sensation, itching and tearing, and dry eyes; ptosis, decreased corneal sensitivity; cystoid macular edema; visual disturbances including refractive changes and diplopia; pseudopemphigoid; choroidal detachment following filtration surgery (see **WARNINGS AND PRECAUTIONS, 5.12**); *Urogenital:* Retroperitoneal fibrosis, decreased libido, impotence, and Peyronie's disease.

6.2 Postmarketing Experience

Oral Timolol/Oral Beta-blockers: The following additional adverse effects have been reported in clinical experience with ORAL timolol maleate or other ORAL beta-blocking agents and may be considered potential effects of ophthalmic timolol maleate: *Allergic:* Erythematous rash, fever combined with aching and sore throat, laryngospasm with respiratory distress; *Body as a Whole:* Extremity pain, decreased exercise tolerance, weight loss; *Cardiovascular:* Worsening of arterial insufficiency, vasodilatation; *Digestive:* Gastrointestinal pain, hepatomegaly, vomiting, mesenteric arterial thrombosis, ischemic colitis; *Hematologic:* Nonthrombocytopenic purpura; thrombocytopenic purpura, agranulocytosis; *Endocrine:* Hyperglycemia, hypoglycemia; *Skin:* Pruritus, skin irritation, increased pigmentation, sweating; *Musculoskeletal:* Arthralgia; *Nervous System/Psychiatric:* Vertigo, local weakness, diminished concentration, reversible mental depression progressing to catatonia, an acute reversible syndrome characterized by disorientation for time and place, emotional lability, slightly clouded sensorium and decreased performance on neuropsychometrics; *Respiratory:* Rales, bronchial obstruction; *Urogenital:* Urination difficulties.

DRUG INTERACTIONS

7.1 Beta-Adrenergic Blocking Agents: Patients who are receiving a beta-adrenergic blocking agent orally and Istalol® should be observed for potential additive effects of beta-blockade, both systemic and on intraocular pressure. The concomitant use of two topical beta-adrenergic blocking agents is not recommended.

7.2 Calcium Antagonists: Caution should be used in the co-administration of beta-adrenergic blocking agents, such as Istalol, and oral or intravenous calcium antagonists because of possible atrioventricular conduction disturbances, left ventricular failure, and hypotension. In patients with impaired cardiac function, co-administration should be avoided.

7.3 Catecholamine-Depleting Drugs: Close observation of the patient is recommended when a beta blocker is administered to patients receiving catecholamine-depleting drugs such as reserpine, because of possible additive effects and the production of hypotension and/or marked bradycardia, which may result in vertigo, syncope, or postural hypotension.

7.4 Digitalis and Calcium Antagonists: The concomitant use of beta-adrenergic blocking agents with digitalis and calcium antagonists may have additive effects in prolonging atrioventricular conduction time.

7.5 CYP2D6 Inhibitors: Potentiated systemic beta-blockade (e.g., decreased heart rate) has been reported during combined treatment with CYP2D6 inhibitors (e.g., quinidine) and timolol.

7.6 Clonidine: Oral beta-adrenergic blocking agents may exacerbate the rebound hypertension which can follow the withdrawal of clonidine. There have been no reports of exacerbation of rebound hypertension with ophthalmic timolol maleate.

USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects: Pregnancy Category C: Teratogenicity studies have been performed in animals. Teratogenicity studies with timolol in mice, rats, and rabbits at oral doses up to 50 mg/kg/day (7,000 times the systemic exposure following the maximum recommended human ophthalmic dose) demonstrated no evidence of fetal malformations. Although delayed fetal ossification was observed at this dose in rats, there were no adverse effects on postnatal development of offspring. Doses of 1000 mg/kg/day (142,000 times the systemic exposure following the maximum recommended human ophthalmic dose) were maternotoxic in mice and resulted in an increased number of fetal resorptions. Increased fetal resorptions were also seen in rabbits at doses of 14,000 times the systemic exposure following the maximum recommended human ophthalmic dose, in this case without apparent maternotoxicity. There are no adequate and well-controlled studies in pregnant women. Istalol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

8.3 Nursing Mothers: Timolol has been detected in human milk following oral and ophthalmic drug administration. Because of the potential for serious adverse reactions from Istalol in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

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

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

OVERDOSAGE

There have been reports of inadvertent overdosage with Istalol resulting in systemic effects similar to those seen with systemic beta-adrenergic blocking agents such as dizziness, headache, shortness of breath, bradycardia, bronchospasm, and cardiac arrest. An *in vitro* hemodialysis study, using ^{14}C timolol added to human plasma or whole blood, showed that timolol was readily dialyzed from these fluids; however, a study of patients with renal failure showed that timolol did not dialyze readily.

NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility: In a two-year study of timolol maleate administered orally to rats, there was a statistically significant increase in the incidence of adrenal pheochromocytomas in male rats administered 300 mg/kg/day (approximately 42,000 times the systemic exposure following the maximum recommended human ophthalmic dose). Similar differences were not observed in rats administered oral doses equivalent to approximately 14,000 times the maximum recommended human ophthalmic dose. In a lifetime oral study in mice, there were statistically significant increases in the incidence of benign and malignant pulmonary tumors, benign uterine polyps and mammary adenocarcinomas in female mice at 500 mg/kg/day, (approximately 71,000 times the systemic exposure following the maximum recommended human ophthalmic dose), but not at 5 or 50 mg/kg/day (approximately 700 or 7,000, respectively, times the systemic exposure following the maximum recommended human ophthalmic dose). In a subsequent study in female mice, in which post-mortem examinations were limited to the uterus and the lungs, a statistically significant increase in the incidence of pulmonary tumors was again observed at 500 mg/kg/day. The increased occurrence of mammary adenocarcinomas was associated with elevations in serum prolactin which occurred in female mice administered oral timolol at 500 mg/kg/day, but not at doses of 5 or 50 mg/kg/day. An increased incidence of mammary adenocarcinomas in rodents has been associated with administration of several other therapeutic agents that elevate serum prolactin, but no correlation between serum prolactin levels and mammary tumors has been established in humans. Furthermore, in adult human female subjects who received oral dosages of up to 60 mg of timolol maleate (the maximum recommended human oral dosage), there were no clinically meaningful changes in serum prolactin. Timolol maleate was devoid of mutagenic potential when tested *in vivo* (mouse) in the micronucleus test and cytogenetic assay (doses up to 800 mg/kg) and *in vitro* in a neoplastic cell transformation assay (up to 100 mcg/mL). In Ames tests the highest concentrations of timolol employed, 5,000 or 10,000 mcg/plate, were associated with statistically significant elevations of revertants observed with tester strain TA100 (in seven replicate assays), but not in the remaining three strains. In the assays with tester strain TA100, no consistent dose response relationship was observed, and the ratio of test to control revertants did not reach 2. A ratio of 2 is usually considered the criterion for a positive Ames test. Reproduction and fertility studies in rats demonstrated no adverse effect on male or female fertility at doses up to 21,000 times the systemic exposure following the maximum recommended human ophthalmic dose.

PATIENT COUNSELING INFORMATION

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Get the Most From Your Kamra

Here are the experts' tips and techniques for implanting the recently approved Kamra inlay for presbyopia.

Walter Bethke, Managing Editor

With the recent U.S. Food and Drug Administration approval of the AcuFocus Kamra inlay, surgeons in the United States can finally drill down to the details of what it takes to implant these unique presbyopic inlays successfully and avoid complications. Experts say implanting these new devices takes some skill, as well as the instinct to know when to stop your intracorneal manipulations and simply let the implant be. Here's advice from skilled Kamra surgeons on how to work with the new device.

The Kamra Candidate

To understand what makes a good Kamra patient, it helps to quickly review the device's design. The Kamra is a small, thin, ring-shaped inlay 3.8 mm in diameter, 5 µm thick, with a central 1.6-mm aperture. The ring itself is riddled with approximately 8,400 holes that are each 5 to 11 µm wide, which allow the flow of nutrients to the cornea. The Kamra procedure involves the use of a femtosecond laser to create a pocket at a depth of 200 µm in a patient's non-dominant eye, into which the Kamra is placed using special forceps. Once in place, the Kamra is designed to increase the depth of focus in emmetropic presbyopes through the pinhole effect, while having a minimal effect on distance vision.

Tokyo surgeon Minoru Tomita has implanted just over 10,000 Kamra inlays, and has learned a good deal about how to make them work in patients. "In the United States, the prospective patient's spherical equivalent refraction should be between -0.75 and +0.5 D," says Dr. Tomita. "So the candidate pool is very small." Surgeons outside the United States have learned to expand the candidate pool by combining the Kamra with LASIK, though this isn't in the official FDA labeling for the device. "I'm combining it with LASIK, so if the patient has hyperopia of +3 D I can make it -0.75 D with a hyperopic LASIK procedure. Similarly, if the patient is -5, I can make him -0.75 with a myopic LASIK," says Dr. Tomita. Jay Pepose, one of AcuFocus's clinical investigators in the U.S. trial, says this range of vision is ideal for these patients. "Probably the -0.75 D is really the sweet spot, because you're extending the depth of field."

Even when the preop refraction is acceptable, however, Dr. Tomita says in his experience there are still certain patients who shouldn't receive the Kamra. "For us, we wouldn't select it for a person who is a driver or a pilot by trade," he says. "It's very good for an office worker, though. The reason it's not a good choice for a driver is the pinhole reduces the amount of light admitted into the eye. At night, when the dilated pupil will usually admit more light, the Kamra inlay will block this extra light and the patient can feel that things are dark when driving. In some patients, though, the Kamra causes no problem, and most drive themselves home after the inlay is implanted. But for others, it can take six months to get used to the new vision that might make some situations feel dark. If one of this latter type of patients is also a driver, he can't take a six-month holiday from work to get used to his vision."

Dr. Tomita says that, as in other areas of refractive surgery, a patient who is very nervous or tends to obsess over imperfections may not be a good candidate. "If the patient is very sen-

sitive or nervous, we wouldn't choose the Kamra for him," he says. "This is because, sometimes, it takes time to recover the vision with the Kamra inlay. Most patients get their distance and near vision back in a week, but some patients take several weeks to one month. A nervous patient can get very worried about that, and can take a lot of your time having many discussions about it."

Implantation Pearls

Between the U.S. study and the experience of surgeons outside the United States, physicians have developed certain best practices when approaching a Kamra implantation.

• ***Laser settings.*** Though it was initially thought the Kamra would go beneath a LASIK flap, the device's labeling specifically calls for a femtosecond-created pocket, so the Kamra surgeon needs access to a femtosecond laser. "Prior to the study, many surgeons were using a flap, but this created more dry eye," says Dr. Pepose. "The pocket is clearly the preferred way to go about implanting it. Also, as we carried out the FDA study of the device, it turned out that the laser settings were critical. A tight line and spot setting, less than or equal to 6 x 6, is important. When we started to go higher in the line/spot separation, the tissue around the pocket that needed to be separated was like Velcro, and you'd encounter areas that weren't lased in between the spots. This led to the creation of more inflammation as the surgeon dissected the pocket, and these patients would not fare as well as the patients who had the tighter spot. The tighter laser spacing reduces the wound-healing response and enhances refractive stability."

• ***Depth.*** Surgeons say the 200-µm depth is a good spot for avoiding corneal issues. "We didn't really stratify the data from the study at different depths, but you don't want to go too shallow," says Dr. Pepose. "In previous studies, when they went too shallow they had issues with corneal thinning, and you also don't want issues from the change in shape of the cornea by going too shallow; you don't want changes in topography. At 200 µm, you're also not so deep that you have concerns of ectasia."

• ***Centration.*** Though it's important to have the Kamra centered properly, surgeons say it's actually very forgiving when it's not dead center. In addition to a femtosecond laser, Dr. Pepose notes that surgeons will need access to AcuFocus's AcuTarget HD device to implant the Kamra. The device helps surgeons locate landmarks and Purkinje images to guide Kamra centration. "A lot of the centration depends on the eye's angle kappa," Dr. Pepose explains. "Usually, we target the first Purkinje image. If there's

From Femto to Zepto?

For surgeons who are interested in an easier way to make circular capsulotomies but don't want to spend $500,000 to do it, Mynosys, a small start-up company in Northern California, may be developing the solution. Here, Los Altos, Calif., surgeon David Chang, MD, who is working with the company to help develop the device, describes how this experimental technology works.

"Mynosys is developing a device called Zepto, which is a novel capsulotomy system with a disposable handpiece and tip that should be far less expensive compared to the capital and per-case costs of the femtosecond laser," Dr. Chang says. "The device consists of a nitinol ring that creates a precise, round capsulotomy of a specific predetermined diameter. Because nitinol is a shape-memory alloy, it can be deformed in order to squeeze through a clear corneal incision, after which it assumes its original round shape within the anterior chamber *(See image, right)*. Once inside the eye, slight suction from a surrounding silicone shell apposes the ring to the anterior capsular surface. A proprietary nanopulse technology then uses phase transition of trapped water molecules to instantaneously cleave a 360-degree continuous capsulotomy. It is neither plasma energy nor cautery, but the application of energy is extremely fast and confined to a microscopic area. The resulting smooth capsular edge resembles a manual capsulorhexis edge on scanning electron microscopy."


David Chang, MD

In terms of the equipment needed for operation, Dr. Chang says Zepto will use a separate portable power supply, but won't involve any other expensive capital acquisition cost. "What's more, using the Zepto capsulotomy device should not lengthen or change the normal operating room workflow," Dr. Chang says. "Rather than inserting a cystotome or capsulotomy forceps, the surgeon would simply insert this device into the viscoelastic-filled anterior chamber instead.

"We have done extensive testing in both human cadaver and animal eyes so far," adds Dr. Chang, "and our preliminary results suggest that the Zepto capsulotomy edge appears as strong—or possibly stronger than—either a manual capsulorhexis or a femtosecond laser capsulotomy."

Dr. Chang is a consultant to Mynosis.

—W.B.

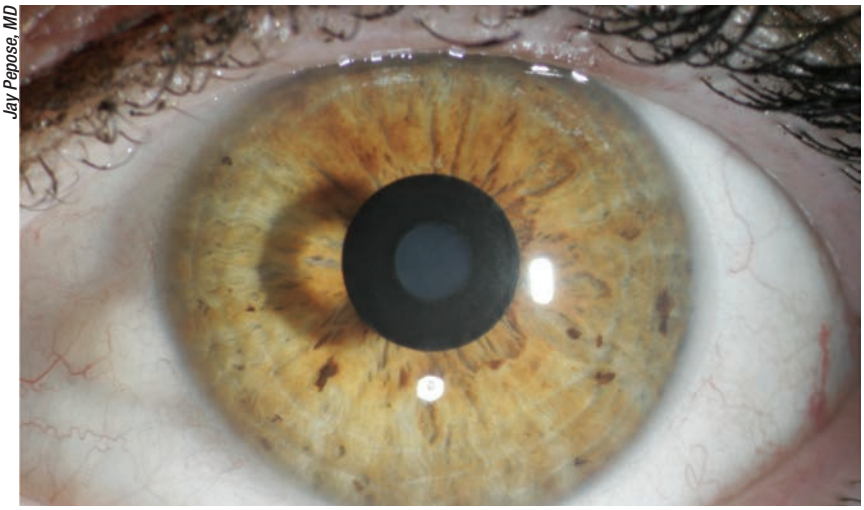
a large angle kappa, then we'll usually split the difference and aim between the first Purkinje and the center of the pupil." Surgeons say the inlay can be off by up to 300 µm and still yield good results.

Dr. Tomita says the design of the operating microscope you use during implantation also can make a difference. "You have to make sure that the fixation light strikes the cornea at a 90-degree angle," he says. "There can't be an oblique angle from the light to the corneal surface. The Takagi microscope company has a special microscope for the Kamra inlay, and the WaveLight Allegretto 400 and AMO/Visx excimer laser microscopes are usable. You can also use a microscope that you use for cataract surgery. However, you can't use the Allegretto EX 500 or the iFS microscopes."

• ***Don't fiddle with it.*** Surgeons say trying too hard to center the device perfectly will backfire. "During implantation, the surgeon, especially the beginner, can be very nervous," says Dr. Tomita. "In an effort to place it on the center of the Purkinje image, he might try to move it, then find he's moved it too far, then try to move it back. If you move the Kamra too much, however, patients take more time to recover their vision. If you think it may not be perfectly centered, just wait until the postop period. If the patient doesn't have good vision, then you can move it. But if you touch the Kamra too many times during the surgery, the patient's vision will be decreased."

Dr. Pepose advises using a particular placement technique when situating the device in the corneal pocket. "Note that the pocket goes beyond the spot you need the Kamra to be," he says. "With the special implantation forceps, go beyond where you want the inlay to sit and then pull it back. Then, when you're at the spot, you just slowly release the forceps. This prevents a fold or a dog ear on the distal edge of the inlay."

Jay Pepose, MD



The Kamra inlay, implanted inside a 200-µm deep corneal pocket, increases depth of field through the use of the pinhole effect created by its small central aperture.

Postop Management

In addition to visual results, surgeons say there are other things to watch for in the postoperative period.

In the pivotal FDA study, at 12 months 84 percent of the patients (399/478) could see 20/40 or better uncorrected at near in the Kamra eye. Binocularly, 94 percent could see 20/40 or better uncorrected at near. In terms of uncorrected distance vision in the implanted eye, patients lost an average of three letters at 12 months.[1]

Forty-five patients (8.9 percent) had to have their inlays removed over the course of the first five years postop. Two of the removals were for the appearance of the inlay, four removals were medically indicated, and 25 were removed due to visual complaints (25 of these due to hyperopic refractive shifts). All but one of the explanted eyes returned to 20/20 best-corrected distance vision, with the remaining one seeing 20/25, possibly due to a corneal scar. Dr. Pepose says that the explantation rate was higher in the study than it is currently because the study surgeons didn't yet know about the proper spot/line separation or the optimum preop refraction. "The explantation rate is now around 2 percent in current Kamra usage," he says.

Surgeons say steroids can help handle some postop situations. "We use a steroid for at least six months to prevent a haze reaction," says Dr. Tomita. "If they develop haze, patients will get a hyperopic shift—becoming +1 or +2. If this occurs, we'll use dexamethasone five times daily, and patients will improve after a month or a little longer. After they improve, we'll reduce the steroid. If there's no improvement, though, we'll have to remove the inlay."

Dr. Pepose says that, if patients know what to expect ahead of time, they can do well with the Kamra. "Like any refractive surgery, you want the patient to have reasonable expectations," he says. "If the patient wants to be able to take out his smartphone and read it, that's OK. But, if he wants to sit for five hours and read *War and Peace*, he may still have to put on low-power readers. The nice thing though, is with the Kamra you're not changing the second eye's refraction, so store-bought readers work. In the end, just be sure to establish realistic expectations." REVIEW

1. AcuFocus Kamra labeling. http://www.acufocus.com/int/sites/default/files/Physician%20Labeling.pdf. Accessed 15 May 2015.

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Managing & Preventing Tube Shunt Problems

Christopher Kent, Senior Editor

This alternative to trabeculectomy is increasing in popularity as new insights and techniques improve outcomes.

Most surgeons treating glaucoma have mixed feelings about trabeculectomy, given its high complication and failure rates. New alternatives such as minimally invasive glaucoma surgeries have attracted a lot of attention, but don't appear to be a replacement for trabeculectomy since they don't lower pressure as dramatically. However, a more time-honored alternative—tube shunts—can often provide that greater level of pressure reduction.

Tube shunts have their own challenges and complications, of course, which is why most surgeons haven't simply given up trabeculectomy and switched to using them as their mainstay surgical option. Their use is increasing, however, at least partly because of improvements in surgical technique and in the devices themselves, as well as new ideas about preventing tube erosion and fibrosis.

Here, three surgeons with extensive experience using these devices offer their suggestions for minimizing unwanted complications, improving long-term bleb survival and making sure that a second tube—when necessary—is effective.

The Case for Using Tubes

Herbert P. Fechter III, MD, who practices at Eye Physicians & Surgeons of Augusta in Augusta, Ga., says he typically implants two to four glaucoma shunts per week, mostly Baerveldts but also some Ahmeds. "I've noted a shift from trabeculectomy to glaucoma drainage implants over the past 12 years," he says. "I think the Tube vs. Trabeculectomy Study had a lot to do with that, along with top-tier academic centers promoting the use of tube surgery. More recently, the Ahmed vs. Baerveldt Study has also persuaded many surgeons that tube surgery has a place earlier in glaucoma management."

Dr. Fechter notes that he uses tube shunts as his primary glaucoma surgery for cases of moderate to severe glaucoma. "Many other surgeons prefer to do a trabeculectomy first," he says. "If the trabeculectomy fails, they move on to a tube shunt. I've heard surgeons express concern about 'painting ourselves into a corner' with the tube-first approach, asking what we'll do if the tube fails, since glaucoma is a lifelong disease. But the majority of our glaucoma patients are more than 65 years old, and some may have only 10 or 15 years of life expectancy left. I'd be more concerned about follow-up options if I were managing a 22-year-old who still has 60 years left to live; but even in that situation

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***Richard Lindstrom**, MD*
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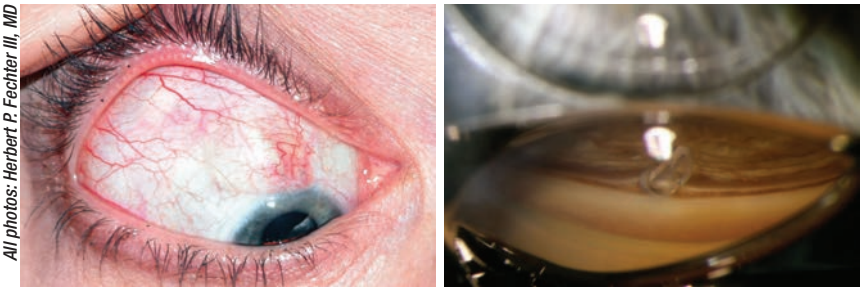

Left: How a tube should look after healing. This 46-year-old Caucasian female had pigment dispersion syndrome and Graves' disease. The tube was routed superiorly underneath a corneal patch graft, and the plate is at least 11 mm from the limbus in the supratemporal quadrant. Eight years after the surgery this patient is doing fine with a pressure of 11 mmHg on no medications. Right: Gonioscopy of the same patient showing the surgeon's recommended placement of the tube behind Schwalbe's line between the iris and the trabecular meshwork, where no endothelial cells can come into contact with it. (A video of this patient's surgery, titled "Bread and Butter Baerveldt," can be viewed on the Web at youtube.com/watch?v=P40TsszQBEo.)

I believe I'd still choose a tube over trabeculectomy with mitomycin-C."

