Supplement to

September/October 2014

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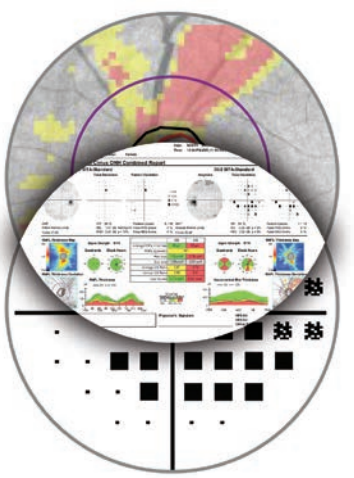

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Changing Paradigms in Glaucoma Therapy


STEVEN D. VOLD, MD

These are exciting times for glaucoma patients and their doctors, as our understanding of the disease is evolving rapidly, along with our ability to both diagnose and manage it. In the past, glaucoma was treated primarily with topical medications that at best only stalled its progression. Surgery was generally considered only as a last-resort therapeutic option due to significant postoperative complications and prolonged recovery times. Furthermore, many patients' prognosis suffered due to limitations to early diagnosis and challenges to medical compliance.

Today, glaucoma patients' future quality of life appears brighter than ever before. Recent improvements to our diagnostic testing, novel developments in drug delivery, and transformative advances in microsurgical techniques and technology are raising the standard of care. The following articles give glaucoma specialists a review of the latest developments in the field so they may assess their utility for their own practices.

CONTENTS

Visual Fields Are One Piece of the Glaucoma Puzzle

When in doubt, repeat the visual field test.

BY CHRIS A. JOHNSON, PHD

The visual field (VF) is among the essential factors to test when diagnosing and managing glaucoma. However, the information a VF test provides is only as important as the complementary findings afforded by other equally relevant factors, such as the status of the optic disc, IOP, and central corneal thickness, among other things.

CLINICAL APPLICATIONS

The exact way in which clinicians should incorporate VF testing will vary from case to case, depending on whether they are using it for glaucoma detection or to monitor changes or the rate of disease progression (Figure 1). Glaucoma specialists may ask themselves, 'is the purpose of this test to look at efficacy of medical or surgical management; to detect the earliest signs of glaucoma; or to distinguish glaucoma from some other type of ocular disease, such as optic neuropathy?' The application and frequency of VF testing may vary depending on the intended use.

Given that glaucoma most commonly affects peripheral vision first, a VF test offers an important measure of the extent of damage to the optic nerve from elevated IOP. Clinicians should perform this test at the initial visit or as soon as they suspect glaucoma in order to determine the severity of disease. This staging information is naturally useful in choosing a target IOP and determining follow-up.

VF COMPARED WITH IMAGING TECHNIQUES

Among the ways that VF testing contrasts with imaging techniques with respect to glaucoma diagnosis and management is that VF testing detects information about the stage of glaucoma and provides some hints about the patient's quality of life; his or her ability to perform tasks and participate in daily activities. Identifying the stage of glaucoma gives us a handle on daily problems the individual might be facing, and whether he or she might benefit from assistance with low-vision aids or other similar interventions. Images of a thinning retinal nerve fiber layer do not provide a window into those kinds of practical matters. For example, it has been found that even in the early stages of glaucoma, individuals may suffer impairment while driving and with eye-hand coordination, among many other activities.[1,2]

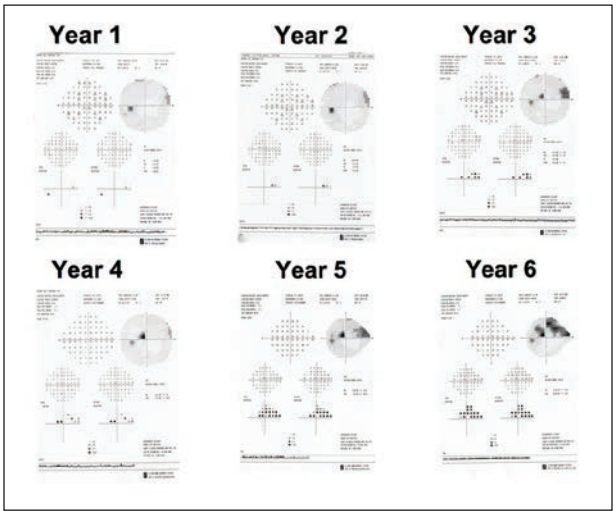

Figure 1. One of the primary uses of VF testing is to monitor disease progression, as in this case of a superior nasal step (OS) that progressed to become a superior arcuate nerve fiber bundle defect.