Dr. Fechter says he implants a Baerveldt about 90 percent of the time and an Ahmed the other 10 percent of the time. "The one I choose depends on the patient," he explains. "I tend to reserve the Ahmeds for cases of neovascular glaucoma or angle closure where the pressure is very high and I need to get it down quickly. But if I think I can manage to maintain moderate pressure in the early postoperative period, I prefer to put in a Baerveldt. It has a lower profile than the Ahmed, and the five-year treatment outcomes in the Ahmed Baerveldt Comparison Study show that pressures are a couple of points lower with the Baerveldt. I also have a bias; during my fellowship training the majority of tube patients received the Baerveldt implant.

"At the outset, surgeons usually have some apprehension about the complications associated with each of these implants," he adds. "They may be reluctant to put in a tube out of fear of hypotony, diplopia or hyphema. The package insert lists a number of complications, and over the years, I've observed each one of them at one time or another. For most patients, though, it's a very reliable technique for lowering pressure."

Scar Tissue and Fibrosis

Darrell WuDunn, MD, PhD, professor of ophthalmology at the Eugene and Marilyn Glick Eye Institute, Indiana University School of Medicine in Indianapolis, notes that the most common cause of tube shunt failure is scar tissue forming around the plate. "Over time you may get a really thick capsule around the plate that prevents the fluid from getting out of the reservoir," he explains. "You can usually tell that this is the problem because the bleb overlying the plate will be thick, dome-shaped and very elevated—higher than you'd expect it to be. In contrast, if the bleb is very low that probably means a tube blockage is the source of the problem. Fluid has to travel through the tube to the reservoir to create the bleb, so if the bleb is flat, you know the fluid is not getting into it.

"If the problem is scar tissue around the implant, you can revise it either of two ways," he continues. "You can take a 27- or 30-ga. needle and poke holes into the capsule beneath the conjunctiva to see if you can get the fluid to flow through the holes. Of course, you have to be careful that you don't cause leakage. Usually you start by inserting the needle far away from the bleb itself and track beneath the conjunctiva; then when you get to the capsule, you start poking holes in it. That maneuver can release some of the fluid from the reservoir so it can leak into the surrounding space and out through the conjunctiva."

Dr. WuDunn notes that this approach is not guaranteed to be successful. "Back in 1997 Philip Chen and Paul Palmberg published a study which looked at a series of 21 eyes that underwent needle revisions.[1] They found that it worked only 43 percent of the time after one year," he says. "However, it's a simple procedure that can be done in the office, which is a big advantage.

"If that doesn't work, you can bring the patient to surgery and do a surgical revision of the bleb over the plate by excising the capsule," he continues. "That means opening the capsule, removing the thickened scar tissue and then sewing it closed again. Three or four articles have looked at the success rate of this approach, including one we published back in 2000. The success rate isn't all that great; this only succeeds in restoring pressure control long-term—say, for more than one year—40 to 60 percent of the time. All of those studies showed similar results, and they weren't much better than needling of the bleb. So one could argue that if your success rate isn't going to be better than needling, you might as well try needling in the office rather than bringing the patient to the operating room."

The Cytokine Connection

As with many things in life, the best solution to the problem of bleb scarring may be prevention. Jeffrey Freedman, MD, PhD, professor of clinical ophthalmology at SUNY Downstate Medical Center in Brooklyn, has recently made notable progress in that area. (In the past, Dr. Freedman has worked closely with Professor Anthony

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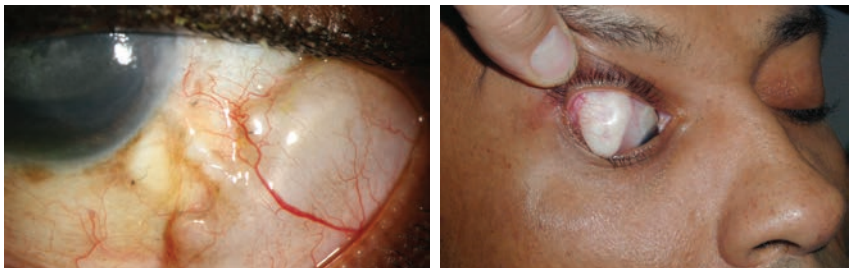

Two examples of how an implant should not look. Left: An Ahmed shunt was placed in the inferotemporal quadrant where it is exposed, easily noticed by others, uncomfortable and at risk of infection; it was also placed too close to the limbus. It's far preferable to place the device in the supratemporal quadrant where it's covered by the eyelid, with the inferonasal quadrant as a second choice. Right: a Baerveldt implant that was not placed properly underneath the lateral rectus muscle, causing the implant to ride forward. The patient suffered serious diplopia, but did very well once the shunt was repositioned.

Molteno, developer of the Molteno shunt.) "The major problem that affects all of these implants is fibrosis, which is the primary reason a bleb stops draining," he says. "Once they stop draining, they're worthless. So the real concerns here have to do with bleb physiology. That's the issue Dr. Molteno and I have spent most of our time working on in recent years."

Dr. Freedman explains that there's a profound connection between elevated pressure and the development of fibrosis, a connection moderated by cytokines. "I learned about the connection between pressure and cytokines from one of my early collaborators who was a rheumatologist," Dr. Freedman says. "Rheumatologists work with cytokines all the time because cytokines are associated with arthritis and similar problems. My colleague introduced me to the concept of a Selye pouch, invented by Hans Selye, MD, a doctor who did a lot of research on how the body responds to stress. If one injects air under the skin of a rat and increases the pressure inside it to stress the tissues, one creates what is known as a Selye pouch. Research has shown that increasing the pressure inside the pouch causes the tissues to produce TGFβ-2 (transforming growth factor beta). My colleague noted that the bleb we create is exactly the same as a Selye pouch.

"What our own research has shown," Dr. Freedman continues, "is that when the pressure in the eye goes up, proinflammatory cytokines are formed, particularly TGFβ-2. These cytokines lead to the formation of fibrosis. What's important to understand is that the stimulus for development of these cytokines is the elevated pressure itself. The pressure causes a breakdown of the blood-aqueous barrier and the formation of the cytokines. We have also shown that the level of TGFβ-2 in the aqueous is prognostic of whether or not the bleb will survive or fail.

"Recently we compared the aqueous of normal eyes that were having cataract surgery and eyes in which we did glaucoma implants—in other words, eyes in which the pressure was elevated," he says. "Furthermore, we compared both of these to the fluid inside the bleb during the hypertensive phase, where the pressure is very elevated. The data showed clearly that as the pressure goes up, the concentration of cytokines becomes higher, especially the very proinflammatory TGFβ-2 and monocyte chemotactic protein1 [MCP-1]."

Dr. Freedman notes that there are also other substances in the aqueous that act to interfere with the fibrotic process. "Professor Molteno has demonstrated that a bleb will form well when pro-apoptotic substances called fas ligand are present," he says. "They undermine the fibrotic process. The levels of those substances are inversely related to the levels of cytokines, so when cytokine levels are high there's less fas ligand to reduce fibrotic formation. It's another piece of evidence that the way to get a good bleb is to eliminate the cytokines."

Minimizing Fibrosis

Dr. Freedman says the aqueous present in the eye at the time of surgery is referred to as glaucomatous aqueous. "This aqueous is called that because having been exposed to high IOP, it's laden with cytokines," he explains. "Allowing this aqueous onto the plate surface will result in an immediate pro-inflammatory reaction, which may result in the development of a more fibrotic and less functional bleb. This has been shown to occur in valved implants, which do allow aqueous onto the plate surface immediately.[2] Non-valved implants don't allow this to happen because the tubes are temporarily occluded; aqueous only reaches the plate surface after the IOP has been lowered by other means. Our research has shown quite clearly that if the aqueous doesn't reach the plate until the pressure has been lowered, the cytokine content is much lower, which results in a less-severe fibrotic reaction." Dr. Freedman points out that allowing cytokine-laden fluid onto the surface of the plate also results in a more frequent and severe hypertensive phase. "This in turn results in a bleb that ultimately is more fibrotic and less functional," he says.[2]

"The reason for the use of valved implants is the ability of these implants to prevent postoperative hypotony in most cases," he adds. "Nevertheless, it's becoming more apparent that blebs associated with non-valved implants are likely to be less fibrotic and more functional in the long term.

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I believe this can be explained by the cytokine content of the aqueous. We have recently submitted a paper for review which illustrates this concept.

"Several researchers from Iran saw a poster of mine at ARVO back in 2006 discussing the presence of cytokines in the aqueous and explaining that the stimulus for the development of the cytokines was pressure," he continues. "So, they conducted a study focused on Ahmed implants. They had the patients in one group take carbonic anhydrase inhibitors [following surgery] to decrease the formation of aqueous and keep the pressure low. Their data showed that if you can keep the pressure low during the development of the bleb, the Ahmed does much better. They surmised that this was because cytokines were not being formed, due to the low pressure.[3] Our studies have shown this explanation to be correct."

Dr. Freedman says this has caused him to modify his technique when implanting glaucoma tube shunts. "Now, we look at our blebs very carefully," he says. "As soon as the pressure goes up, I tap the bleb. If the bleb is tapped by removing aqueous whenever the pressure becomes elevated, the pressure can be controlled, with or without the use of medications, thus reducing the level of cytokines in the aqueous. If the cytokine content is lowered, it results in a more successful bleb."

Managing Tube Blockage

"One of the things that can cause a tube to fail is blockage," notes Dr. WuDunn. "The tube can be blocked by vitreous or fibrin caught in the opening. It can also be blocked by iris tissue, if the iris is floppy or inflammation causes the iris to migrate into the tube.

"To resolve the problem, it's important to determine the etiology of the blockage," he says. "If you can see the block, whether vitreous, fibrin or iris, you may be able to use a laser to disrupt it. Typically you'd use the Nd:YAG laser, although sometimes the argon laser will work. The Nd:YAG laser is very precise, and the inside diameter of the tube is large enough that you can create a microexplosion inside the tube and not damage the tube itself. In this way a blood clot, for example, is easily lasered, and fibrin or vitreous can sometimes be lasered with the YAG.

"In the case of a blood clot, you may also be able to inject tissue plasminogen activator into the anterior chamber to dissolve it," he notes. "If there's some bleeding inside the eye after surgery, a clot can sometimes block the tube, at least temporarily. This is usually not a long-term cause of failure, because left alone a clot will eventually dissolve anyway. Vitreous and iris, of course, won't dissolve on their own; the laser is the easiest way to attempt to clear those blockages.

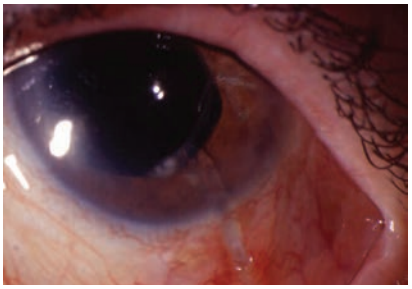
"In any case, clearing the blockage will often restore functioning," he says. "At least in the short term, this can often solve the problem and get the pressure back down; usually you'll see an immediate pressure reduction. However, there's still a risk of the tube getting blocked again in the same way if you don't resolve the primary problem, or if there's a lot of inflammation. Any inflammation such as chronic uveitis can cause a lot of synechial formation. When the tube is sitting close to the iris, as the iris is pulled forward by the synechiae it starts to engulf the tube, eventually blocking it. If you catch this early enough you can sometimes poke a hole through the iris with the laser to restore the flow through the tube. Unfortunately, in most cases that's only a temporary solution; the continued inflammation will cause the iris to close up on the tube again."

Dr. Fechter says he hasn't had much trouble with tubes being blocked by iris. "I create an anterior bevel to keep the tube opening away from the iris," he explains. "If you put the tube posteriorly and the tube does become occluded with iris, you can punch a hole in the iris with the laser and allow the tube tip to extend through the iridotomy.

"Tube occlusion by vitreous should be prevented by performing a vitrectomy to remove any vitreous that has made its way into the anterior chamber," he adds. "If vitreous does manage to clog the tube, the YAG laser probably will not help. The best approach is to perform a vitrectomy to remove the source of the obstruction."

Preventing Tube Exposure

"Exposure is a common issue with tubes, usually due to the upper eyelid eroding the conjunctiva overlying the tube," notes Dr. WuDunn. "The eyelid is normally right up against the globe, and the tube is slightly elevated because it's sitting on top of the sclera



Inferonasal tube exposure. Tube exposure is a common problem over time because of the eyelid rubbing against the elevated conjunctiva that covers the tube. Strategies for prevention include placing a graft over the tube; directing the tube more toward the 12 o'clock position to allow for lid coverage of the course of the tube; and creating a long scleral tunnel.

before it goes in. So there's a little bit greater pressure as the lid closes over the area where the tube is. The conjunctiva there is getting extra rubbing, and it can wear thin over time and eventually break down. Usually this happens several years after the implant; I've had tubes become exposed after 10 years of being in place."

He admits that resolving this problem can be tricky. "There are different approaches, and no matter what you do it often recurs," he says. "You think you've closed the conjunctiva with a couple of sutures; but you haven't addressed the real problem—the eyelid rubbing against it where it overlies this elevated foreign body. Closing it with sutures will work temporarily; but after a few months it may wear down again, leaving the tube exposed."

One common strategy for addressing this concern is to place a patch graft over the tube. "There's a lot of debate about how best to use patch grafts," notes Dr. WuDunn. "The idea of putting a graft on the tube is that you don't want the conjunctiva to be sitting right on top of the tube, because when the lid comes down over the conjunctiva it's going to rub against the tube, leading to exposure. The thought is that if you cover the tube with a graft, that will spread out the elevation over a broader area so you're less likely to get erosion."

Dr. WuDunn points out that a pericardium graft is often chosen because it's pretty thin. "Scleral grafts tend to be a little thicker and more expensive," he says. "The third option is cornea, and that's now coming into vogue because it's clear. You can see the tube all the way along its length; if there's a blockage, you can see where it is. This can also help if you've tied an absorbable suture around the tube. If you need to cut the suture early—say the pressure is really high after three weeks and you want the pressure to be down now, instead of waiting five weeks for the ligature to absorb—you can go ahead and laser it with an argon laser, because you can see where the ligature is through the clear graft."

Changing Tube Placement

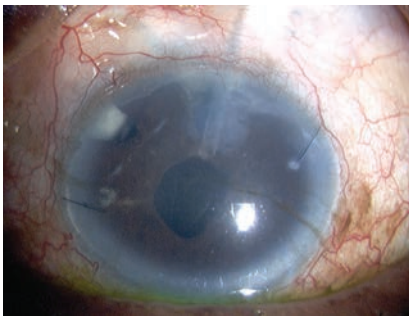
Another approach that attempts to minimize this problem involves placing the tube differently. Dr. Freedman says that Dr. Molteno's original approach to managing this concern was to do a lamellar scleral flap and bury the tube under the flap before it went into the eye. "I did that for a number of years, but it became clear that because the path was lamellar rather than full thickness, the tube would erode," he says. "Furthermore, tying the flap down posteriorly caused the tube to come up inside the eye and touch the corneal endothelium. So I began putting on a scleral patch.[4]

"Many other patches have been developed subsequently," he adds. "The problem has been that there is still erosion because the tube is curved. The curve of the tube produces pressure on the undersurface of the flap, and that can also lead to erosion. As a result, many surgeons today put the tube through a scleral tunnel instead of directly into the anterior chamber; they then cover that with a patch as well. This has decreased the curvature

of the tube and made it flatter, so the erosion problem is not as frequent as it used to be." (Dr. WuDunn notes that some surgeons who make a long tunnel through the patient's sclera do not put a graft on top, in an attempt to reduce overall elevation and potentially reduce the likelihood of tube erosion.)

Another approach involves changing the location at which the tube enters the eye. "Many surgeons direct the tube along a straight course from the plate to the anterior chamber," notes Dr. Fechter. "Dr. Paul Palmberg at Bascom Palmer initially trained me to direct the tube more toward the 12 o'clock position, to allow for lid coverage of the course of the tube. I believe this helps to prevent tube erosion.

"I think it's extremely important to route the tube this way," he continues. "Most tube erosions occur where the eyelid crosses over the tube at the 2 and 10 o'clock positions; all the erosions I've seen in referred patients were in that region. So, if you never put your tube in that region to begin with, it greatly reduces the chance of erosion. I also pass the 23-ga. needle about 3 to 4 mm from the limbus, near the 12 o'clock position, so the tube is protected by the upper eyelid. The conjunctiva covering the tube is well-protected, and you don't get constant rubbing of the eyelid margin over the tube. There may be some patients with chronic rheumatoid arthritis with scleral melt that you really can't help anyway, but I've been using this technique for more than 10 years and my patients have had a very low incidence of tube or plate erosion.



A tube protruding too far into the anterior chamber. Sometimes this results from an Ahmed plate riding forward, because an Ahmed is not placed beneath the superior lateral rectus muscle the way a Baerveldt would be. If the tube is pushed too far into the anterior chamber, it may touch the cornea when the patient blinks or rubs his eyes. Cloudiness in the area of the tube suggests that endothelial cells have been damaged and the tube needs to be trimmed.

"I also make my tube entry into the eye more distal to the limbus than many surgeons," he says. "I use the long scleral tunnel technique described by Felix Gil Carrasco, MD. Dr. Carrasco showed that in a large

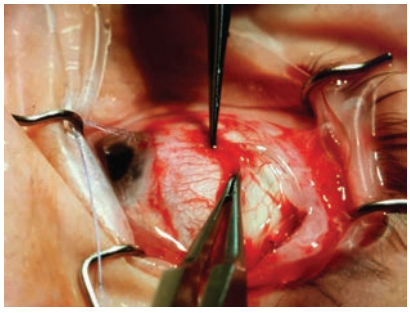
series of Ahmed implants using long scleral tunnels without any patch grafts there was a low incidence of tube erosion. When I heard that Medicare had stopped paying for patch grafts in conjunction with tube surgery, I thought that surgeons would stop using patch grafts over tubes, due to Dr. Carrasco's success. However, due to subsequent negotiations, glaucoma surgeons can now get reimbursed by Medicare for corneal patch graft material. As a result, I think that many surgeons will switch from their current patch graft material to cornea patches, if they continue to cover their tubes."

Dr. Fechter admits that the long scleral tunnel approach is not totally risk-free. "The potential complication with this technique is that the tube tends to be more posterior," he says. "As a result, there's not only an increased risk of hyphema, but also an increased risk of the tube causing pupil peaking. The peaked pupil, however, is more of a cosmetic concern than a major complication.

"This long scleral tunnel technique makes patch grafts appear unnecessary," he adds. "However, I continue to use a corneal patch to cover the tube anyway— since patches are still considered the standard of care for tube surgery. I find that Tutoplast patches in many eyes are no longer visible after several months, so I don't think the patch is contributing to my low-erosion success. I believe the major contributor is proper tube placement. Longer scleral tunnels routed to the 12 o'clock position may one day eliminate the need for patches and become the new standard of care."

A Supra-Tenon's Pocket

Dr. Freedman has developed another effective way to minimize tube exposure, one that appears to be gaining popularity. "In this approach I place the implant in a supra-Tenon's pocket," he explains. "Most surgeons put the implant under both the conjunctiva and Tenon's capsule. However, it was shown some years ago that Tenon's capsule contains the messenger RNA for TGFβ-2. In fact, it's a major producer of TGFβ-2, and that's what triggers all the fibrosis.



Inserting a tube through a long scleral tunnel. This technique is believed to reduce the likelihood of tube erosion. (A graft was later placed over the tube as well.)

"Back in the 1990s it occurred to me to make a pocket for the implant within Tenon's instead of placing it underneath Tenon's," he continues. "This approach has been published in the *British Journal of Ophthalmology* and *Archives of Ophthalmology*.[5,6] We compared the two approaches in a group of African Americans with aggressive disease. The data clearly showed that the supra-Tenon's method eliminates about half of the Tenon's capsule from participating in the final bleb, resulting in a thinner bleb capsule. The assumption is that we are eliminating some of the TGFβ-2 and thereby decreasing the fibrotic potential of the bleb; as a result, we get much better blebs. Other surgeons are now trying this technique, but many of them are simply putting the devices under the conjunctiva, not in a Tenon's pocket; this variation could make the potential for conjunctival erosion much higher. I would suggest that eliminating Tenon's entirely is ill-advised.

"Based on this concept, I convinced the Moltenos to develop a new Molteno implant, the M3S, which is now on the market," he adds. "This version is much easier to use and can be implanted in a supra-Tenon's pocket without fear of conjunctival erosion."

Managing a Second Tube

Given that tubes may fail after a period of time, surgeons are occasionally faced with deciding what to do next. Dr. WuDunn notes that because there's only about a 40 percent success rate when rescuing a failed tube, many surgeons just put in a second tube in a different place. "I don't advocate revising a tube shunt, although some surgeons do," he says. "I think if you're taking the patient to the operating room, you might as well put a second tube in there. You could do both—put in a second tube and revise the first. That might work OK. But you're probably going to get the most bang for your buck from the second tube.

"Second tubes generally work very well," he continues. "They do about as well as the first implant, so you can get another four to seven years of good pressure control. That may not seem like a lot, but by the time you get to the second tube, these patients have already had a trabeculectomy and the first tube shunt. They tend to be more advanced, complicated cases than the primary surgeries. These are the cases that haven't gone well with other surgeries."

Dr. Fechter has also placed many second tubes. "Placing a second tube is a viable option," he says. "My second tubes tend to be placed in African-American patients who have a thick bleb around their plate. Depending on the pressure, I like to wait five months for the hypertensive phase to resolve before considering a second drainage implant. If after five months the pressure is still not acceptable, then I would consider placing a second tube in the inferior-nasal quadrant. During that five-month period, Diamox is often a useful adjunct for pressure control, but patients often complain

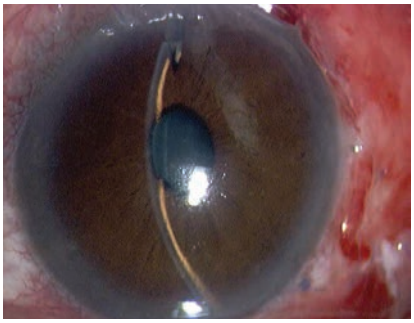
about its side effects.

"Tube positioning is also very important," he continues. "The first tube should be placed supratemporally, the second inferonasally. An inferiortemporal tube often provides a poor cosmetic result and may increase the risk of tube and plate exposure."

Dr. WuDunn adds that there are alternatives to placing a second tube shunt. "My preference would be to do the second tube; but sometimes there may be some reason I don't want to put in a second tube," he says. "Perhaps there's so much scar tissue that I don't think I can get a second tube in there, or the patient may already have two failed tubes and we're looking at a third. I have put third ones in, but the success rate is definitely not as good as that of the primary tubes. One alternative is laser cyclophotocoagulation, either with endolaser or from an external approach. This can sometimes be done in the office. It also might be feasible to try one of the new MIGS procedures. Whether they would work in this situation is not known, but one could try a Trabectome or iStent procedure to see if that would help drain fluid through the regular outflow pathway. You might need to put in several iStents, of course. The good thing is that having tubes in place doesn't prevent you from trying one of these angle surgeries."

What About the First Shunt?

Implanting a second shunt raises the question of what to do—if anything—with the first implant. Dr. Fechter says he usually leaves the first implant as it is. "It's probably contributing somewhat to pressure control," he notes. However, if I think the first tube has failed I'd either revise it or remove it surgically. Another option is to replace the first implant with a different one. On three occasions I removed an Ahmed implant that failed due to a thick, fibrosed capsule and replaced it with a Baerveldt implant in the same quadrant. This approach produced good results in younger patients, while reserving the inferotemporal quadrant for possible future surgery."



A slit beam reveals a shallow anterior chamber. This can occur with a Baerveldt shunt if the tube (seen here at the top) opens earlier than expected. The chamber can be reinflated using viscoelastic.

"Some people advocate removing the first tube when putting in the second one," says Dr. WuDunn. "Considering the extra hardware you're going to put on the eye, you're potentially going to create some problems with motility. So, if the first one's not working, you might as well take it out and not have to deal with it. Of course, you have to put the second tube at a different location because there will be a lot of scar tissue where the first tube was located.

"However, removing the first tube will be tricky, because it's not just a matter of taking the tube out of the eye and pulling out the implant," he continues. "The implant becomes very adherent to the globe, for two reasons: First, if it's a Baerveldt implant, it's usually placed beneath the muscles. The second, bigger problem is that all of these implants have little holes in them to allow scar tissue to create little rivets through the holes. In the old days, before the implants had these little holes, the fluid would flow through the tube into the reservoir and create a very large and elevated bleb that caused motility problems. Allowing scar tissue to form through these holes tacks down the device and the bleb, limiting the elevation that the bleb develops over time.

"Unfortunately, when you try to remove the tube you have to cut each one of those scar rivets that have formed through the holes that are anchoring the implant to the globe," he says. "The Baerveldt has four holes, and they're pretty far back, and they're pretty wide and close to the muscle. That makes it a little tricky to remove the big Baerveldts. The Ahmeds only have two holes, and they're near the middle of the tube, so that's not quite as hard."

Dr. Freedman's study of the connection between fibrosis and elevated cytokine levels—resulting from elevated pressure—has led him to come up with a novel approach to managing this situation. He has observed that leaving the first, failed implant in the eye often results in rapid failure of the second implant, and he believes that this may be because the failed implant becomes a factory for the production of cytokines. "That's a big problem, because the aqueous goes in and out of the shunts with the pumping of the heart," he notes. "That's true of all the shunts [even those with a valve]. Thanks to the two-way flow and the failed bleb essentially becoming a factory for making cytokines, those cytokines will make their way into the aqueous and then into the second implant, causing it to fibrose.

"Knowing this, I've begun trying a new approach," he says. "Instead of removing the failed implant, I pull out its tube and tie it off using a 7-0 prolene suture. Then I insert it back into the eye. It takes three or four weeks for the prolene to loosen itself, allowing the bleb to work again. We've found that during this period of time the failed bleb loses its potential as a factory for producing TGFβ-2, and as long as the pressure remains low, it doesn't regain it. So once the suture releases, the bleb is exchanging fluid with the eye again, but it's no longer encouraging the fi-

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Bimatoprost ophthalmic solution 0.03% has been reported to cause darkening (pigmentation) of eye color, eyelid skin, and eyelashes as well as increased growth of eyelashes. Pigmentation changes can increase as long as bimatoprost ophthalmic solution 0.03% is used. After stopping bimatoprost ophthalmic solution 0.03%, darkening of eye color is likely to be permanent, while darkening of the eyelid skin and eyelash changes may be reversible. The effects of increased darkening beyond 5 years are not known. When only one eye is treated, there is a possibility of eyelash changes in the eye treated with bimatoprost ophthalmic solution 0.03%. These changes may result in differences between the eyes in eyelash length, thickness, darkness, number of eyelashes, and/or direction of eyelash growth. These changes are usually reversible upon stopping bimatoprost ophthalmic solution 0.03% therapy. Patients should avoid allowing the tip of the dispensing container to contact the eye, surrounding structures, fingers, or any other surface in order to avoid contamination of the solution by common bacteria known to cause ocular infections. Serious damage to the eye and subsequent loss of vision may result from using contaminated solutions. In the event patients develop an intercurrent ocular condition (e.g., trauma or infection), have ocular surgery, or develop any ocular reactions, particularly conjunctivitis and eyelid reactions, they should immediately seek their physician's advice concerning the continued use of bimatoprost ophthalmic solution, 0.03%. Contact lenses should be removed prior to instillation of bimatoprost ophthalmic solution, 0.03% and may be reinserted 15 minutes following its administration. The most common side effects are conjunctival hyperemia, growth of eyelashes, and ocular pruritus.

Please see Brief Summary of Prescribing Information on the adjacent page.
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BRIEF SUMMARY OF FULL PRESCRIBING INFORMATION

BIMATOPROST Ophthalmic Solution, 0.03%

INDICATIONS AND USAGE

Bimatoprost ophthalmic solution, 0.03% is indicated for the reduction of elevated intraocular pressure in patients with open angle glaucoma or ocular hypertension.

In clinical studies of patients with open angle glaucoma or ocular hypertension with a mean baseline IOP of 26 mmHg, the IOP-lowering effect of bimatoprost ophthalmic solution, 0.03% once daily (in the evening) was 7 to 8 mmHg.

WARNINGS AND PRECAUTIONS

Pigmentation

Bimatoprost ophthalmic solution has been reported to cause changes to pigmented tissues. The most frequently reported changes have been increased pigmentation of the iris, periorbital tissue (eyelid) and eyelashes. Pigmentation is expected to increase as long as bimatoprost 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 bimatoprost, pigmentation of the iris is likely to be permanent, while pigmentation of the periorbital tissue and eyelash changes have been reported to be reversible in some patients. Patients who receive treatment should be informed of the possibility of increased pigmentation. The long term effects of increased pigmentation are not known.

Iris color change may not be noticeable for several months to years. Typically, the brown pigmentation around the pupil spreads concentrically towards the periphery of the iris and the entire iris or parts of the iris become more brownish. Neither nevi nor freckles of the iris appear to be affected by treatment. While treatment with bimatoprost ophthalmic solution, 0.03% can be continued in patients who develop noticeably increased iris pigmentation, these patients should be examined regularly.

Eyelash Changes

Bimatoprost ophthalmic solution, 0.03% may gradually change eyelashes and vellus hair in the treated eye. These changes include increased length, thickness, and number of lashes. Eyelash changes are usually reversible upon discontinuation of treatment.

Intraocular Inflammation

Prostaglandin analogs, including bimatoprost, have been reported to cause intraocular inflammation. In addition, because these products may exacerbate inflammation, caution should be used in patients with active intraocular inflammation (e.g., uveitis).

Macular Edema

Macular edema, including cystoid macular edema, has been reported during treatment with bimatoprost ophthalmic solution. Bimatoprost ophthalmic solution 0.03% 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.

Bacterial Keratitis

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

Use with Contact Lenses

Contact lenses should be removed prior to instillation of bimatoprost ophthalmic solution, 0.03% and may be reinserted 15 minutes following its administration.

ADVERSE REACTIONS

In clinical trials, the most frequent events associated with the use of bimatoprost ophthalmic solution, 0.03% occurring in approximately 15% to 45% of patients, in descending order of incidence, included conjunctival hyperemia, growth of eyelashes, and ocular pruritus. Approximately 3% of patients discontinued therapy due to conjunctival hyperemia.

Ocular adverse events occurring in approximately 3 to 10% of patients, in descending order of incidence, included ocular dryness, visual disturbance, ocular burning, foreign body sensation, eye pain, pigmentation of the periocular skin, blepharitis, cataract, superficial punctate keratitis, periorbital erythema, ocular irritation, and eyelash darkening. The following ocular adverse events reported in approximately 1 to 3% of patients, in descending order of incidence, included: eye discharge, tearing, photophobia, allergic conjunctivitis, asthenopia, increases in iris pigmentation, and conjunctival edema. In less than 1% of patients, intraocular inflammation was reported as iritis.

Systemic adverse events reported in approximately 10% of patients were infections (primarily colds and upper respiratory tract infections). The following systemic adverse events reported in approximately 1 to 5% of patients, in descending order of incidence, included headaches, abnormal liver function tests, asthenia and hirsutism.

USE IN SPECIFIC POPULATIONS

Pregnancy Category C

Nursing Mothers

It is not known whether bimatoprost is excreted in human milk, although in animal studies, bimatoprost has been shown to be excreted in breast milk. Because many drugs are excreted in human milk, caution should be exercised when bimatoprost is administered to a nursing woman.

Pediatric Use

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

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brotic process. The end result is that you're left with two functioning blebs, providing a double pressure-reducing effect. We're conducting an ongoing study to demonstrate this."

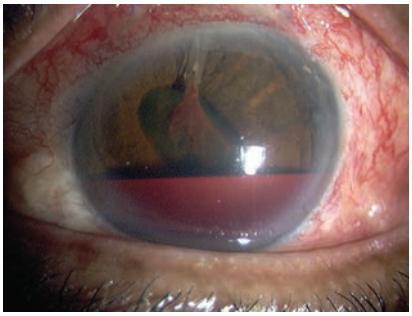
Other Complications

Dr. Fechter offers suggestions for other complications that can sometimes arise:

• ***Hyphema.*** Dr. Fechter says that currently, one of the most common complications he encounters with tube surgeries is a mild hyphema, which he attributes to his technique. "I make long scleral tunnels and try to get my tube as far posterior as possible, away from the cornea," he says. "By doing this, I'm more likely to route the tube near some of the ciliary body vessels and put the patient at higher risk of a hyphema. However, I've never had to drain a postoperative hyphema; they resolve on their own. I'd say I get a small hyphema in one out of 15 patients and a major hyphema in one out of 30 patients."

• ***Diplopia.*** Dr. Fechter says he hasn't had much trouble with this issue, unlike some other surgeons. "I think that has to do with clearing a space for the implant to fit beneath the muscles," he says. "You have to clear the Tenon's attachment to the lateral borders of the muscles. When I do that I find I can slip the implant in without much resistance and suture it posterior to the muscles by at least a millimeter. Since using this technique I've seen a reduction in diplopia.

"The one patient group in which I still see diplopia is my African-American patients with thick Tenon's capsules," he adds. "They can form large, exuberant blebs during the healing process, and the pressure of that bleb pushing against the globe can lead to diplopia. Fortunately, the diplopia usually resolves on its own; there was only one instance in which I had to reoperate to fix the diplopia."



Hyphemas may occur in a few patients, particularly if you try to place the tube more posteriorly to protect the cornea. However, as long as the pressure remains low, hyphemas usually resolve on their own without draining. This was the largest hyphema ever seen by this surgeon, and it resolved within six weeks.

• ***Bullous keratopathy.*** "Bullous keratopathy is often due to corneal endothelial damage in patients who have been on chronic glaucoma therapy," Dr. Fechter explains. "They have compromised epithelium from long-term medication use and also compromised endothelium from years of elevated pressure.

"Many surgeons believe that the tube itself causes endothelial cell loss," he continues. "I believe that if you can place the tube behind Schwalbe's line, you may decrease the chance of endothelial cell loss. Some surgeons will put the tube behind the iris in pseudophakic eyes. I will do that on occasion, but that has its own set of complications; sometimes the pressure is elevated and you're not sure why and you can't see the tube. So my preference is to place the tube anterior to the iris but as close to the iris as possible, not touching the cornea, and behind Schwalbe's line. If the patient has iris neovascularization or chronic angle closure with peripheral anterior synechiae, then I'll place the tube through a prior peripheral iridotomy or direct it behind the iris with the tube tip extending up to the pupil border."

• ***Choroidal effusions.*** "Choroidal effusions can be an issue when the tube opens," Dr. Fechter notes. "I'd say one out of 20 patients will experience noticeable hypotony when the tube opens, and there is some choroidal effusion and shallowing of the anterior chamber. If the hypotony persists, I treat it with viscoelastic injected into the anterior chamber. The only time I drain a choroidal is if it's long-standing, in which case I'm worried about hypotony maculopathy or choroidal touch. I rarely need to drain choroidals—maybe once every three or four years, and I put in more than 100 tubes a year."

Surgical Pearls

Drs. Fechter and WuDunn offer these additional strategies to help improve outcomes:

• ***Leave extra tube length.*** "If you think you may need to revise the tube later, it's important to allow extra length," says Dr. WuDunn. "If the tube gets moved out of position or you find it's blocked by iris tissue, you may need to move the tube to a different location. That means you need to leave a little extra length on the tube during your initial procedure.

"One good way to do that is to curve it around a little to the left or right before it goes into the eye," he notes. "You want to keep the amount of tube inside the eye fairly limited, because the longer your tube is, the more likely you're going to damage the cornea. Every time you blink, the eyelid pushes the cornea backwards a little bit, so if the tube is very close to the cornea it will touch or push on the tube, and that can lead to corneal edema. This means you need to leave any extra length outside, along the sclera."

• ***Don't pass your sutures too deep in the sclera.*** "There's a possibility of retinal detachment if you do this," says Dr. Fechter. "One of the few times I've seen it happen was in a nanophthalmic eye, when we were

(continued on page 72)

New Frontiers in Sustained Release

Walter Bethke, Managing Editor

An update on the most viable strategies for releasing glaucoma drugs over time.

"A chain is only as strong as its weakest link," goes the old aphorism, and it's never been more true than in glaucoma treatment: A company spends millions developing a blockbuster glaucoma drop; researchers spend thousands of hours testing it; and then the physician spends days of chair time examining the patient and selecting the ideal drug for him … only to have the patient go home and not take it. Like death and taxes, patient non-adherence looked like it was one of the immutable facts of life; but there may be hope. Companies are hard at work on methods for generating sustained release of glaucoma medication in the eye, taking patient adherence out of the equation. Here's a look at several of the most promising strategies for sustained-release glaucoma medications that might be coming to your clinic in a couple of years.

Amorphex Therapeutics

Amorphex (Andover, Mass.) has combined polymers that allow sustained release of drug with a device platform called the Topical Ophthalmic Drug Delivery Device to create a sustained-release modality that floats on the tear film beneath the lid. The device without the drug has been tested for tolerability in humans, and the company is currently securing funding to perform a Phase I trial.

Robert Thompson, president and chief executive officer of Amorphex says the TODDD material matrix can be modified to achieve the proper balance of drug loading and release. Through the process, the selected drug is polymerized directly into the material. So far, most of the company's work has focused on timolol and prostaglandins.

In a formal clinical study of the device's tolerability, researchers placed it beneath the lids of 20 subjects at the New England College of Optometry. "We had the subjects wear it on a daily-wear basis, and then transition to a 30-day, uninterrupted wearing of it," explains Mr. Thompson. "We quickly learned that if you can wear it successfully for a week, you'll be able to wear it successfully for an extended period of time." One of the subjects had to discontinue the study due to grade 2 eye redness that resulted from a lot of eye motion during a volleyball game. Another subject had to have it removed due to excessive movement of the device. "In both patients, we should have put our foot down and said, 'This isn't right for you,' because it was moving and rotating out of position in the office," recalls Mr. Thomp-

son. Even though the TODDD rides on the tear film, Mr. Thompson says it doesn't cross over onto the cornea. "It has a corneal relief curve on it that prevents it from riding up and onto the cornea," he says. "I've worn 10 of them myself and have never had it go into my field of vision."

If a subject doesn't experience movement of the device initially, chances are it will be able to sit there unnoticed, says Mr. Thompson. "The only time you'll feel it, not feel pain, but literally just be aware of it, is when you do an upward look," he says.

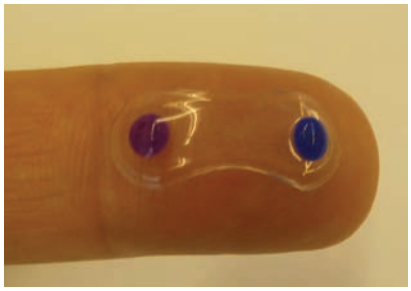
The company has also placed timolol-laden TODDDs into the eye of a glaucoma patient over a six-month period and monitored the intraocular pressure response. "The timolol devices averaged an IOP reduction percentage of 16 to 22 percent," says Mr. Thompson. "This is consistent with the reduction you'd expect from timolol drops. However, the subject was being exposed to 15 to 20 percent of the drug he'd get from drops since, with drops, a good amount goes down the tear ducts and nasal passages and is swallowed."

One of the potential benefits of the device is that it doesn't necessarily need to be placed or removed in an eye-care provider's office. "If the patient is at an assisted-care facility, you could teach a nurse or another employee how to insert and remove it in 10 minutes," says Mr. Thompson. "In our clinical trial, we taught all the subjects how to remove it."

As mentioned, the company is in the process of securing funding for the device's next step, a Phase I trial. "The Phase I trial will be with drug," says Mr. Thompson. "In it, we'd probably be limited to 90 days maximum but, in the case of glaucoma, that's certainly long enough to monitor the IOP."

Ocular Therapeutix

Ocular Therapeutix (Bedford, Mass.) has a sustained-release dexamethasone punctal plug delivery system that's in Phase III trials for post-cataract pain and inflammation; it may also be a viable way to deliver glaucoma medications over an extended period. The company is currently enrolling patients for a Phase IIb trial of a punctal plug designed to release travoprost for a period of up to 90 days.



Amorphex's TODDD system delivers drug while floating on the tear film.

In addition to tackling compliance problems and issues with patients limiting their doses to save money on drug co-pays, Amar Sawhney, PhD, president, chief executive officer and chairman of Ocular Therapeutix, says a sustained-release system can also help overcome side-effect problems. "These drugs often have side-effect profiles," Dr. Sawhney says. "One aspect is they can have preservatives that can interfere with the long-term health of the ocular surface. Second, one peak-dose effect of prostaglandin analogs is a hyperemia that occurs in 20 to 40 percent of patients, depending on the agent that's used.

"Approaches were tried in the past, such as Ocusert," Dr. Sawhney continues. "This was placed in the upper fornix and released pilocarpine. However, it was a fairly decent-sized disk and the problem was it didn't stay in place very consistently, and fell out or was uncomfortable. So, while it worked, it didn't catch on enough due to these drawbacks. We felt there had to be an approach that lets you deliver this medication over a meaningful duration—for us that was two to three months—in a non-invasive way. We didn't want to put needle holes in people or have to perform implant surgery in anyone, because that clearly wouldn't be a great option if you're going to be doing it every two to three months."

Dr. Sawhney says he and his fellow researchers liked the punctal plug approach to delivering drug, but that certain issues needed to be addressed. "Punctal plugs that are made of plastic can only hold a small amount of drug in their core," he says. "We also felt we didn't want anything projecting out of the punctum, because that could cause discomfort on the lid. Also, the punctum is a natural place for people to rub their eyes and subsequently eject the plug if it's projecting out. As a result, we took more of a wine-cork design, which would go into the canaliculus—meaning it's more of an intracanalicular placement as opposed to a plug-like placement. We didn't want to expand the punctum too much, because some plugs can dilate the punctum to 0.8 to 1 mm in size, which stresses the sphincter. Our approach is to keep the expansion below 0.8 mm, preferably at 0.7 mm, and to make the plug long and thin. This way, when it comes into contact with bodily fluids in the canaliculus, it expands in diameter while shrinking in length, going from 0.7 mm in diameter to almost 2 mm in diameter, and going from 3 mm long to about 2 mm. As a result, it ends up being more disc-shaped and residing in the ampulla. The sphincter, however, is closed up on top of it, so you wouldn't be permanently stressing the sphincter." Since the plug is so small, and could eject without a patient's knowledge, Ocular Therapeutix has also made it fluorescent; when queried with a small blue keychain light, the plug glows within the canaliculus, allowing the patient to know it's still there.

Ocular Therapeutix conducted a Phase II study outside the United

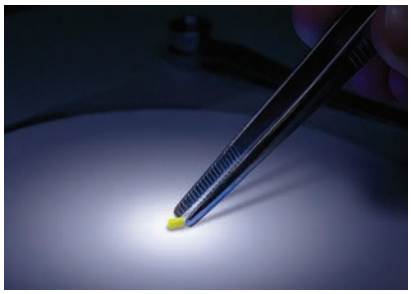
States that showed an intraocular pressure decrease similar to travoprost drops, but Dr. Sawhney says it wasn't statistically powered. The company is currently enrolling a Phase IIb study in the United States that will look at the size of the effect and pave the way for a Phase III trial. The Phase II trial did help them learn more about the device, however. "There are some adverse events, but nothing that's unusual for glaucoma therapy, and nothing that appears to be serious," says Dr. Sawhney. "What you do get is possibly some localized itching for a short duration because a prostaglandin is a pro-inflammatory drug. But, you don't get hyperemia, which can occur with prostaglandins and Rho kinase inhibitors up to 40 percent of the time. You don't get the hyperemia because you're releasing the drug in a steady fashion."

As with anything inserted through the punctum there's a risk of ejection. "We have done a number of non-significant risk studies," says Dr. Sawhney. "In these, we take placebo plugs and optimize their design, looking at shape, profile, means of insertion, hardness/softness and different physical dimensions in order to optimize retention. In these studies to date, we've seen up to 92-percent retention."

Another thing physicians, and regulators, are on the lookout for with punctal plug delivery systems is the possibility of systemic dosing of the drug. "We actually had to do a clinical study looking at that for the dexamethasone plug," says Dr. Sawhney. "I can definitely say that we didn't see [systemic levels] with that device. In the prostaglandin work, we haven't done that yet, but we don't expect to see systemic levels because the amounts are generally quite tiny and released over a continuous period of time."

Ohr Pharmaceutical

Ohr Pharmaceutical's (New York City) plan to overcome compliance



Ocular Therapeutix uses a punctal plug to deliver latanoprost to the eye over time.

issues with glaucoma medication is to inject micro- or nanoparticles into the eye that would then release a glaucoma drug/drugs over an extended period of time. However, the existing emulsion methods make it difficult to use narrow-gauge needles to do this. In response, Ohr has developed a new template fabrication method for these particles that makes it easier to get them into the eye. The company is developing delivery approaches for primary open-angle glaucoma as well as steroid-induced glaucoma.

"A big advantage of our template approach is its control of particle size, resulting in greater uniformity," explains Nikita Malavia, PhD, senior scientist at Ohr Pharmaceutical. "Currently used emulsion-based methods generate a very broad particle size distribution, meaning that small micro- or nanoparticles are mixed in with the large ones, making it difficult to deliver them through small-gauge needles, as well as creating greater variability in drug release. In addition, emulsion-based methods are limited as to the type of polymer that you can use in the process, as well as the amount of drug that can be loaded into these formulations. Since sustained drug delivery is contingent upon the properties of both the biodegradable polymers as well as the amount of loaded drug, a proper balance between the these two factors is required for efficacious dosing for an extended period of time. Emulsion-based methods usually don't allow more than 10 percent by weight of drug loading. If you wanted to replace monthly injections with an injection every three to six months, you typically need to have a greater than 10 percent drug load. Our technology allows the incorporation of much more than 10 percent of drug by weight, and we've been able to incorporate more than 50 percent by weight of some molecules. This means that as much as half of the actual formulation going into the eye is drug, and just the remaining half is polymer, which makes for much more efficient ocular drug delivery."

Dr. Malavia describes the process: "Our process uses microfabrication technology, which is similar to what is currently used in the semiconductor industry," she explains. "We use a silicon wafer master template, that has our customized pattern on it, onto which we pour a hydrogel material that we then let cure. We then fill this hydrogel template with our formulation, which includes both polymer and drug. We use a solvent to dissolve away this hydrogel, leaving just the uniformly sized and shaped microparticles as a result. The pattern we lay down on our wafer controls the size of our final micro- or nanoparticles. So, if we want a nanoparticle size, we'd pattern down nano-range features on our wafer. If we want microparticle size, we'd pattern down micron-sized features."

Dr. Malavia says the fabrication process allows a unique layering approach different from other microparticle processes. "We can control the initial release of drug from the formulation by using an approach called layering. We can put down a layer of one sort of polymer that degrades slowly or quickly, and then follow with another layer with the drug, and finally layer with a polymer without drug. In this way, we create a sandwiched microparticle formulation of polymer and drug layers. For some indications, we might want a loading dose which requires high initial release, while in others we might need a lower initial release. We can provide

Choose BAK-free TRAVATAN Z® Solution for sustained IOP lowering

Sustained 30% IOP lowering

at 12, 14, and 20 hours post-dose in a 3-month study[1,2]*

TRAVATAN Z® Solution has no FDA-approved therapeutic equivalent[3]

Help patients start strong and stay on track with the Openings Patient Support Program

INDICATIONS AND USAGE

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

Dosage and Administration

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

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

IMPORTANT SAFETY INFORMATION

Warnings and Precautions

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

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

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

Adverse Reactions

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

Use in Specific Populations

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

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

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

References: 1. Data on file, 2013. **2.** Lewis RA, Katz GJ, Weiss MJ, et al. Travoprost 0.004% with and without benzalkonium chloride: a comparison of safety and efficacy. *J Glaucoma.* 2007;16(1): 98-103. **3.** Drugs@FDA. FDA Approved Drug Products: TRAVATAN Z. www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.DrugDetails. Accessed July 31, 2014.

TRAVATAN Z®

(travoprost ophthalmic solution) 0.004%

Alcon®
a Novartis company

TRAVATAN Z®

(travoprost ophthalmic solution) 0.004%

BRIEF SUMMARY OF PRESCRIBING INFORMATION

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

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

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

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

CONTRAINDICATIONS
None

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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9/14 TRV14066JAD

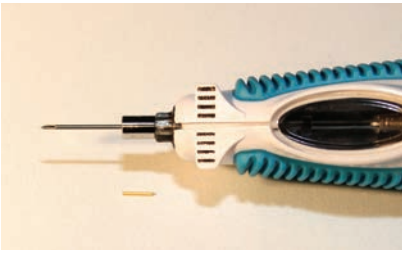
both types of therapies with the layering process." She says it's possible to load more than one drug into the same particle using the layering process as well.

Ohr is currently testing both injectable and topical glaucoma drugs alone, without them being put into a polymer, on humans, and is testing the drug/polymer injection on animals. The company is also experimenting with different injection sites. "We've already taken two compounds forward in glaucoma, one hydrophilic and one hydrophobic," says Dr. Malavia. "We've been able to achieve release for four to six months with these therapeutic agents. We're not limited as to the type of polymer nor the targeted particle sizes in our formulation process, so we can create designs around a whole list of parameters to achieve the desired effective release profiles. As a result, we are performing preclinical animal studies and hope to start human clinical trials next year."

Another company pursuing the injectable route is Envisia Therapeutics (Research Triangle Park, N.C.), which uses biodegradable particles to deliver travoprost. In a canine study, the microparticle injection reduced IOP by an average of 35 percent (6.4 ±0.6 mmHg) over eight months, with the pressure reverting to baseline at nine months. *(Navratil T, et al. IOVS 2015;55:ARVO E-Abstract 5706)* The company is currently planning a Phase II study.

pSivida

As part of a collaboration agreement with Pfizer, pSivida (Watertown, Mass.) is investigating the use of its Durasert implantable, bioerodable technology to release latanoprost over an extended period of time, possibly six months to a year. Durasert is the same technology licensed for use by Alimera Sciences' Iluvien implant for diabetic macular edema. The Iluvien



pSivida's 3-mm glaucoma implant is injected using a 27-ga. needle.

implant is 3 mm long, 0.5 mm wide, and is injected through a 27-ga. needle. Pfizer and pSivida are currently conducting a Phase I/II safety and efficacy trial of the latanoprost implant in patients with elevated intraocular pressure.

Paul Ashton, PhD, president and chief executive officer of pSivida, says a glaucoma application may involve slight tweaking to the implant. "The one thing we've been looking at is to change the implant a little to make it bioerodable," he says. "When we're putting those Iluvien devices in the eye for DME, it's a three-year duration device with a lot of space in the back of the eye anyway, and it's kind of hard to find it. That's not necessarily going to be the case if you're putting it in a different location in the eye. So, for glaucoma, for that type of implant, you're probably looking at either subconjunctival or intracameral as being the places to put it. The intent, though, is the same: to have a long-term, sustained-release system in the eye releasing a drug that we know works in the disease."

In terms of the time period, and the possible objections patients might have to getting an injection rather than just putting in drops, Dr. Ashton offers a unique perspective. "Being a glaucoma patient myself, I've got something of an inside track on that," he says. "Like most patients, I see my physician every six months, so a treatment that doesn't last at least six months isn't going to be very interesting. I'd be fine having an injection in my eye once a year. It would make my life easier because I tend to leave my Xalatan bottles scattered throughout various hotels since I travel a lot.

"So, a six or 12-month implant would be the goal," Dr. Ashton continues. "It should also be bioerodable, but that's not an issue. However, the key to the erosion isn't to control the release rate of the drug, but to dispose of the used device so the eye doesn't become a graveyard of used-up devices. The project is kind of unusual because we already have a pretty good idea of the drugs that are required and the release rate that's required to be efficacious, which are normally guesses in most of the other projects that we've been working on."

Dr. Ashton says he can't provide results from the ongoing Durasert/latanoprost study, but has observed that the implant appears to be stable, and there have been no instances of conjunctival erosion over the implant. Since combinations of drugs for glaucoma are also a popular option for certain patients, he says future trials may look at combining agents. "Combining them is definitely possible," he says. "It gets tricky with respect to clinical trial design. The FDA would expect to see evidence that the combination is more effective than either drug alone."

Down the line a bit, Dr. Ashton thinks one of the more exciting applications of the technology would be not just combining two pressure-lowering drugs, but combining a pressure-lowering drug with a neuroprotectant. "That's the sort of unknown frontier for glaucoma," he says. "Because glaucoma, as we know, isn't really a pressure disease per se. Rather, it's an atrophy, or death, of the optic nerve. So how do you treat that? Now we have a technology that, from a single injection, can provide drug delivery for up to three years, so there's the potential to actually have a neuroprotectant in there as well." REVIEW

OCT's Role in Tracking Glaucoma Progression

Michelle Stephenson, Contributing Editor

As the technology improves, optical coherence tomography is figuring more prominently and earlier in the process of managing glaucoma.

Optical coherence tomography is commonly used to evaluate glaucomatous damage, and it can identify structural changes in the eye before visual field defects occur, making it beneficial for diagnosing or identifying early glaucoma.

OCT is currently the most precise, most sensitive test to identify abnormalities in the eye and their progression over time. "Back in the 1980s, when Goldmann visual field was the best test available, glaucoma was defined either as a pressure of higher than 21 mmHg or as a Goldmann visual field abnormality," says Joel Schuman, MD, who practices at the University of Pittsburgh Medical Center. "Then, automated perimetry was introduced and became widely available, and many people who didn't have Goldmann visual field abnormalities suddenly had visual field abnormalities on automated perimetry because it is the more sensitive test. Now, OCT is able to identify abnormalities and progression that were not identified using automated perimetry because OCT is a more sensitive test. It's more precise, it's more accurate and it's more sensitive. The sensitivity and the precision allow us to detect early disease."

The OCT Advantage

According to Sanjay Asrani, MD, OCT provides an optical cross-section of the optic nerve and the structures around it. "It is able to provide objective measurements of these structures in a precise manner that is not possible with other instruments, such as the GDx or the HRT, which provide an estimate of tissue thickness and not an exact measurement," says Dr. Asrani, who is a professor of ophthalmology at Duke University, Durham, NC.

This is especially advantageous in identifying patients with early glaucoma. "The advantage of OCT in early glaucoma is that it can detect damage that is not measurable with any other technology," Dr. Schuman says. "A person needs to lose approximately 20 percent of her retinal nerve fiber layer before a visual field defect is likely to be present using standard automated perimetry. Before that time, OCT can detect abnormalities or changes and progressive thinning of the nerve fiber layer."

A study conducted by Dr. Schuman and colleagues sought to determine the retinal nerve fiber layer thickness at which visual field damage becomes detectable and associated with structural loss, and they found that substantial structural loss (approxi-

mately 17 percent) is necessary for functional loss to be detectable using current testing methods.[1] The study included 72 healthy subjects and 40 glaucoma patients. All patients had visual field examinations and spectral domain OCT optic disc cube scans with the Humphrey field analyzer and Cirrus HD-OCT. The mean RNFL thickness threshold for visual field loss was 75.2 µm, which corresponded to a 17.3 percent RNFL thickness loss from the age-matched normative value. The slope for RNFL thickness and threshold value was 0.03 dB/µm above the tipping point and 0.28 dB/µm below the tipping point. The difference between the slopes was statistically significant. Quadrant and clock-hour analysis demonstrated similar patterns.

"Generally, if a patient has a clear abnormality, for example, a focal thinning of the nerve fiber layer, and there is a matching abnormality in the retina on the macular scan, but the visual field is still normal and the pressure is normal, I would probably monitor him or her to see if there is progression. However, if that same patient has a pressure of 25 or 26, I would probably start treatment," Dr. Schuman says.

If a patient is identified by OCT as having some structural damage, Dr. Asrani typically follows him every six months with OCT to look for progression. If he doesn't see progression, then he will push the next follow-up out to a year or more, and if he sees progression in the same location, he may initiate treatment depending on how extensive the damage is.

How It Works

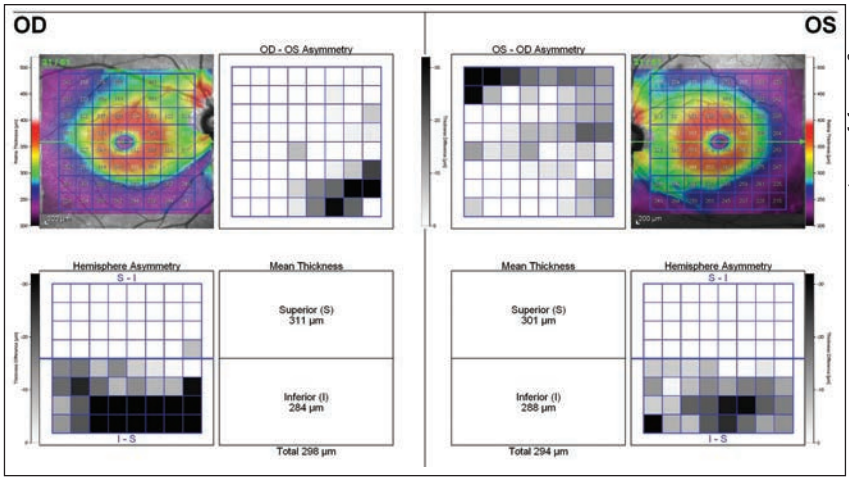
OCT compares an individual patient's measurements to a normative database so ophthalmologists can see if the patient falls into the abnormal or borderline area. However, Dr. Asrani notes that OCT also compares measurements between a patient's two eyes, which is important because asymmetry is a hallmark of glaucoma. "Some patients, especially myopic patients, can fall outside the normative database measurements," he says. "In these cases, it is helpful to compare one eye to the other and look for asymmetry. Asymmetry, especially in the supero- or infero-temporal regions, provides a clue that it could be early glaucoma. In clinical practice, I examine two structures to detect early glaucoma: nerve fiber layer and macular thickness, which is a surrogate for ganglion cell layer thickness. When I see tissue losses in either of these structures that are in an arc shape, I am ready to believe that it could be due to early glaucoma."

Dr. Asrani and colleagues modified the software protocols for detailed retinal thickness measurement by SD-OCT and applied it for diagnosis at different stages of glaucoma.[2] Using the Spectralis SD-OCT, they customized the retinal thickness protocol to acquire detailed retinal thickness measurements of the central 20 degrees of the posterior pole. These customized maps are displayed in a compressed color scale that reveals small losses in retinal thickness. A novel asymmetry analysis protocol was created to highlight differences between the eyes and the two hemispheres within each eye. He found that this strategy shows promise in the diagnosis and management of glaucoma.

In a separate study, Dr. Asrani studied the artifacts of OCT in glaucoma.[3] "When artifacts are present, it can confuse us into thinking that there is glaucoma when there is not, or vice versa," he explains.

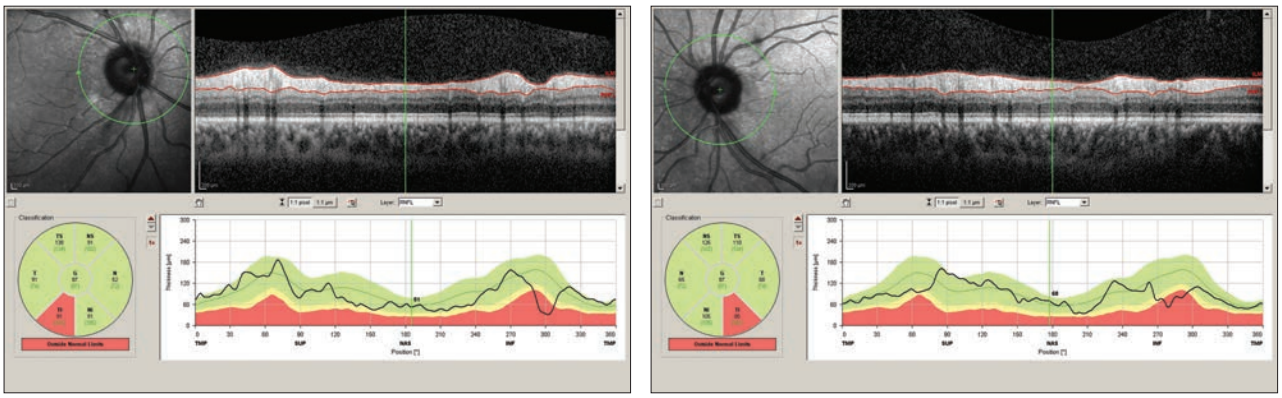
In this study, he found that Spectralis SD-OCT-related imaging artifacts likely occur in 15.2 percent to 36.1 percent of scans obtained in patients being evaluated for glaucoma. Some of these artifacts may not be evident on the final printout. "Physicians should be alert to the possibility of artifacts, particularly in patients with ocular pathologic features, such as an epiretinal membrane," he says.

In this retrospective, cross-sectional study of 277 patients, 131 macular thickness scans were obtained, and 277 retinal nerve fiber layer scans were obtained. Of the macular thickness scans, 37 (28.2 percent) had imaging artifacts, and six of these artifacts were not obvious on the final printout. Of the RNFL scans, 55 (19.9 percent) contained artifacts, and seven of these artifacts were not evident on the final printout. The most common cause of artifacts for macular thickness and RNFL scans was ocular pathologic features, primarily the presence of an



All images: Sanjay Asrani, MD.

Macular loss in both eyes.



Classic focal RNFL loss in the right eye (above) and in the left eye (right)

epiretinal membrane.

Dr. Asrani also notes that structural loss is not necessarily glaucoma. Any structural abnormalities need to be followed over time and assessed for progression of loss. "Once we detect ongoing change, we know it is glaucoma, and then we can start treating it, especially in patients who have normal intraocular pressure measurement and visual fields," he says.

New Capabilities

SD-OCT offers several benefits in glaucoma assessment over the earlier-generation time-domain OCT, such as increased axial resolution and faster scanning speeds. Additionally, it has been shown to have improved reproducibility, but similar diagnostic accuracy. SD-OCT's capabilities are quickly advancing with 3D imaging, reproducible registration, and advanced segmentation algorithms of the macular and optic nerve head regions of the eye.

For example, recently a group of researchers found that a new 3D SD-OCT analysis technique performed at least as well as the conventional circumpapillary RNFL in glaucoma discrimination and was even better at glaucoma suspect discrimination.[4] This new method has the potential to improve early detection of glaucomatous damage.

The study included 192 eyes of 96 patients (44 healthy, 59 glaucoma suspect, and 89 glaucomatous eyes), which were scanned with SD-OCT. Each SD-OCT cube dataset was first converted into a 2D feature map based on RNFL segmentation and was then divided into various numbers of super pixels. The conventional super pixel has a fixed number of points, while the newly developed super pixel is defined as a cluster of homogeneous adjacent pixels with variable size, shape and number.

To automatically identify eyes with glaucoma, features of the super pixel map were extracted and were used as inputs to the machine classifier (LogitBoost adaptive boosting). To discriminate performance assessment, the area under the curve (AUC) of the receiver operating characteristics of the machine classifier outputs were compared with the conventional cpRNFL thickness measurements.

The researchers found that there was a statistically significantly higher AUC in the super pixel analysis than in the cpRNFL (0.855 vs. 0.707, respectively) when glaucoma suspects were discriminated from healthy individuals, while no significant difference was found when confirmed glaucoma eyes were discriminated from healthy eyes.

Additionally, a recent observational, cross-sectional study found that combining structural measurements of macular ganglion cell complex, peripapillary NFL and disc variables from Fourier-domain optical coherence tomography created a glaucoma structural diagnostic index (GSDI) that improved the accuracy for glaucoma diagnosis.[5] In this study, GCC and NFL of healthy and perimetrical glaucoma subjects were mapped with the RTVue FD-OCT. Global loss volume and focal loss volume parameters were defined using NFL and GCC normative reference maps, and optimal weights for NFL, GCC and disc variables were combined using multivariate logistic regression to build the GSDI. Glaucoma severity was classified using the Enhanced Glaucoma Staging System. Diagnostic accuracy was assessed by sensitivity, specificity and the AUC.

The study included 118 normal eyes of 60 patients, 236 matched eyes of 166 individuals with perimetrical glaucoma, and 105 eyes of 61 healthy people. The GSDI included composite overall thickness and focal loss volume with weighted NFL and GCC components and the vertical cup-to-disc ratio. The AUC of 0.922 from leave-one-out cross validation was better than the best component variable alone, and the partial AUC in the high specificity region was also better, with a sensitivity of 69 percent at 99 percent specificity, and a sensitivity of 80.3 percent at 95 percent specificity. Additionally, the sensitivity was 98 percent at 99 percent specificity and 100 percent at 95 percent specificity

for GSS2 stages 3 to 5.

Another study found that the clinical use of an OCT linear discriminant function (LDF) had better diagnostic ability for differentiating between healthy eyes and eyes with early glaucoma than individual OCT parameters.[6] The LDF was based on retinal nerve fiber layer and ganglion cell-inner plexiform layer thickness measurements obtained using Cirrus HD-OCT. The study included 214 healthy individuals and 152 patients with glaucoma (teaching set) and another independent sample of 86 healthy individuals and 71 patients with glaucoma (validating set). Each patient had a macular scan and a peripapillary RNFL scan. Using binary logistic regression analysis, the linear discriminant function was calculated on the teaching set. Then, in the validating set of patients, receiver operating characteristic curves were plotted and compared between the OCT-provided parameters and the linear discriminant function.

The proposed LDF was 16.529-(0.132×superior RNFL)-(0.064×inferior RNFL)+(0.039×12 o'clock RNFL)+(0.038×1 o'clock RNFL)+(0.084×superior GCIPL)-(0.144×minimum GCIPL). In the validating set of patients, the LDF showed significantly higher area under the receiver operating characteristic curve than the best RNFL (inferior RNFL=0.91) and GCIPL parameter (minimum GCIPL=0.88). Additionally, the LDF yielded a sensitivity of 93.0 percent at a fixed specificity of 85.0 percent.

OCT Use in Screening

According to Dr. Schuman, OCT is a good tool for screening, but the yield is low in the general population. "Most people fall in the normal range," he says. "So, if you are screening the general population, the yield will be low, and the patients whom you pick up as being abnormal or suspicious during a screening are not typically easy to get to a doctor's office for follow-up. However, if you are conducting a screening, in my opinion, OCT is the best tool that we have." REVIEW

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The Secrets of Ocular Microbiomes

The placid ocular surface is actually teeming with life that might hold the secret to treating ophthalmic disease.

Mark B. Abelson, MD, CM, DSc, FRCSC, FARVO, Keith Lane, and Connie Slocum, PhD, Andover, Mass.

The Human Microbiome Project, stepchild of the earlier and grander Human Genome Project, is finally starting to make a name for itself. Beyond the remarkable success of bacteriotherapy for *C. difficile*[1] are studies suggesting complex physiological interactions between us humans and our microbial passengers throughout the body.[2,3] While the first efforts at cataloging and characterizing the human microbiome overlooked the eye, there is now a concerted effort aimed at a comprehensive description of conjunctival and corneal microbes. In this month's Therapeutic Topics we look at what we've learned about the ocular microbiome, and how understanding the microbial communities on the ocular surface may hold the key to future ophthalmologic therapies.

Mapping the Microbiome

The microbial communities that inhabit our bodies are far more extensive than previously appreciated, outnumbering our own cells by an estimated factor of at least 10 to one.[4,5] Although it has long been recognized that many of these microbes are critical participants in a variety of human diseases, their possible role in maintaining human health as commensal or symbiotic species has been unclear.[6]

In 2008, the National Institutes of Health launched the Human Microbiome Project with the goal of mapping the diversity of microbial species that cohabit the human body, and in doing so laid the groundwork for understanding the importance of these communities in human health.[6] A key goal of this project was the identification of a "core" microbiome in healthy individuals to establish a benchmark from which variants could be identified and correlated with specific diseases.[4] Samples were collected from 300 healthy subjects from five main body areas: dermal; urogenital; gastrointestinal; oral; and nasal.[7] Subsequent studies revealed that healthy individuals differed remarkably in the microbes that colonize the different parts of their bodies.[7] However, strong niche specializations were identified, giving rise to the concept of unique site-specific microbiomes.[5,7] Much of this diversity remains unexplained, though diet, environment, host genetics and early microbial exposure have all been implicated.[7]

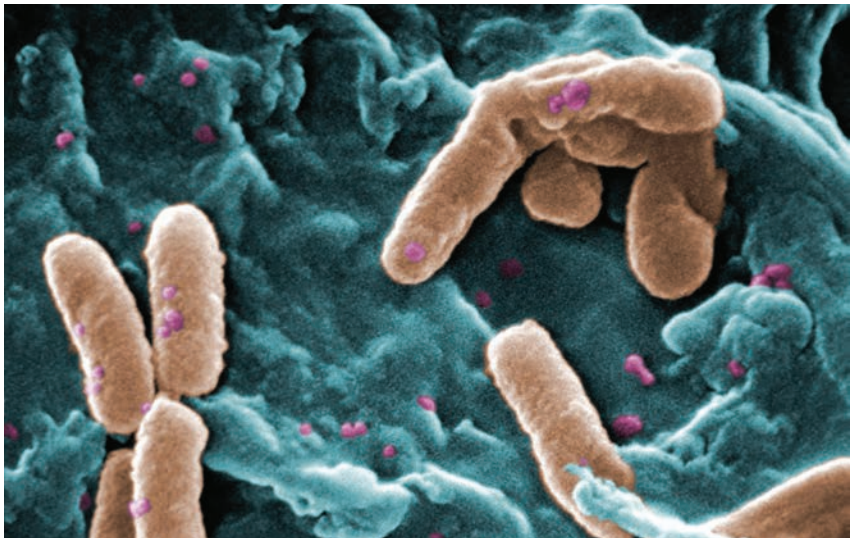
Studies from the Human Microbiome Project demonstrate a great deal of variation between individuals for each of the body areas examined. In addition, the microbial footprint within a given body habitat, or the diversity and abundance of different types of organisms, appears to have some predictive value when viewed in relation to various diseases.[7] For instance, low diversity in the gut is associated with obesity and inflammatory bowel disease.[7] Local biomes also serve functions that are indispensable for the well-being of the host, such as educating the immune system in tolerance towards commensal organisms.[8] Dysregulation of this process has been shown to be associated with gastrointestinal diseases such as *C. difficile* colitis and irritable bowel syndrome.[5] Remarkably, therapies utilizing fecal transplants are now providing successful treatment of *C. difficile*, demonstrating a compelling example of therapeutic manipulation of existing microbiomes for the alleviation of disease.[1,5]

This article has no commercial sponsorship.

What About the Eye?

Studies from the Human Microbiome Project gave rise to the question of whether mucosal membranes such as those at the ocular surface also possess a resident microbiota and, if so, do these too play a role in disease physiology?[5,9] The conjunctival epithelium forms a barrier to ocular infection and represents an interface between diverse and abundant skin microbiota and the ocular surface.[10] Communication between commensal microbial flora and the conjunctival epithelium may be critical to ocular surface homeostasis and the induction of immune tolerance.[10] Therefore, it's conceivable, as is the case in the intestine, that dysregulation of an ocular surface microbial community could contribute to ocular disorders. Furthermore, as in the case with fecal transplants, it may be possible to intervene in ocular surface diseases by introducing an appropriate commensal microbial flora.[5]

The first study documenting the presence of microbes on the ocular surface dates back to 1930, when researchers utilized conventional culture techniques to identify microorganisms.[11] These methods have been invaluable from a historical perspective, but they're limited by the specific growth requirements of individual microorganisms, resulting in a bias towards faster-growing or less-temperamental species that can be easily cultivated on standard media.[9,12] It's likely that many microbes remained undetected utilizing these methods.[9] Today, gene sequencing has become the gold standard for phylogenetic studies of microbial communities and for assigning taxonomies to bacteria.[6] Sequencing methods focus on minor, species-specific differences in the sequences of bacterial ribosomal RNA using the same powerful, high-fidelity technologies developed for the Human Genome Project. By this criterion we can measure which bacteria are resident, not simply which residents can grow on an agar plate.[12] Although sequencing-based techniques provide improved sensitivity, it's important to keep in mind that they lack the clinical relevance that cultures provide: In cases of microbial infection, you can't test for antibiotic sensitivity with polymerase chain-reaction products.[12,13] In addition, identification of species-specific rRNAs cannot, by itself, confirm that the species are viable residents of the ocular surface.[5]



A core ocular microbiome remains to be established. In some studies, healthy eyes harbor pathogens such as *Pseudomonas (above)*, while others have different bacterial genera.

Additional challenges to characterizing the ocular biome result from the physiological differences between the eye and other sites on the human body. Lid wiper function and bactericidal peptides in the tear film exert a constant disinfecting pressure on the ocular surface. Recent estimates project the number of bacteria on the ocular surface to be much less than that on other mucosal surfaces; the tear film may harbor ~100 colony-forming units per ml, while the oral or gastrointestinal mucosa contains between 107 and 108 CFUs/ml.[14] Furthermore, the ocular surface is in close proximity to other human microbial communities, including on the skin at the eyelid margin or on the hands (from rubbing of the eyes), and all of these can contribute contaminating species to ocular samples.[9,12] This fact raises the possibility that the noise from contaminants may easily overwhelm signals of the actual microbiome.[5] These variables, among others, make it difficult to distinguish stable colonizers from more transient or contaminant species.

Despite these challenges, recent studies have set out to identify an ocular surface microbiota that represents a persistent and stable consortium of viable organisms on the ocular surface, and to assess how this population varies in health and disease. One of the first examples of these efforts dates to a 2002 study showing that both the number of CFUs and diversity of bacterial species are increased in individuals who wear contacts.[14] In 2007, researchers investigated the normal ocular surface bacterial flora, comparing healthy patients to those with dry eye.[12] These investigators reported that 97 percent of patients with dry eye had positive bacterial cultures, while only 75 percent were positive among healthy subjects. However, both culture and DNA-sequencing

techniques revealed common genera between dry-eye and healthy subjects, making identification of a disease-specific ocular microbiome inconclusive.

In 2009, scientists at the Bascom Palmer Eye Institute initiated the Ocular Microbiome Project, and in 2010, they published initial results classifying species from four healthy subjects to the phylum level by utilizing 16s rRNA gene-based sequencing.[9] This study identified 59 distinct bacterial genera; 42 of these had not yet been previously reported in healthy eyes, demonstrating the power of rRNA sequencing to reveal a more diverse ocular microbiome than what had been previously reported. While the results showed significant variability among the analyzed subjects, they identified a putative core ocular surface microbiome, with 12 of the 59 genera identified found to be ubiquitous among all examined subjects. This analysis was limited by a small sample size, so further studies will be needed to confirm the core designation.

Leveraging the Microbiome

Based upon the lessons from other microbiomes, a key feature seems to be the population diversity that's associated with disease states. Patients with chronic rhinosinusitis, for example, show the same types of nasal bacteria as unaffected patients, but their populations are altered such that diversity of species is reduced.[15] Such reductions in microbiome diversity are observed in a number of diseases.[10] Alteration in bacterial diversity and /or bacterial numbers may induce detrimental effects on host function through quorum-sensing mechanisms, or bacterial cell-to-cell signaling systems through which gene expression is regulated.[12,16] Quorum-sensing is used by a number of bacterial species to coordinate the expression of genes involved in virulence, biofilm formation and pathogenicity.[17] Studies are currently under way exploring the potential relationship between quorum-sensing mechanisms of bacterial populations and ocular disorders, such as dry eye.[12]

An alternative example of the potential importance of the ocular biome comes from a 2002 study of the role of commensal bacteria in mucin metabolism.[14] This study showed that healthy individuals had higher levels of bacterial-derived mucinolytic enzymes, which presumably function to cleave bound mucins from the epithelial surface, releasing them into the tear film. These soluble mucins, in turn, reduce the growth of ocular bacteria, creating a regulatory feedback loop that acts to control the tear bacterial load. It's easy to imagine how a shift away from such commensal species could disrupt this cycle and potentially allow for pathogenic bacterial growth.

How might identification of an ocular biome affect future therapies? One recent study explored the possibility of microbiome-based therapies for the treatment of ocular disorders through the use of probiotic eye drops.[18] A four-week treatment with a *Lactobacillus* probiotic in eye drops was associated with a modest reduction in signs and symptoms of patients with mild to moderate vernal keratoconjunctivitis.[18] The treatment caused no side effects and was well-tolerated. This novel use of topical probiotics suggests a potential role for ocular surface bacteria in regulating immune responses in the eye, and confirms the need for further exploration of probiotic therapy for ocular inflammation in humans.

Until a core ocular flora is defined with greater precision, it will be difficult to identify bacteria as symbiotics, commensals, pathogens or some combination of these.[12] Perhaps more important is the realization that it's not likely to be that simple. Thus, we have a long way to go before understanding the microbiomes that cohabit our bodies. Despite this, it is becoming increasingly apparent that rather than freeloaders or silent passengers, the microbes we carry are part of a continuous communication, a give-and-take that may be as much a part of our physiology as the autonomic impulses telling us to breathe and blink. It's possible that many of the disorders that we now don't fully understand will be explicable in the context of a symbiosis between the ocular biome and the ocular surface. REVIEW

Dr. Abelson is a clinical professor of ophthalmology at Harvard Medical School. Mr. Lane is director of Research and Development at Ora Inc. Dr. Slocum is a medical writer at Ora Inc.

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Stem Cell Treatments: What's Happening in 2015

The use of stem cells to treat retinal disease has moved beyond the theoretical and proof-of-concept stages and into clinical trials.

Theodore Leng, MD, MS, Stanford, Calif.

Stem cells are specialized cells of the body that possess the ability to self-renew through mitosis and the potency to differentiate into specialized cell types. These cells also possess the ability to regenerate and renew cells that are lost through disease, injury or normal wear and tear.[1] Given their potential to re-create lost cellular functions, stem cells have been applied to address specific degenerative diseases of the retina, like geographic atrophy in non-exudative age-related macular degeneration *(See Figure 1)* and Stargardt's disease *(See Figure 2)*. There are several clinical programs in different stages of development *(See Table 1)* and the aim of this review is to describe the current state of these programs as of early 2015.

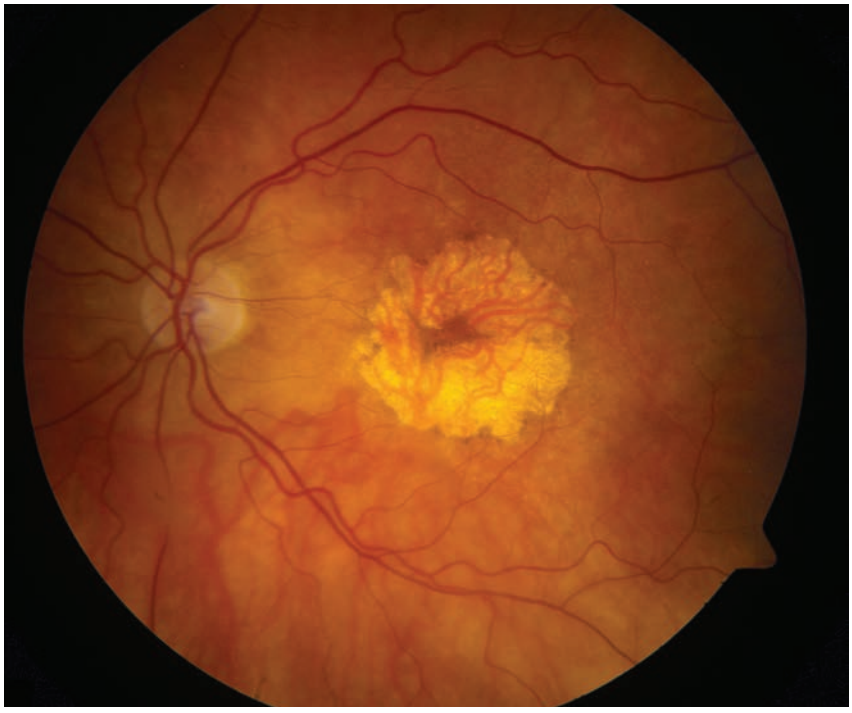

Figure 1. Color fundus photo of a left eye with advanced dry age-related macular degeneration. Geographic atrophy is present in the center of the macula.

Embryonic Stem Cells

Human embryonic stem cells (hESC) are the earliest and most basic component of our bodies. They are pluripotent and have the ability to differentiate into all cell types of the body. In theory, hESCs can be made into specific retinal cell types and used to replenish degenerating or malfunctioning cell in many disease states. Animal studies have shown retinal pigment epithelium derived from hESCs can preserve vision after transplantation.[2] Ocata Therapeutics Inc. (formerly Advanced Cell Technology) has been running a clinical program since 2011 with a Phase I/II open-label, multicenter, nonrandomized, prospective study to determine the safety and potential efficacy of subretinal RPE cells spontaneously produced from hESCs (MA09-

This article has no commercial sponsorship.

Table 1. Active Stem Cell Investigations in Retinal Disease

Investigational Product	Cell Type	Sponsor	Administration Route	Number of Cells	Patient Population	Clinical Trials	Status	Length	# Subjects
MA09-hRPE	hESC-derived RPE	Ocata Therapeutics	Subretinal transplantation	50K - 200K	Dry AMD with GA	Phase I/II, NCT01344993	Ongoing, Not recr.	12 months	16
MA09-hRPE	hESC-derived RPE	Ocata Therapeutics	Subretinal transplantation	50K - 200K	Stargardt's disease	Phase I/II, NCT01345006	Ongoing, Not recr.	12 months	16
MA09-hRPE	hESC-derived RPE	UCLA	Subretinal transplantation	Unknown	Myopic macular degeneration	Phase I/II, NCT02122159	Not yet recruiting	12 months	Unknown
HuCNS-SC	Adult neural SC	StemCells Inc.	Subretinal transplantation	200K - 1M	Dry AMD with GA	Phase I/II, NCT01632527	Closed	12 months	15
CNTO 2476	UCSC	Janssen R&D	Subretinal transplantation	60K - 300K	Dry AMD with GA	Phase I, IIa NCT01226628	Closed	12 months	24
PF-05206388	hESC-derived RPE	Pfizer	Subretinal transplantation	17 mm^2 sheet	Wet AMD	Phase I, NCT01691261	Not yet recruiting	12 months	
	BM-derived SC	Univ. San Paulo	Intravitreal injection	1M	Dry AMD, wet AMD and Stargardt's	Phase I/II, NCT01518127	Enrolling	12 months	10

hRPE). In these trials, patients with GA in dry AMD (NCT01344993) and Stargardt's disease (NCT01345006) had pars plana vitrectomies and were subretinally transplanted with 50,000 to 200,000 hESC-derived RPE cells.

In a recent report, nine eyes in patients with GA and nine eyes in patients with Stargardt's disease were transplanted and followed for a median of 22 months.[3] No treated eyes developed abnormal tissue proliferation, teratoma formation, rejection or inflammation. Of treated eyes, 72 percent had patches of increasing subretinal pigmentation consistent with viable, transplanted RPE. Visual acuity increased in 10 of 18 eyes and decreased in one eye. The remaining seven eyes showed no change in vision at 22 months.

Induced Pluripotent Stem Cells

Induced Pluripotent Stem (iPS) cells are adult cells, such as fibroblasts, that have been genetically reprogrammed to behave like hESCs. Thus, they are fully mature tissue cells that are "regressed" *in vitro* to become pseudo-hESCs. iPS cells are able to replicate themselves and are pluripotent enough to differentiate into any cell type, just like hESCs. However, it is not known whether they differ in clinically meaningful ways from hESCs.

One potential benefit of iPS cells is that they can be induced from cells harvested from an individual patient. Once prepared, those same cells can be transplanted back into the same person—theoretically reducing the risk of immune rejection.

The Laboratory for Retinal Regeneration at the RIKEN Center in Kobe, Japan has initiated a trial in AMD using iPS-derived RPE cells in sheets. This is the first trial to use iPS cells in AMD and is ongoing. Final results have yet to be reported.[4-6]

Adult Stem Cells

Like embryonic stem cells, adult stem cells are undifferentiated and can self-renew. However, adult stem cells are not pluripotent and can only differentiate into specific tissue lineages. Theoretically, this reduces the risk of teratoma formation and other hESC-related side effects.

One active eye program that is using adult stem cells is managed by StemCells Inc., which is conducting a Phase I/II study to assess the safety and preliminary efficacy of adult human central nervous system stem cells (HuCNS-SC) in AMD with GA (NCT01632527). HuCNS-SCs were found in pre-clinical models to preserve photoreceptors in the RCS rat model and as adult stem cells, HuCNS-SCs can theoretically only differentiate into cells in the neural lineage.[7]

In the study, pars plana vitrectomy was performed and HuCNS-SCs were subretinally transplanted. Subjects received either 200,000 or 1 million HuCNS-SCs and were enrolled in two cohorts—one with 20/400 or worse vision and the second with 20/320 to 20/100 vision. The study is now closed to enrollment with 15 subjects from three U.S. clinical sites.

Preliminary data presented to date suggested that the these transplanted cells have not been associated with any adverse reactions. There has been no tumor formation or epiretinal membrane proliferation reported. Eyes that received HuCNS-SCs also had better contrast sensitivity and visual acuity when compared to the fellow control eye. Lastly, treated eyes had about a 70-percent reduction in GA growth rate when compared to the fellow control eye. There is a controlled Phase II study planned to begin this year.

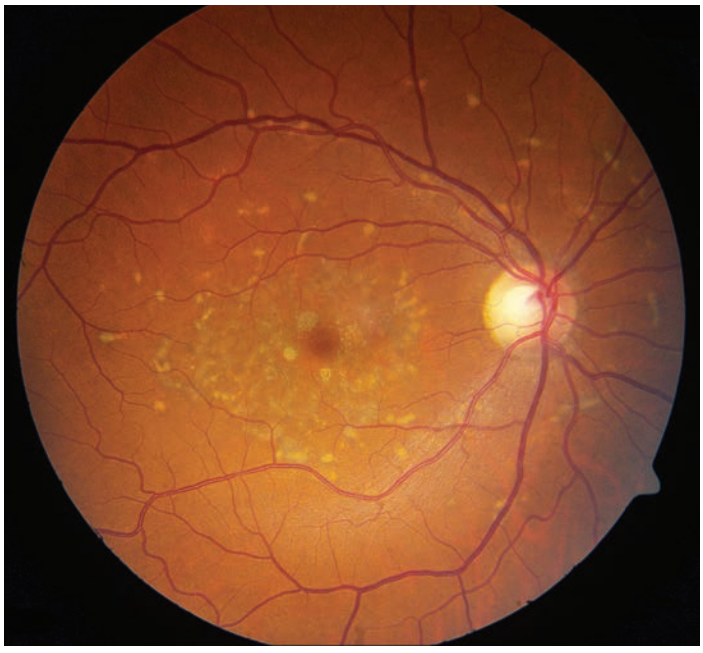

Figure 2. Color fundus photo of a right eye with Stargardt's disease. Characteristic pisciform flecks are present in the macula along with a beaten bronze appearance.

Umbilical Cord Stem Cells

Stem cells from the umbilical cord can contribute to blood and mesenchymal tissue lineages and have the potential to slow degeneration by releasing growth or trophic factors. One such program is being run by Janssen Biotech Inc. The investigational product, CNTO 2476, has been shown to slow vision loss in the RCS rat model after subretinal transplantation.[8] A Phase I trial was performed to treat patients with RP (NCT00458575), but this was halted in 2010. The same year, a Phase I/II trial was initiated to assess the safety and preliminary efficacy of these cells in the subretinal space of patients with GA in dry AMD (NCT01226628). In the study, 60,000 to 300,000 cells were subretinally administered in 24 patients using an iTrack Model 275 microcathether. Patients were then followed for 12 months. Preliminary results demonstrated improved vision in selected eyes following transplantation, but there were cases of retinal detachments following surgery—perhaps owing to the technical challenges related to delivering cells using a subretinal microcathether.

Bone Marrow Stem Cells

Bone Marrow Stem Cells (BMSC) have been shown to rescue retinal degeneration in mouse models.[9,10] Early clinical trials were conducted to evaluate the short-term safety (10 months) of 1 million cells in three patients with retinitis pigmentosa and two patients with cone-rod dystrophy.[11,12] No detectable structural or functional toxicity was observed. Current studies included intravitreal injections of 1 million BMSCs in RP patients in Brazil (NCT01560715) and Thailand (NCT01531348), AMD patients in Brazil (NCT01518127) and ischemic retinopathy patients in Brazil (NCT01518842). Results have yet to be reported.

The use of stem cells to treat retinal disease has gone from the theoretical to proof of concept to controlled clinical trials. The next few years will be telling and should provide adequate data to determine whether this treatment approach will be both efficacious and well-tolerated. REVIEW

Dr. Leng is the director of ophthalmic diagnostics at the Byers Eye Institute at Stanford and is a clinical assistant professor of ophthalmology at the Stanford University School of Medicine. He is an investigator for StemCells Inc. He can be reached via phone: (650) 498 4264; fax: (888) 565 2640; or e-mail: tedleng@stanford.edu.

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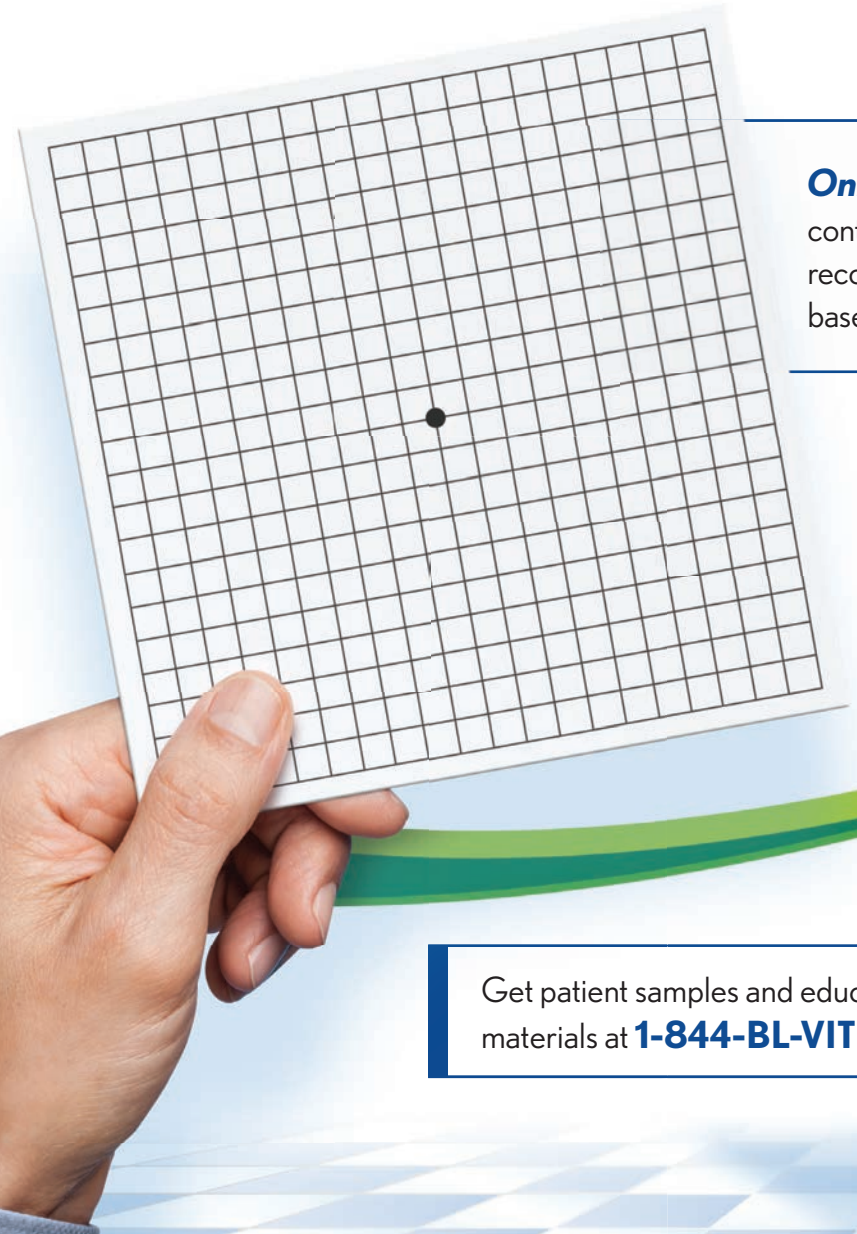

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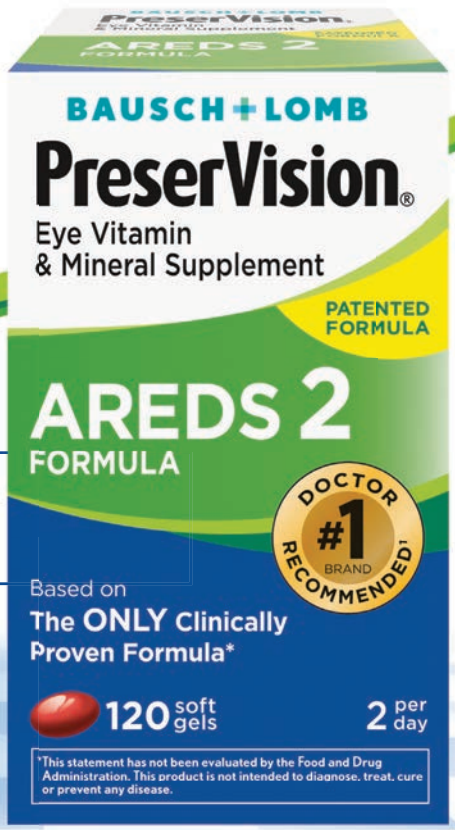

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Managing Glaucoma with Structure and Function

Learning the strengths and weaknesses of OCTs and visual fields makes it possible to follow progression much more effectively.

Felipe A. Medeiros, MD, PhD, San Diego

Effective management of glaucoma depends on having accurate information about both a patient's current state and his risk of progressing. To assess those factors, clinicians have long relied on tests of function such as visual fields, in addition to stereo photographs and, more recently, technologies such as optical coherence tomography that allow us to quantify structural components of the eye.

OCT in particular has been evolving rapidly; we have seen an improvement in resolution and speed, and there has been improvement in the algorithms that isolate the layers of the retina. We can now get reliable measurement of nerve fiber layer thickness, better topographic information about the optic nerve head and good information regarding macular damage. But despite the availability of this technology in most practices, clinicians are still frequently confused about how to incorporate the information provided by OCT into clinical practice. Part of the reason for this is that combining structural and functional information can be a challenge.

Different Strengths

Structural scans such as OCT and functional tests such as visual fields perform better and provide more useful information at different stages of the disease. At the same time, they are complimentary; in many respects each compensates for the weaknesses of the other technology.

For example, visual fields usually perform poorly at detecting early damage in glaucoma. It is common to see patients develop substantial loss of nerve tissue while their visual fields remain within statistically normal limits. Because visual fields tend to underestimate the amount of neural damage in the early stages of the disease, they also tend to underestimate the rate of progression that may be occurring. *(See example, p. 55.)* That can give the misleading impression that your patient is progressing relatively slowly when he actually may be progressing quite rapidly.

On the other hand, in early stages of the disease you can usually get a good assessment of structural damage using OCT. As a result, you can also measure early rates of change more accurately with OCT, alerting you to progression at a time when visual fields tend to show little damage. But like visual fields, OCT has its limitations; as the disease gets more advanced, OCT becomes ineffective. It has the problem of a floor effect; once glaucomatous damage reaches a certain point, OCT can't detect any further damage or progression.[1] *(See example, p. 56.)*

The result is that there's sort of an inverse relationship between the efficacy of structure and function in detecting change, tied to disease severity. In early disease, visual fields usually tend to underestimate rate of progression, so you have to rely more on OCT. But later on, OCT starts to fail because of the floor effect so you need to rely more on visual fields. However, it is difficult to determine the exact point at which one test might perform better than the other for monitoring a specific patient. That's why you really need to combine these two approaches—so you can evaluate progression and measure rates of change through all the stages of the disease. If you rely on the functional information provided by visual fields

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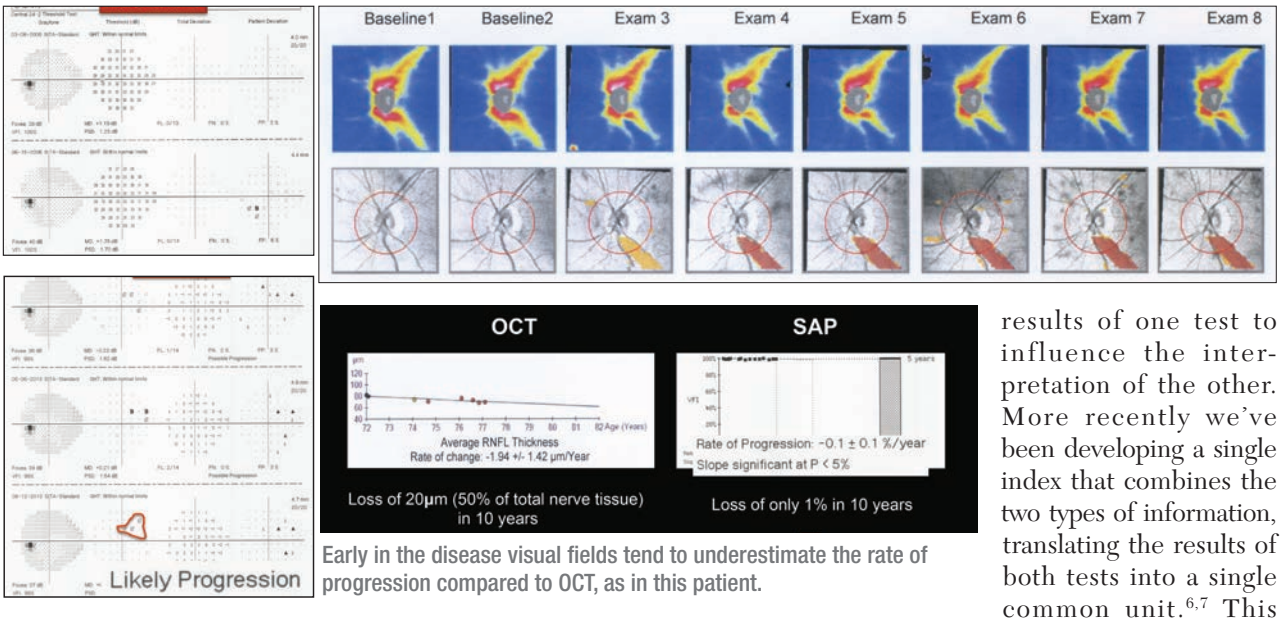


Early in the disease visual fields tend to underestimate the rate of progression compared to OCT, as in this patient.

or OCT alone, you won't detect every patient that is progressing.

At the practical level, this means changing your focus depending on the stage of each patient's disease. In early disease, before the patient has a clearly established visual field loss, visual fields will frequently miss disease progression and underestimate the rate of neural loss. At that point in the disease you should rely more on a tool like the nerve fiber layer thickness assessment provided by OCT. Early in the disease, you should be acquiring these scans over time and looking for the rate of change. If that rate of change is fast, it could mean that your patient is at serious risk of future problems.

In fact, we have shown in a series of studies that these rates of change, measured with OCT, are indeed predictive of future visual field loss.[2-4] We have also shown that they are predictive of functional impairment, as in patient-reported disability and difficulty doing everyday tasks.[5] We demonstrated that if you have progression on these structural measures, that increases your chance of reporting a decrease in quality of life over time. In other words, what you're measuring on OCT has clinical relevance, and it's important for the patient.

However, when you get to moderate or more advanced stages of the disease, OCT will probably be performing poorly in terms of measuring rates of progression. So, once the patient has a visual field defect, you should pay close attention to rates of visual field loss. From that point forward, a visual field will probably provide you with more information than the OCT.

Simplifying the Combination

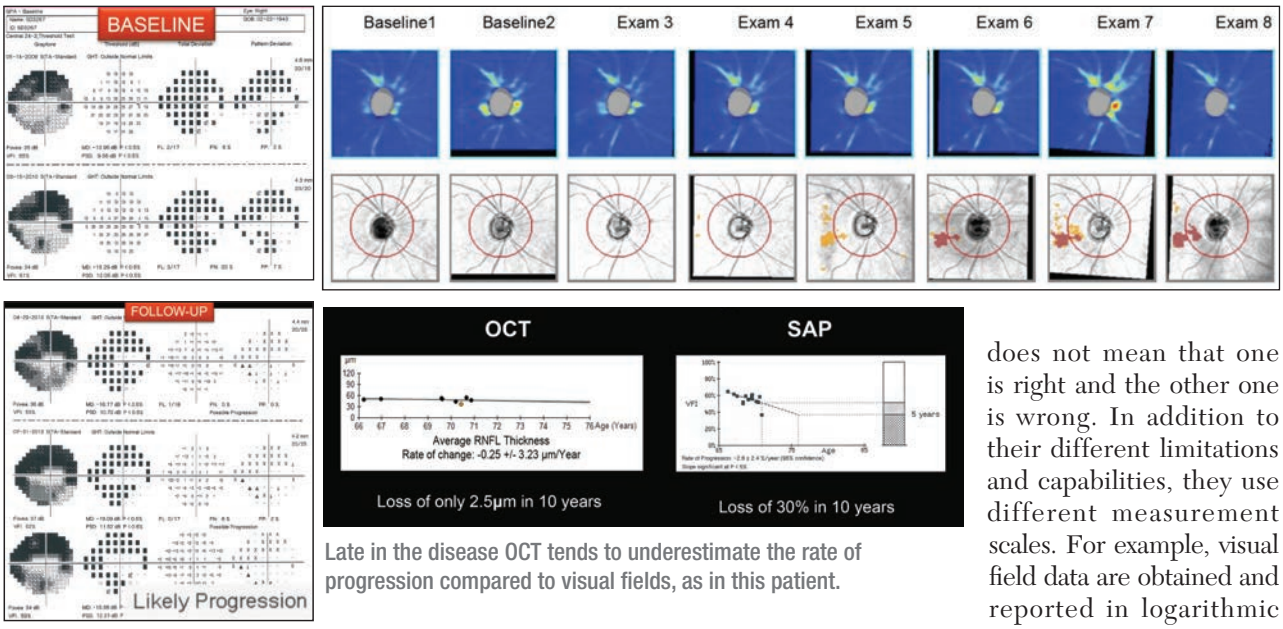
Unfortunately, combining structural and functional information can be easier said than done. Clinicians are often very confused about how to integrate information from a visual field and OCT scan—which will often disagree. Furthermore, even if a clinician understands that OCT is a better tool in early disease while visual fields are better in late disease, it may not be obvious how much the data from each test should be weighted at any given point in the disease.

Our group has been working on finding a simple way to combine these types of information for many years. We initially published some approaches that would allow the results of one test to influence the interpretation of the other. More recently we've been developing a single index that combines the two types of information, translating the results of both tests into a single common unit.[6,7] This will provide clinicians with a much simpler way to use the information. We've published several studies validating our approach, and we hope that it will soon be incorporated into the software of commercially available instruments for widespread clinical use.

The Pros & Cons of Photos

With visual fields and OCT so popular today, stereo photographs have taken a back seat when it comes to glaucoma management. That's partly because of their limitations: In particular, they're relatively difficult to evaluate. You need skilled examiners to judge whether there is a change from one photograph to another, and even then there's often poor agreement between examiners. Another limitation of photos is that they cannot provide you with a quantitative assessment of rates of change over time. As a result, many clinicians today don't bother acquiring stereo photographs.

However, stereo photographs have some important advantages. For one thing, they're not very susceptible to technology change. If you have a photo that was taken 20 years ago, you



Late in the disease OCT tends to underestimate the rate of progression compared to visual fields, as in this patient.

can get a new photograph and compare them. Photos provide you with a time-tested way of obtaining documentation of the optic nerve appearance. That's not true with technology like OCT, which may change every few years, making it difficult or impossible to compare current scans with previous ones. Another advantage of stereo photographs is that there are things you can see on a photograph that are difficult to see on an OCT scan, such as optic disc hemorrhages.

For these reasons, I believe it's still important to take stereo photographs. I take them in my clinical practice, although not as frequently as I get OCTs. That's because a series of OCTs will allow you to estimate the rate of disease progression—something you can't really do with photographs. So, there's no need to take stereo photographs as often as you get OCTs. Nevertheless, I do think it's worth getting them in all patients because of their other advantages.

Strategies for Success

At the present time, there are several things clinicians can do to help ensure they use the information from structure and function most effectively:

• ***If you have OCT, use it to assess progression.*** Although many clinicians are using OCT, some only use it for a cross-sectional assessment. The greatest benefit of this technology is to assess rates of structural damage over time, especially early in the disease, so you can estimate the risk that your patient is going to have trouble in the future. Most of the commercially available OCTs have algorithms that can estimate rates of disease progression.

• ***Don't rely on a single-visit risk assessment.*** Current risk calculators for glaucoma are designed to estimate risk based on a single visit, but you can get a far more meaningful estimate by following patients over time. If you're seeing deterioration on your structural measurements—whether it's something like rim area or retinal nerve fiber layer thickness—that tells you what the trend is. (We have shown that the accuracy of your estimate of risk of progression improves as you incorporate longitudinal information over time.)[2]

• ***Be aware that structural and functional measurements may disagree.*** The fact that they disagree does not mean that one is right and the other one is wrong. In addition to their different limitations and capabilities, they use different measurement scales. For example, visual field data are obtained and reported in logarithmic scale; OCT data are calculated in linear scale. This is a source of disagreement, which can also come from the fact that OCT and visual fields may have different variability throughout the stages of disease. All of this means that they will often disagree—maybe even in the majority of cases. That doesn't mean that one test is right and the other is wrong.

• ***Rate of progression is key.*** One thing many clinicians are still not doing is paying attention to the rate of disease progression. It's not enough to know that progression has occurred; you need to know how fast the deterioration is occurring so you can decide how aggressively you need to treat and how frequently you need to monitor the patient. A patient may be progressing at a slow rate that will not cause her any problems over her expected lifetime; or she could be progressing rapidly, making it very likely that she'll end up disabled during her lifetime.

• ***Keep the strong points of each technology in mind.*** Remember to rely more heavily on information such as change picked up by OCT, as long as a patient has not yet shown a defect on visual field tests. Once defects begin to show up on the visual

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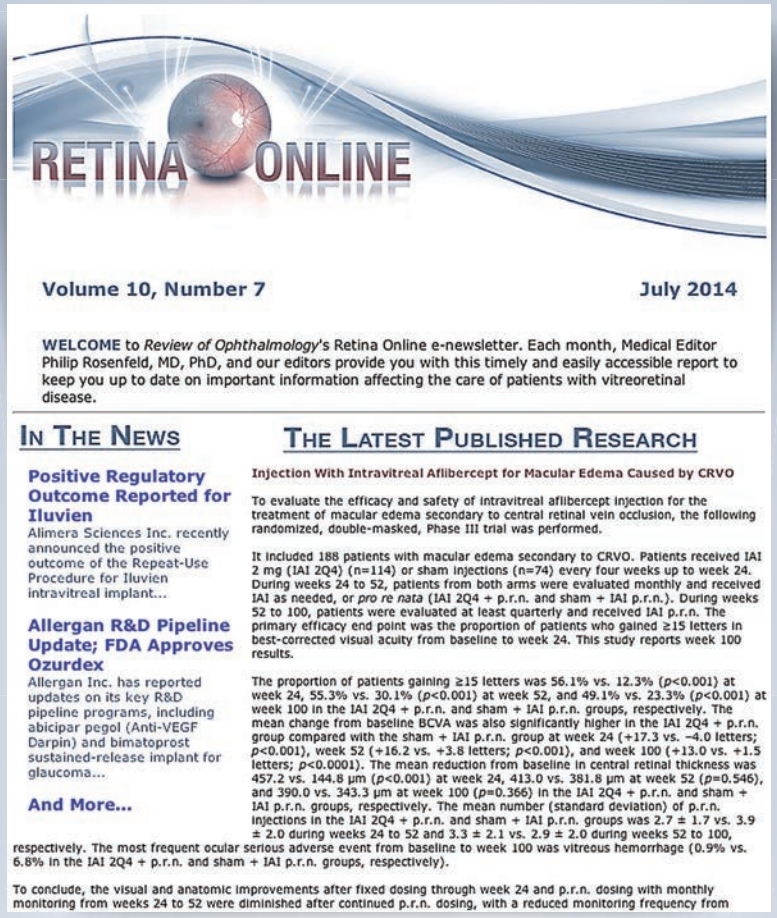

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Volume 10, Number 7 July 2014

WELCOME to *Review of Ophthalmology*'s Retina Online e-newsletter. Each month, Medical Editor Philip Rosenfeld, MD, PhD, and our editors provide you with this timely and easily accessible report to keep you up to date on important information affecting the care of patients with vitreoretinal disease.

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Injection With Intravitreal Aflibercept for Macular Edema Caused by CRVO

To evaluate the efficacy and safety of intravitreal aflibercept injection for the treatment of macular edema secondary to central retinal vein occlusion, the following randomized, double-masked, Phase III trial was performed.

It included 188 patients with macular edema secondary to CRVO. Patients received IAI 2 mg (IAI 2Q4) (n=114) or sham injections (n=74) every four weeks up to week 24. During weeks 24 to 52, patients from both arms were evaluated monthly and received IAI as needed, or *pro re nata* (IAI 2Q4 + p.r.n. and sham + IAI p.r.n.). During weeks 52 to 100, patients were evaluated at least quarterly and received IAI p.r.n. The primary efficacy end point was the proportion of patients who gained ≥15 letters in best-corrected visual acuity from baseline to week 24. This study reports week 100 results.

The proportion of patients gaining ≥15 letters was 56.1% vs. 12.3% (p<0.001) at week 24, 55.3% vs. 30.1% (p<0.001) at week 52, and 49.1% vs. 23.3% (p<0.001) at week 100 in the IAI 2Q4 + p.r.n. and sham + IAI p.r.n. groups, respectively. The mean change from baseline BCVA was also significantly higher in the IAI 2Q4 + p.r.n. group compared with the sham + IAI p.r.n. group at week 24 (+17.3 vs. −4.0 letters; p<0.001), week 52 (+16.2 vs. +3.8 letters; p<0.001), and week 100 (+13.0 vs. +1.5 letters; p<0.0001). The mean reduction from baseline in central retinal thickness was 457.2 vs. 144.8 µm (p<0.001) at week 24, 413.0 vs. 381.8 µm at week 52 (p=0.546), and 390.0 vs. 343.3 µm at week 100 (p=0.366) in the IAI 2Q4 + p.r.n. and sham + IAI p.r.n. groups, respectively. The mean number (standard deviation) of p.r.n. injections in the IAI 2Q4 + p.r.n. and sham + IAI p.r.n. groups was 2.7 ± 1.7 vs. 3.9 ± 2.0 during weeks 24 to 52 and 3.3 ± 2.1 vs. 2.9 ± 2.0 during weeks 52 to 100, respectively. The most frequent ocular serious adverse event from baseline to week 100 was vitreous hemorrhage (0.9% vs. 6.8% in the IAI 2Q4 + p.r.n. and sham + IAI p.r.n. groups, respectively).

To conclude, the visual and anatomic improvements after fixed dosing through week 24 and p.r.n. dosing with monthly monitoring from weeks 24 to 52 were diminished after continued p.r.n. dosing, with a reduced monitoring frequency from

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fields, both structural and functional information become valuable. As the disease becomes more advanced, OCT won't be able to measure any further change, so visual fields will become your best monitoring tool.

• ***Consider other risk factors.*** Most clinicians do this in a subjective and not very precise way; if the patient has high pressure and you see a suspicious change in the visual field, that change acquires more importance. If everything looks very well-controlled and you see a suspicious change you're not sure about, you know it's less likely that it represents real progression. Of course, it would be helpful to have some clinically proven algorithms to help us make these kinds of decisions more objectively. We published data a few years ago demonstrating that it's possible to create such algorithms,[8] but we haven't yet translated that into a tool clinicians can use in everyday practice—something similar to what we did when we developed a validated risk calculator based on the results of the OHTS study.[9]

• ***Do as many tests as you can (according to the patient's condition).*** In general, the more tests you do the better, because you get better estimates of how fast patients are changing. Of course, there are limitations on how many tests we can do. We don't want to burden patients excessively by bringing them to the office all the time, and there are also practical limitations as a result of limited reimbursements.

In my practice, I make sure to get a good set of reliable baseline tests and then I try to obtain these tests about every six months during follow-up, although I tailor the frequency of testing according to the risk. If a patient is at lower risk, I might consider testing him every year instead. If a patient is at high risk, then he will need frequent testing, but that will also depend on other factors, such as life expectancy. For example, a patient who is relatively young and has higher pressures may need to be followed more closely. If you have a 90-year old patient, you probably don't need to test as often.

• ***Beware of false positives.*** One problem with technology like OCT is that it provides a huge amount of information. If you're going to look at every single parameter or piece of information it produces, that's going to increase your chances of getting a false positive and drawing a wrong conclusion. Because there are so many measurements, one of them will eventually be abnormal or show a change just by chance. This is what we sometimes call "red disease," where printouts show abnormalities but the patient is fine. That's another advantage of having a combined index like the one we've developed. Instead of making clinical decisions based on printouts with dozens of parameters that you may not be sure how to interpret, you'd have a single index that integrates the structural and functional information.

For now, when you're looking for signs of progression, I'd say it's very important to pay attention to parameters such as the global average thickness of the retinal nerve fiber layer, which has been shown to have very high reproducibility and accuracy for detecting progression.[10] Of course, it does have some limitations; the most obvious one is that because it's a global parameter, you may end up missing some small, localized changes. But it's a trade-off; if you start off looking at very small areas to try to detect these localized changes, there's a good chance you will end up making mistakes in terms of false positives. So it makes sense to pay attention to changes in global parameters like average thickness over time. You will end up catching most patients who are in trouble, with a relatively high specificity. For spectral-domain OCT, a change in average thickness of more than 5 µm between tests should be considered very suspicious for indicating true glaucomatous change. However, it is very important to emphasize that any suspicious change should be always confirmed by subsequent testing. REVIEW

Dr. Medeiros is a professor of clinical ophthalmology at the University of California, San Diego and the Ben and Wanda Hildyard Chair for Diseases of the Eye. He is also director of the Visual Performance Laboratory at the Shiley Eye Institute and medical director of the Hamilton Glaucoma Center at UCSD.

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Topo-guided Tips for Normal Corneas

Though topography-guided is often associated with irregular astigmatism, surgeons say it can treat virgin corneas, too.

Walter Bethke, Managing Editor

When someone mentions topography-guided laser vision surgery, it often conjures up images of treatments for highly irregular corneas. Surgeons say, however, that these topography-guided treatments can also be effective in normal corneas. Here, surgeons experienced in topography-guided treatments share their tips for getting the best results, and avoiding complications, in run-of-the-mill laser vision correction patients.

Centering on Success

Surgeons say one of the key aspects of topography-guided treatments in virgin corneas is centration, since these systems center differently than non-topo-guided systems.

"Centration is very important, and needs to be on the corneal vertex in topography-guided procedures," says Arun Jain, MD, of Chandigarh, India, who performs topography-guided treatments with a MEL-80 laser but says the general tips on centration can be applied to other devices. "Preoperatively, with the CRS Master device, topography is captured along the line of sight, or what we call the corneal vertex, but then the device overlays the ablation pattern onto the center of the pupil, even in topography-guided procedures. There is a provision in the CRS Master software, however, that lets you recenter it along the corneal vertex—also called the corneal apex or line of sight. Once we do that, we transfer this data to the MEL-80. On the MEL-80 we have to do an offset, asking the laser to center on the coaxially sighted corneal light reflex. This is because, normally, the software in the MEL-80 will center the ablation on the pupillary center. During the procedure, we tell the patient to fixate on the light, and we center the ablation on the coaxially sighted light reflex. In this way, we counteract the effect of angle kappa."

Assessing Astigmatism

Aleksandar Stojanovich, MD, of Tromso, Norway, actually performs topography-guided ablation on all patients, using a transepithelial PRK approach. He says surgeons will have to make a few decisions when addressing the patient's astigmatism.

"An example of a typical case would be a patient with 3 D of astigmatism on refraction, but 4 D of corneal astigmatism on topography," says Dr. Stojanovich. "This is because the crystalline lens is partially compensating for the corneal astigmatism with its own astigmatism at the opposite axis. This leads to the question: Should we treat all 4 D in the cornea, or treat only that measured by refraction? Usually, in young people, we opt for the latter; we treat just the refractive astigmatism, treating the amount that will allow the patient to be emmetropic postop. For an older patient, however, a surgeon might say, 'OK, the patient is older and will have cataracts soon, so we shouldn't correct for all the astigmatism—which includes astigmatism from the lens—because we'll then end up with corneal astigmatism that will remain as extra astigmatism when the cataract is removed.' You have to judge it from patient to patient. However, usually, in younger patients it's quite common to treat all the astigmatism on refraction."

The Transition Zone

One of the ways that a topography-

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INDICATION

LUMIGAN® (bimatoprost ophthalmic solution) 0.01% is indicated for the reduction of elevated intraocular pressure in patients with open angle glaucoma or ocular hypertension.

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

LUMIGAN® 0.01% causes changes to pigmented tissues, mostly increased pigmentation of the iris, eyelid, and eyelashes as long as LUMIGAN® 0.01% is administered. Iris color change may not be noticeable for several months to years. After discontinuation of bimatoprost, iris pigmentation is likely to be permanent, while eyelid and eyelash changes have been reported to be reversible in some patients. Patients should be informed of the possibility of increased pigmentation. The long term effects of increased pigmentation are not known.

Prostaglandin analogs, including bimatoprost, have been reported to cause intraocular inflammation. These products may also exacerbate inflammation, so use with caution in patients with active intraocular inflammation (e.g., uveitis).

Macular edema, including cystoid macular edema, has been reported with LUMIGAN® 0.01%. LUMIGAN® 0.01% 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. Remove contact lenses prior to instillation of LUMIGAN® 0.01% and reinsert after 15 minutes.

ADVERSE REACTIONS

The most common adverse reaction was conjunctival hyperemia (31%). Approximately 1.6% of patients discontinued therapy due to conjunctival hyperemia. Other adverse drug reactions (reported in 1 to 4% of patients) with LUMIGAN® 0.01% included conjunctival edema, conjunctival hemorrhage, eye irritation, eye pain, eye pruritus, erythema of eyelid, eyelids pruritus, growth of eyelashes, hypertrichosis, instillation site irritation, punctate keratitis, skin hyperpigmentation, vision blurred, and visual acuity reduced.

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

1. US Food and Drug Administration. Drugs@FDA. Drug details: LUMIGAN® 0.01%. FDA website: www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm. Accessed May 19, 2015. **2.** Katz LJ, Cohen JS, Batoosingh AL, Felix C, Shu V, Schiffman RM. Twelve-month, randomized, controlled trial of bimatoprost 0.01%, 0.0125%, and 0.03% in patients with glaucoma or ocular hypertension. *Am J Ophthalmol*. 2010;149(4):661-671. **3.** IMS Health, Inc. *Vector One®: National* (VONA). April 2015.

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Brief Summary—Please see the LUMIGAN® 0.01% package insert for full Prescribing Information.

INDICATIONS AND USAGE

LUMIGAN® (bimatoprost ophthalmic solution) 0.01% is indicated for the reduction of elevated intraocular pressure in patients with open angle glaucoma or ocular hypertension.

CONTRAINDICATIONS

None

WARNINGS AND PRECAUTIONS

Pigmentation: Bimatoprost ophthalmic solution has been reported to cause changes to pigmented tissues. The most frequently reported changes have been increased pigmentation of the iris, periorbital tissue (eyelid) and eyelashes. Pigmentation is expected to increase as long as bimatoprost 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 bimatoprost, pigmentation of the iris is likely to be permanent, while pigmentation of the periorbital tissue and eyelash changes have been reported to be reversible in some patients. Patients who receive treatment should be informed of the possibility of increased pigmentation. The long term effects of increased pigmentation are not known.

Iris color change may not be noticeable for several months to years. Typically, the brown pigmentation around the pupil spreads concentrically towards the periphery of the iris and the entire iris or parts of the iris become more brownish. Neither nevi nor freckles of the iris appear to be affected by treatment. While treatment with **LUMIGAN®** (bimatoprost ophthalmic solution) 0.01% can be continued in patients who develop noticeably increased iris pigmentation, these patients should be examined regularly *[see Patient Counseling Information (17.1)]*.

Eyelash Changes: LUMIGAN® 0.01% may gradually change eyelashes and vellus hair in the treated eye. These changes include increased length, thickness, and number of lashes. Eyelash changes are usually reversible upon discontinuation of treatment.

Intraocular Inflammation: Prostaglandin analogs, including bimatoprost, have been reported to cause intraocular inflammation. In addition, because these products may exacerbate inflammation, caution should be used in patients with active intraocular inflammation (e.g., uveitis).

Macular Edema: Macular edema, including cystoid macular edema, has been reported during treatment with bimatoprost ophthalmic solution. **LUMIGAN®** 0.01% 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.

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 *[see Patient Counseling Information (17.3)]*.

Use with Contact Lenses: Contact lenses should be removed prior to instillation of **LUMIGAN®** 0.01% and may be reinserted 15 minutes following its administration.

ADVERSE REACTIONS

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

In a 12-month clinical study with bimatoprost ophthalmic solutions 0.01%, the most common adverse reaction was conjunctival hyperemia (31%). Approximately 1.6% of patients discontinued therapy due to conjunctival hyperemia. Other adverse drug reactions (reported in 1 to 4% of patients) with **LUMIGAN®** 0.01% in this study included conjunctival edema, conjunctival hemorrhage, eye irritation, eye pain, eye pruritus, erythema of eyelid, eyelids pruritus, growth of eyelashes, hypertrichosis, instillation site irritation, punctate keratitis, skin hyperpigmentation, vision blurred, and visual acuity reduced.

Postmarketing Experience: The following reaction has been identified during postmarketing use of **LUMIGAN®** 0.01% in clinical practice. Because it was reported voluntarily from a population of unknown size, estimates of frequency cannot be made. The reaction, which has been chosen for inclusion due to either its seriousness, frequency of reporting, possible causal connection to **LUMIGAN®** 0.01%, or a combination of these factors, includes headache.

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

USE IN SPECIFIC POPULATIONS

Pregnancy: Pregnancy Category C

Teratogenic effects: In embryo/fetal developmental studies in pregnant mice and rats, abortion was observed at oral doses of bimatoprost which achieved at least 33 or 97 times, respectively, the maximum intended human exposure based on blood AUC levels.

At doses at least 41 times the maximum intended human exposure based on blood AUC levels, the gestation length was reduced in the dams, the incidence of dead fetuses, late resorptions, peri- and postnatal pup mortality was increased, and pup body weights were reduced.

There are no adequate and well-controlled studies of **LUMIGAN®** (bimatoprost ophthalmic solution) 0.01% administration in pregnant women. Because animal reproductive studies are not always predictive of human response **LUMIGAN®** 0.01% should be administered during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not known whether **LUMIGAN®** 0.01% is excreted in human milk, although in animal studies, bimatoprost has been shown to be excreted in breast milk. Because many drugs are excreted in human milk, caution should be exercised when **LUMIGAN®** 0.01% is administered to a nursing woman.

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

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

Hepatic Impairment: In patients with a history of liver disease or abnormal ALT, AST and/or bilirubin at baseline, bimatoprost 0.03% had no adverse effect on liver function over 48 months.

OVERDOSAGE

No information is available on overdosage in humans. If overdose with **LUMIGAN®** (bimatoprost ophthalmic solution) 0.01% occurs, treatment should be symptomatic.

In oral (by gavage) mouse and rat studies, doses up to 100 mg/kg/day did not produce any toxicity. This dose expressed as mg/m^2 is at least 210 times higher than the accidental dose of one bottle of **LUMIGAN®** 0.01% for a 10 kg child.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility: Bimatoprost was not carcinogenic in either mice or rats when administered by oral gavage at doses of up to 2 mg/kg/day and 1 mg/kg/day respectively (at least 192 and 291 times the recommended human exposure based on blood AUC levels respectively) for 104 weeks.

Bimatoprost was not mutagenic or clastogenic in the Ames test, in the mouse lymphoma test, or in the *in vivo* mouse micronucleus tests.

Bimatoprost did not impair fertility in male or female rats up to doses of 0.6 mg/kg/day (at least 103 times the recommended human exposure based on blood AUC levels).

PATIENT COUNSELING INFORMATION

Potential for Pigmentation: Advise patients about the potential for increased brown pigmentation of the iris, which may be permanent. Also inform patients about the possibility of eyelid skin darkening, which may be reversible after discontinuation of **LUMIGAN®** (bimatoprost ophthalmic solution) 0.01%.

Potential for Eyelash Changes: Inform patients of the possibility of eyelash and vellus hair changes in the treated eye during treatment with **LUMIGAN®** 0.01%. These changes may result in a disparity between eyes in length, thickness, pigmentation, number of eyelashes or vellus hairs, and/or direction of eyelash growth. Eyelash changes are usually reversible upon discontinuation of treatment.

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

When to Seek Physician Advice: Advise patients that if they develop an intercurrent ocular condition (e.g., trauma or infection), have ocular surgery, or develop any ocular reactions, particularly conjunctivitis and eyelid reactions, they should immediately seek their physician's advice concerning the continued use of **LUMIGAN®** 0.01%.

Use with Contact Lenses: Advise patients that **LUMIGAN®** 0.01% contains benzalkonium chloride, which may be absorbed by soft contact lenses. Contact lenses should be removed prior to instillation of **LUMIGAN®** 0.01% and may be reinserted 15 minutes following its administration.

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

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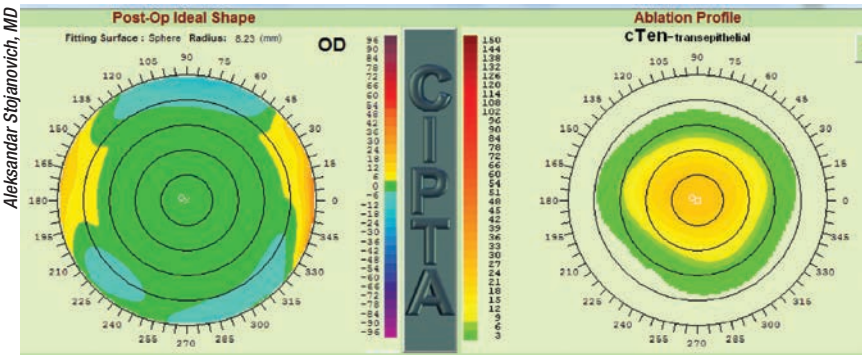
guided ablation potentially differs from a wavefront-guided one is the ability to have more control over the transition zone.

Dr. Stojanovich says his system allows him to impart a dioptric gradient between treated and untreated areas. "You can make the transition super-smooth, taking as much tissue as necessary to make it as wide as possible," he says, "or you can economize things and use less tissue to create a transition zone.

"In the Alcon system, though, you don't have that ability," he adds. "But you still can look at the topography and see where the ablation is going to land. You can then look at your ablation map and your topography and see what the conditions are. If you see a very rough transition, then you can increase the transition zone so it will land smoothly on the untreated cornea. Fortunately, however, the Alcon/WaveLight system is designed primarily for LASIK, where transition zones are a little less critical. The flap will smooth over the transition somewhat, like placing a rug over an uneven area of floor."



Aleksandar Stojanovich, MD

Surgeons say one of the benefits of a topography-guided ablation in a virgin cornea is the ability to see what the cornea will look like postoperatively.

Topo-guided Results

Surgeons have also studied the results from topography-guided procedures and found them equivalent to—and by some measures, better than—other laser procedures.

Alcon performed a Food and Drug Administration study of its topography-guided custom ablation treatment in virgin corneas of 249 eyes of 212 patients (though not all eyes were available at all follow-up points).[1] In terms of efficacy, at 12 months the average manifest refraction spherical equivalent had been reduced to 0 D from a preop average of -4.61 D; 99 percent of eyes saw 20/32 or better uncorrected, 93 percent saw 20/20 or better and 65 percent saw 20/15 or better. At that same time point, 99.6 percent of eyes were within 1 D of the intended target, and 94.8 percent were within 0.5 D.

On the safety side, in the T-CAT FDA study, at one month postop, 4 percent of eyes had lost a line of best-corrected vision. This percentage decreased to 2.2 percent at a year. At a year, 0.4 percent had lost two lines of vision.

Also at a year, 57 percent had no change in BCVA, while 27 percent gained one line, 10.4 percent gained two lines and 3 percent gained greater than two lines of vision. Comparing postop UCVA to preop BCVA, at one year 30 percent had an UCVA one or more lines better than their preop BCVA, and 11 percent had an UCVA that was two or more lines better.

At his practice, Dr. Jain has also performed a study of the safety and efficacy of topography-guided LASIK. In his study, however, he added the wrinkle of performing the topo-guided ablation in one eye of each patient and a wavefront-optimized procedure in the other in order to compare the two. He performed the surgeries in 20 patients.

"We only took eyes in which the spherical equivalent was no more than 6 D," Dr. Jain explains. "A main difference that we found postop was in ablation depth: In topography-guided eyes, we saved an average of 15 µm of corneal tissue compared to wavefront-optimized eyes. The average depth was around 66 µm in topography-guided vs. an average of 80 µm in wavefront-optimized. This could possibly translate to increased biomechanical stability of the cornea in the long term, or might allow us to correct higher amounts of refractive error. In terms of refractive results, 100 percent of the eyes in the topography-guided group were within 1 D of intended, and 90 percent were within 0.5 D at six months. In the wavefront-optimized group, 90 percent were within 1 D and 80 percent were within 0.5 D at six months. But the main visual difference, which was also reported in a similar way in the FDA trial study, was that, in our study, almost 30 percent of eyes in the topography-guided group gained more than one line of BCVA, compared to only 20 percent in the wavefront-optimized group."

Dr. Jain says that, though both topography-guided and other custom procedures provide excellent results now, the future will see a melding of the technologies. "As of now, none of the topography-guided laser systems also uses higher-order aberrations in planning the ablation pattern," he says. "The future will involve the use of a combination of corneal aberrations, topography and the total eye refraction to correct the complete visual status of the eye." REVIEW

1. https://www.myalcon.com/products/surgical/wavelight-t-cat-study/clinical-study-results.shtml. Accessed 1 May 2015.

Topical NSAID Effects On Corneal Sensitivity

Researchers have shown that four currently available topical nonsteroidal anti-inflammatory drugs (generic diclofenac, generic ketorolac, brand bromfenac and brand nepafenac) have similar anesthetic effects to branded diclofenac and branded ketorolac.

Baseline corneal sensitivity was measured on 10 healthy adult volunteers with a Cochet-Bonnet esthesiometer. One drop of the agent being studied was applied to the right eye every five minutes for a total of four drops. Corneal sensitivity was measured immediately after the last topical application and every 15 minutes for 60 minutes. After a one-week washout period, a different agent was studied until all four NSAIDs were evaluated.

Corneal sensitivity profiles over time were similar for all NSAIDs. Corneal sensitivity decreased significantly from baseline immediately after topical application, remaining flat from zero to 30 minutes and then rising from 45 to 60 minutes back toward baseline in all treatment groups ($p<0.001$). The maximal absolute drop in corneal sensitivity as measured by pressure thresholds was greatest for diclofenac (28.6 mm; 95 percent confidence interval, 19.8 to 37.4), followed by ketorolac (21.1 mm; 95 percent CI, 15.1 to 27.1), bromfenac (16.9 mm; 95 percent CI, 10.7 to 23.1) and nepafenac (16.4 mm; 95 percent CI, 12.7 to 20.1). Only diclofenac and nepafenac were statistically significant in maximal decrease in sensitivity.

Cornea 2015;34:541-543.
Singer D, Kennedy J, Wittpenn J.

Safety of 5-FU Injection After Eyelid Skin Grafting

A retrospective chart review of patients who underwent eyelid skin grafting for various etiologies with adjunctive postoperative 5-fluorouracil (50 mg/ml, with or without added kenalog 5 mg/ml) injections suggests that this procedure is safe, with good surgical results, minimal scarring and high patient and surgeon satisfaction.

In total, 19 patients from a multiyear period (2011 to 2013) were identified. Patient average age was 66, and a follow-up of 10 months was included in the chart review. Surgical indications for eyelid skin grafting included reconstruction of cancer excision defects, repair of lower eyelid ectropion or retraction, benign eyelid lesion excision and effacement of a canthal web. At each visit, patients were evaluated for redness, swelling, wound healing, scar formation, telangiectasis and pigmentary disturbances. Patient interpretation of outcome was determined subjectively by asking if they were satisfied and objectively by their separate responses to specific questions graded on a Likert-type scale.

On average, patients had a total of four separate 0.3 to 0.5 ml 5-FU (n=8) or 5-FU/kenalog (n=11) injections spaced two to three weeks apart. There were no cases of skin thinning, color/texture change, atrophy, telangiectasis or infection after injection, and all patients had uneventful healing of their grafts. In 95 percent of the cases, the surgeon was satisfied with the surgical result; 89 percent of the patients were satisfied with their outcome (graded 4.73/5) and the appearance of the skin graft.

Ophthal Plast Reconstr Surg 2015;31:122-126.
Yoo D, Azizzadeh B, Massry G.

Using Peripheral Lesions to Track Diabetic Retinopathy Progression

Boston researchers have determined that the peripheral diabetic retinopathy lesions identified on ultrawidefield imaging are associated with increased risk of diabetic retinopathy progression over four years, independent of baseline diabetic retinopathy severity or hemoglobin A1c levels. An increasing extent of predominantly peripheral lesions substantially increased the risk of diabetic retinopathy progression and progression to proliferative diabetic retinopathy, especially with less severe diabetic retinopathy at baseline.

Two hundred eyes of 100 participants previously enrolled in a com-

parative instrument validation study were enrolled in this study as a prospective, longitudinal cohort. Baseline mydriatic seven-standard field Early Treatment Diabetic Retinopathy Study photographs and ultra-widefield images were obtained. On ultra-widefield images, diabetic retinopathy lesions with a greater extent outside versus inside standard ETDRS fields were defined as predominantly peripheral lesions. Follow-up ETDRS photographs were obtained at 4.2 ±0.3 years after baseline measurements. Baseline and follow-up diabetic retinopathy severity were graded from ETDRS photographs. The main outcome measures were rates of two or more steps of progression and progression to proliferative diabetic retinopathy in eyes with PPLs compared to eyes without PPLs identified at ultra-widefield imaging at baseline.

In eyes without PDR (n=109) at baseline, 56 (51 percent) had at least one field with PPLs and 43 (39 percent) had diabetic retinopathy progression. Compared with eyes without PPLs, eyes with PPLs had a 3.2-fold increased risk of two-step or more diabetic retinopathy progression (six patients [11 percent] vs. 19 [34 percent]; p=0.005) and a 4.7-fold increased risk for progression to PDR (three patients [6 percent] vs. 14 [25 percent]; p=0.005). These findings remained statistically significant after adjusting for gender, diabetes type, diabetes duration, hemoglobin H1c levels and baseline diabetic retinopathy severity. Increasing extent of fields with PPLs increased the risk for two-step or more diabetic retinopathy progression (p=0.004) and progression to PDR (p=0.009).

Ophthalmology 2015;122:949-956.
Silva P, Cavallerano J, Haddad N, Kwak H, et al.

The Value of Preop Medical Testing for Vitreoretinal Surgery

A retrospective review of all vitreoretinal surgeries performed at Vanderbilt University from January 2002 until November 2011 indicates that preoperative testing does not measurably influence rates of postoperative systemic complications.

The medical charts of 2,215 patients were reviewed for baseline comorbidities, preoperative testing, type of anesthesia during surgery and systemic adverse events occurring within 30 days after surgery. Main outcome measures were the association of baseline characteristics and preoperative testing with postoperative systemic adverse events.

Approximately half of patients had electrolyte, renal function and electro-cardiogram evaluation. The most common comorbidities were hypertension (53 percent), diabetes mellitus (37 percent) and coronary artery disease (18 percent). The most common preoperative testing measure performed was blood glucose (58 percent). A total of 102 systemic adverse events occurred in 89 of 2,215 patients (4 percent) within the first 30 days after surgery, with the majority (72 percent) occurring within the first 24 hours. The most common adverse event was bradycardia (34 percent) followed by desaturation (25 percent). Patients with a history of coronary artery disease, asthma, chronic renal disease or receiving general anesthesia had 2.04 (p=0.91), 2.18 (p=0.03), 2.76 (p<0.001) and 3.72 (p<0.001) increased odds of developing postoperative systemic adverse events, respectively. Multivariate logistic regression analysis demonstrated no significant correlation between preoperative testing and postoperative adverse events.

Retina 2015;35:319-325.
Shalwala A, Hwang R, Tabing A, Sternberg P, et al.

Femto Cataract Outcomes the First Two Years After Adoption

The Singapore National Eye Center analyzed the outcomes of femtosecond laser cataract surgery cases in the first two years of use, determining that there was a low complication rate and that cases compared to controls had a statistically better unaided visual acuity (≤20/25) and manifest refraction spherical equivalence, although mean absolute error was not significant.

The outcomes and intraoperative events of all laser cataract surgeries (5.0 to 5.5-mm diameter laser capsulotomies and nuclear fragmentation) at the center from May 2012 to December 2013 were prospectively audited, with patient data matched to historical controls, a random sample of manual cases with similar age, axial length and preoperative cylinders. The six-weeks postoperative unaided visual acuities, mean absolute error, mean square error and manifest refraction spherical equivalent results of surgeons with >50 laser cases were compared with the control cases. Statistical analysis was performed with SPSS (p<0.05).

A total of 1,105 eyes (803 patients) underwent laser cataract surgery by 18 surgeons. The majority were female (56.9 percent) and Chinese (90.9 percent) with a mean age of 66.1 ±11 years. Intraoperative complications were subconjunctival hemorrhage (290, 26.2 percent), anterior capsule tear (nine eyes, 0.81 percent), posterior capsule rupture (three eyes, 0.27 percent), suction loss (five eyes, 0.45 percent), iris hemorrhage and endothelial incision (one eye each, 0.09 percent). There were no dropped nuclei. Visual outcomes of 794 laser surgeries were compared to 420 controls. The UAVA at 20/25 or better was higher in laser cases (68.6 percent vs. 56.3 percent; p<0.0001) but MAE (0.30 ±0.25 D vs. 0.33 ±0.25 D; p=0.062) and MSE (0.16 ± 0.27 D vs. 0.17 ±0.28 D; p=0.65) were not significant. MRSE comparison was significant (target plano, preoperative cylinder <1.5 D; -0.08 ±0.36 D vs. -0.13 ±0.40 D; p=0.034).

Am J Ophthalmol 2015;159:714-716.
Chee S, Yang Y, Ti S.

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Diagnosed in infancy as a benign nevus, a young child's iris lesion continues to complicate his visual development.

Michelle E. Wilson, MD, and Carol L. Shields, MD

Presentation

A 4-year-old Caucasian male with a history of intermittent exotropia, anisometropia and amblyopia of the right eye was referred to the Ocular Oncology service for evaluation of a pigmented iris lesion of the right eye. The lesion was first noted at 11 weeks of age by the child's pediatric ophthalmologist and was thought to represent a benign nevus. The lesion was photographed and no growth was observed.

Despite patching of the left eye four hours daily since 6 months of age and full correction of refractive error, the amblyopia of the right eye failed to improve. This was presumed to be due to noncompliance with patching. Intermittent exotropia became more constant and at 3 years of age a 30-prism diopter exotropia was corrected with a 9.5-mm recession of the right medial rectus muscle. Following strabismus surgery, the patient was referred to Ocular Oncology by his strabismologist for evaluation of the pigmented iris lesion.

Medical History

The patient was born full-term via cesarean section following an uncomplicated pregnancy. He had a history of gross motor apraxia for which he underwent physical therapy, as well as a mild speech impediment for which he received speech therapy. He was otherwise in good health, with no history of major illnesses. He took no medications and had no known drug allergies. Family history was significant for a multiple relatives with various cancers including ovarian cancer, prostate cancer, thyroid cancer and malignant melanoma of the skin.

Examination

Ocular examination demonstrated a best corrected visual acuity of 20/400 OD and 20/20 OS. Pupils were equal, round and reactive to light with no relative afferent pupillary defect. Finger tensions were normal in both eyes. External examination was normal with no abnormalities of the skin or periorbital adnexa *(See Figure 1)*. Slit-lamp examination revealed an ill-defined, darkly pigmented, vascular iris lesion extending from the pupillary margin to the angle and involving the 5 o'clock to 8 o'clock inferior region without associated feeder vessels *(See Figure 2)*. Anterior segment examination was otherwise normal. Dilated fundus examination was performed in the clinic; however, due to poor cooperation, only limited views of the fundus were obtained.

Figure 1. External photograph demonstrating absence of abnormalities of the skin or periorbital adnexa.

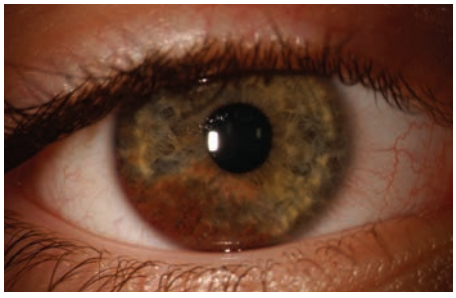

Figure 2. External photograph demonstrating ill-defined darkly pigmented vascular iris lesion.

What is your differential diagnosis? What further workup would you pursue? Please turn to p. 70

Diagnosis, Workup and Treatment

Given the clinical history and examination, a broad differential diagnosis was generated *(See Figure 3)*. The lesion did not appear to be classic for a nevus, as it demonstrated excessive vascularity. A decision was made to perform an examination under anesthesia at which time further evaluation of the lesion could be performed.

Differential Diagnosis: Pigmented Iris Lesion in a Child

- iris nevus
- iris melanocytosis
- iris melanocytoma
- iris melanoma
- iris juvenile xanthogranuloma
- iris leiomyoma or leiomyosarcoma
- iris Lisch nodule
- anterior chamber hyphema
- iris hemosiderosis
- iris pigment epithelial tumor
- congenital Horner's
- Fuchs heterochromic iridocyclitis

Figure 3. Differential diagnosis of pigmented iris lesion in a child.

During exam under anesthesia ultrasound biomicroscopy of the anterior segment was performed, demonstrating diffuse thickening of the iris in the inferotemporal sector with no abnormality of the adjacent ciliary body *(See Figure 4)*. The lesion measured 11 mm in base and 2 mm in thickness.

Anterior segment fluorescein angiography revealed a rapidly filling vascular lesion with no leakage of dye from the vessels *(See Figure 5)*. Ancillary testing to this point proved revealing but non-diagnostic, and the next step in evaluating the lesion was felt to be fine needle aspiration biopsy. Prior to proceeding with biopsy, a dilated examination of the fundus was performed. The left fundus was found to be unremarkable; however the right fundus showed a diffuse, orange-red choroidal lesion involving the entire fundus posterior to the equator with greatest thickness in the inferior macula *(See Figure 6)* associated with an overlying serous retinal detachment; this was confirmed on optical coherence tomography *(See Figure 7)*. Fluorescein angiography of the lesion revealed rapid filling with no leakage *(See Figure 8)*. B-scan ultrasonography revealed an acoustically solid, echogenic mass, measuring 6.5 mm in thickness. A-scan ultrasonography of the lesion revealed high internal reflectivity characteristic of choroidal hemangioma.

Based on these findings, a diagnosis was made of diffuse choroidal hemangioma with sector hemangioma of the iris. The diagnosis was made clinically and biopsy of the lesion was not necessary.

The child was initially treated with oral propranolol (20 mg p.o. t.i.d. or 2 mg/kg/day) to assist in reduction of the choroidal hemangioma and resolution of the subretinal fluid. Care was coordinated with his pediatrician to monitor for cardiovascular compli-

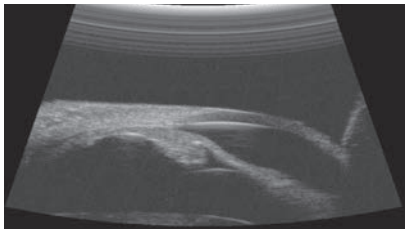

Figure 4. Ultrasound biomicroscopy of the anterior segment demonstrating diffuse thickening of the iris inferotemporally with no abnormality of the adjacent ciliary body.

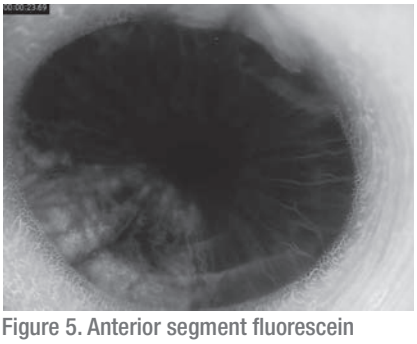

Figure 5. Anterior segment fluorescein angiography revealed rapid filling and no leakage.

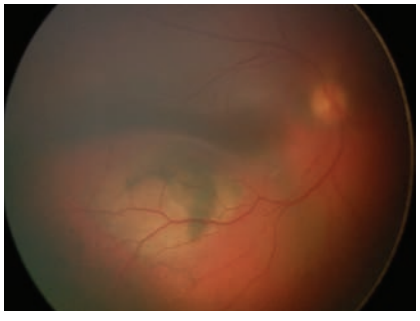

Figure 6. Fundus photograph of the right eye demonstrating an orange-red choroidal lesion involving the entire fundus posterior to the equator with greatest thickness in the inferior macula with overlying serous retinal detachment.

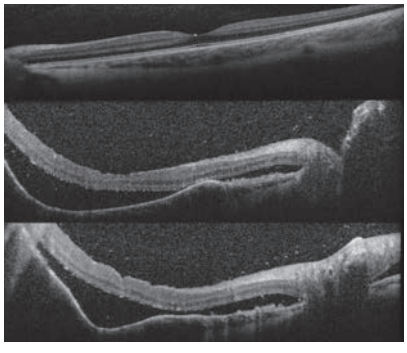

Figure 7. Optical coherence tomography demonstrating normal foveal architecture in the left eye (top image) and serous retinal detachment of the right eye (bottom two images).

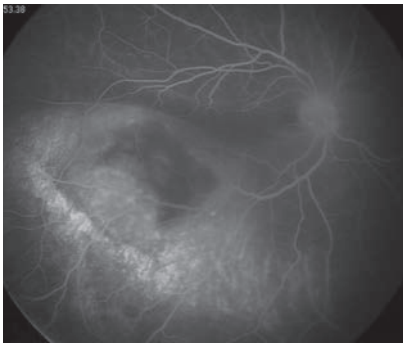

Figure 8. Fluorescein angiography of the right eye showing absence of late leakage. Early frames show rapid filling of the lesion.

cations such as bradycardia and hypotension. The choroidal tumor showed little response to oral propranolol therapy and after five months, tumor thickness was 6.1 mm from an initial thickness of 6.5 mm. Given the poor response to oral propranolol, the decision was made to treat the tumor with plaque radiotherapy. An Iodine-125 plaque was applied to the sclera overlying the tumor with an apex dose of 35 Gray centered over the thickest portion of the lesion. The plaque was left in place for four days and a single injection of intravitreal Avastin (1.25/0.05cc) was administered at the time of plaque removal. The tumor showed excellent response to this regimen, and at six weeks post-plaque choroidal tumor thickness was 3.3 mm, from an initial thickness of 6.5 mm. Further regression of the tumor was noted and at last follow-up tumor thickness was 2.6 mm *(See Figure 9)*. There was complete regression of subretinal fluid and no recurrence of tumor after more than two years of follow-up. Despite regression of the tumor and resolution of chronic serous retinal detachment, visual acuity in the right eye remained poor at 20/400 OD. Polycarbonate lenses were recommended for protection of the better-seeing eye.

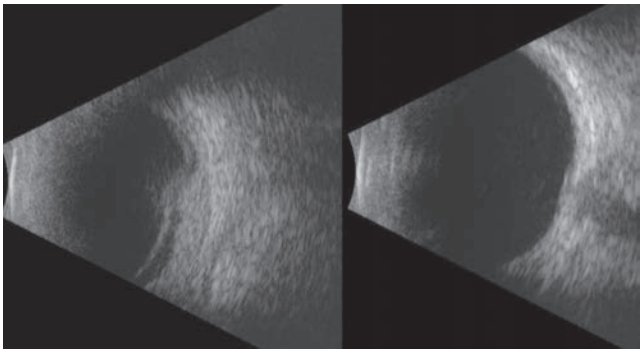

Figure 9. Tumor thickness before (left) and after (right) plaque radiotherapy. Tumor thickness decreased from 6.5 mm to 2.6 mm and the serous retinal detachment completely resolved.

Discussion

Choroidal hemangioma is a benign vascular hamartoma that can be further classified as either circumscribed or diffuse. Diffuse choroidal hemangioma (DCH) appears as an ill-defined reddish-orange choroidal thickening with indistinct margins. The clinical appearance is often termed "tomato catsup fundus" due to the reddish hue of the lesion.[1] Vision loss with DCH often occurs secondary to hemangioma-induced hyperopia, amblyopia and secondary serous retinal detachment, all of which were present in our patient.

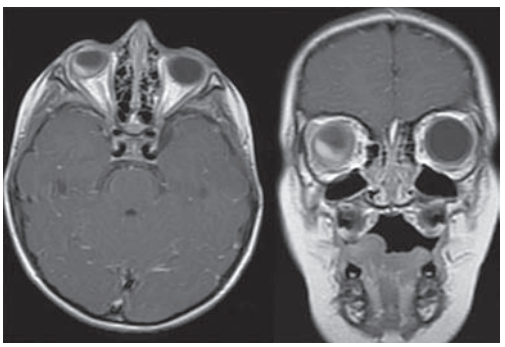

Figure 10. Axial and coronal T1 post contrast images showing contrast enhancement of the choroidal hemangioma with no associated lesions of the leptomeninges.

While asymptomatic patients may be observed, patients with decreased vision secondary to subretinal fluid often benefit from intervention. Treatment options for DCH include oral propranolol, photodynamic therapy and radiation therapy (case reports of external beam radiotherapy, proton beam radiotherapy, plaque brachytherapy[1] and stereotactic radiotherapy have been described).[11] Oral propranolol was incidentally found to induce regression in infantile hemangiomas of the skin and, although ineffective in our patient, case reports exist documenting the utility of oral proranolol in the treatment of diffuse choroidal hemangioma.[2,10] A single report exists in the literature regarding treatment of diffuse choroidal hemangioma with isolated anti-VEGF therapy.[11]

While circumscribed choroidal hemangioma is often isolated, diffuse choroidal hemangioma is commonly found in association with Sturge-Weber syndrome, a rare, congenital, nonhereditary neuro-oculo-cutaneous syndrome associated with facial angioma (nevus flammeus or port wine birthmark), leptomeningeal angioma and vascular malformation of the eye. Our patient did not have the classic port wine birthmark and MRI of the brain revealed an absence of leptomeningeal angioma *(See Figure 10)*. While Sturge-Weber syndrome with isolated cutaneous or leptomeningeal findings has been described, to our knowledge isolated ocular findings are extraordinarily rare.

Although diffuse hemangioma of the choroid is a common ocular manifestation of Sturge-Weber syndrome, hemangioma of the iris is exceedingly rare.[3,6,12] A single other report of iris involvement has been published.[5]

Sturge-Weber syndrome is speculated to be due to a somatic mosaic mutation affecting vascular development in geographically related tis-

sues with the extent of involvement determined by the developmental stage at which the somatic mutation occurs. In 2013, Matthew Shirley, PhD, and colleagues described a single nucleotide mutation in GNAQ present in samples of affected tissue of patients with Sturge-Weber syndrome and non-syndromic port wine birthmarks.[7] While our patient's clinical findings are not classic for Sturge-Weber syndrome, they likely represent a spectrum of disease that occurs when the presumed somatic mutation occurs at a later stage in development affecting the eye only.

This case highlights the importance of dilated fundus examination in pediatric patients and suggests that clinicians should have a low threshold for examination under anesthesia for children with poor vision and a difficult exam. REVIEW

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(continued from page 33)

performing a vitrectomy in addition to the Baerveldt surgery. The retina surgeon made the incisions through the pars plana—and in a nanophthalmic eye there is a smaller-than-usual pars plana. We inadvertently created a retinal detachment while preparing to insert the tube posteriorly. Fortunately, retinal detachments are a rare complication during normal tube surgery."

• ***Consider using only one suture.*** "One thing I do differently from some glaucoma surgeons is that I only use one vicryl suture for my entire case," says Dr. Fechter. "The single vicryl suture acts as a traction suture, secures the plate and patch graft to the sclera, ligates the tube and closes the conjunctiva. I know that some surgeons also place an additional prolene suture in the lumen of the tube to help control the pressure during the early postoperative period. I'm glad that the prolene suture works for them, but my patients do quite well with just the single vicryl ligature that dissolves five weeks after surgery. My technique requires less OR time, is less expensive and eliminates the need to manually remove the prolene stent in the office."

• ***Be careful with uveitic patients.*** "Uveitic patients are perhaps the most difficult glaucoma patients to manage because their pressure is either too high or too low and it's very difficult to keep it just right," notes Dr. Fechter. "With these patients, it's extremely important to keep the inflammation under control and to seek the assistance of a rheumatologist or a uveitis specialist. By doing so, you can prevent the eye from becoming hypotonous as a result of aqueous hyposecretion."

• ***Mitomycin is probably not worth using.*** "There was some thought that using mitomycin-C might decrease the amount of scar tissue that forms around the reservoir, reducing the thickness of the capsule," notes Dr. WuDunn. "Only a couple of sites have tried this, and they were very small studies; they didn't appear to show any advantage to using mitomycin. It may be that when you're talking about a foreign body such as an implant, it's just too hard to prevent scar tissue from forming around it. So unless you're using really high does of mitomycin—and I don't think anyone's tried higher than 0.5 mg—scar tissue forms no matter what. Much higher doses of mitomycin might prevent that, but that would increase the risk of the implant extruding or getting exposed because of the loss of scar tissue around it."

• ***Learn by observation.*** Dr. Fechter notes that the best way to learn good technique is by observing others with more experience. "Find out which surgeons in your community have put in a lot of tubes and ask to observe them in the OR," he says. "During my fellowship I had the opportunity to observe several excellent glaucoma surgeons implanting tubes. I took what I thought was the best from each surgeon's technique and incorporated it into my own."

• ***If you do have a complication, don't be afraid to ask for help.*** Dr. Fechter notes that there's no shame in asking for advice from someone who has done more cases than you. "Many glaucoma surgeons contribute to glaucoma forums on the Web and discuss their complications and problems with other glaucoma surgeons," he says. "Oftentimes another surgeon has had the complication you're faced with and can offer advice on how to fix it." REVIEW

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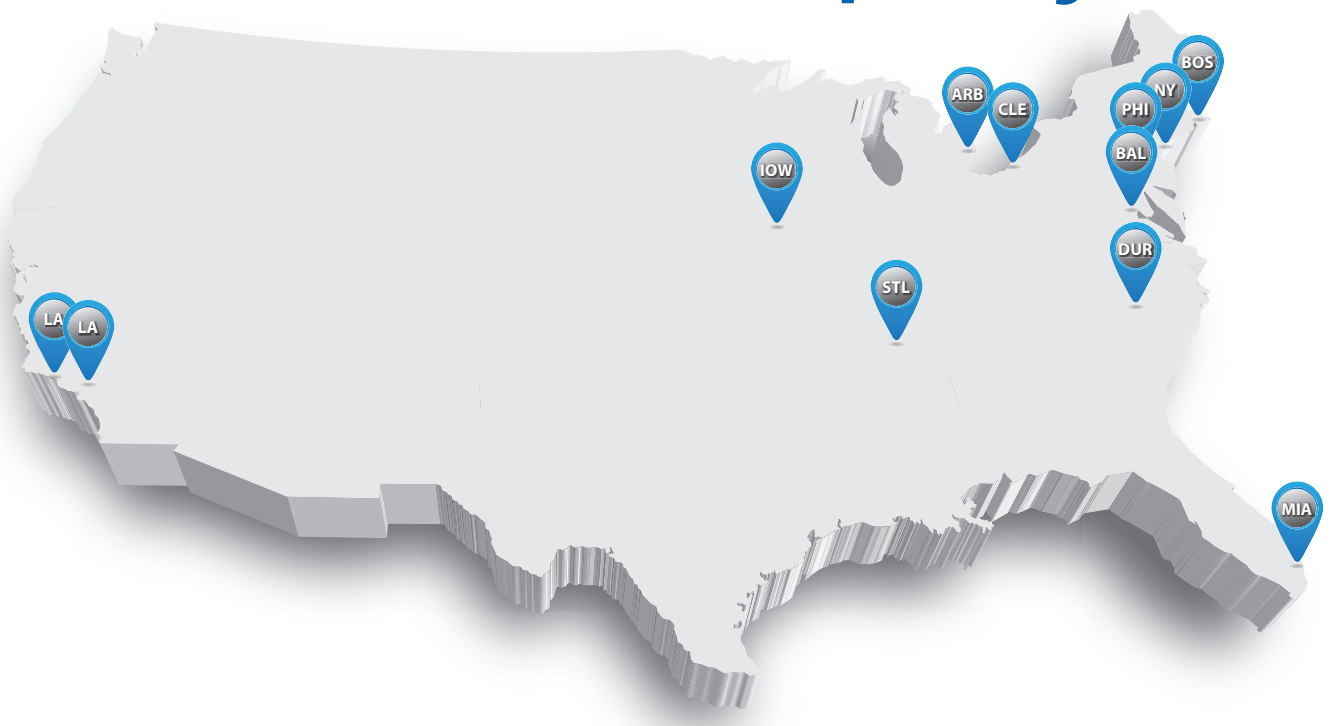

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