VF testing can be tailored to determine various stages of disease development, from early to advanced. Techniques that target specific subgroups of nerve fibers, such as frequency doubling perimetry and short-wavelength automated perimetry, are used for early detection. Newer techniques that are also used to detect early glaucoma include pulsar perimetry, rarebit perimetry, and microperimetry; these are geared toward fine-detail mapping.[3] Clinicians should use a validated form of statistical analysis to monitor and assess changes in the VF over time.

A WIDER FIELD OF VIEWING

VF loss due to glaucoma is usually a combination of diffuse (widespread) and localized sensitivity loss. As glaucoma progresses to a more advanced stage, it begins to affect broader areas of the VF, such as the macula and the far periphery. These regions are usually less susceptible to early and moderate stages of the disease.

Widening the target area of VF testing can help us detect and assess advanced vision loss. Likewise, clinicians can increase the dynamic range of the testing, so if a patient has lost contrast sensitivity, the practitioner can monitor him or her further by using more detectable targets that incorporate larger sizes, motion, flicker, or other salient stimulus features.

Some glaucoma specialists think that if they use larger targets during VF testing, they may be less likely to notice subtle changes. However, we have not yet found that to be the case. We are able to detect VF deficits just as well as with large targets as with small. In fact, using the larger target for VF testing imparts less variability, and it incorporates a larger range of values. Thus, larger VF targets essentially provide a more robust test procedure.[4]

CHANGE AND PROGRESSION

The ability to employ markers to identify intraocular changes that indicate the progression of glaucoma is critically important to managing the disease. One marker that is readily available is the VF index, which allows clinicians to monitor the rate of glaucoma's progression and helps us predict the quality of a patient's vision in 5 years using a linear extrapolation of VF trends.[5] Another marker is the mean deviation, which is essentially the average sensitivity of the VF. However, I think the rate of disease progression is the biggest concern for glaucoma specialists. Once a patient shows evidence of ocular damage from glaucoma, the ability to gauge the effectiveness of a prescribed treatment is vital to their wellbeing.

WHERE VISUAL FIELD TESTING FITS IN THE PRACTICE

It is important for glaucoma specialists to remember that there can be discrepancies between VF testing and other imaging modalities. The Ocular Hypertension Treatment Study (OHTS)[6,7] showed that glaucoma-induced physiological changes to the VF and changes to the optic disc occurred together only about 24% of the time. It has also been reported that VF tests have indicated a loss of function, but nothing looks abnormal on imaging (scanning laser ophthalmoscopy [SLO]) or on a stereo photograph. Thus, at this point in the development of these technologies, I do not think that we have enough clinical information to label one type of imaging as a superior standard of care that can replace the others. For the time being, I really think the effective diagnosis and management of glaucoma depends on using a combination of all these methods.

WHEN IN DOUBT, REPEAT

When there is uncertainty about the results of the VF test or it suggests a change in visual function, it is best to repeat the test several times to confirm the results. I strongly advise repeat testing based on findings from the OHTS, which showed that subjects who showed glaucomatous changes during the study (after testing "normal" numerous times in order to qualify for the study), tested as "normal" 88% of the time when the VF was re-tested. Thus, according to the OHTS, the chances that the glaucomatous change would be confirmed on the next test were only about 1 in 7 or 8.[8]

"Using the larger target for VF testing imparts less variability, and it incorporates a larger range of values."

Although guidelines are not yet firm, I recommend performing VF testing twice a year for early-stage and stable glaucoma. I believe that testing three times per year is appropriate once a significant change has been detected. The literature suggests that there is no clinically meaningful information to be gained from performing VF testing more than three times per year.[9] Ultimately, it is best to determine the frequency of VF testing on a case-by-case basis.

USE ALL AVAILABLE TECHNOLOGIES

Glaucoma specialists should continue to use all of the information at their disposal, because neither VF testing nor imaging will provide all of the necessary data. Take every aspect of the clinical examination—including the structure of the eye, the patient's history, his or her subjective report, IOP, the evidence of adherence to medical treatment, etc.—and then add that to all of the different aspects of the exam to making your clinical judgment. ■

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INDICATIONS AND USAGE

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

Dosage and Administration

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

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

IMPORTANT SAFETY INFORMATION

Warnings and Precautions

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

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

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

Adverse Reactions

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

Use in Specific Populations

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

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

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

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

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BRIEF SUMMARY OF PRESCRIBING INFORMATION

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

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

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

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

CONTRAINDICATIONS
None

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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Current OCT Strategies in Glaucoma

The benefits and limitations of OCT to diagnose and manage glaucoma.

BY STEVEN D. VOLD, MD, AND JOEL S. SCHUMAN, MD

For glaucoma specialists, the ability to see, document, and track changes to the optic nerve fiber layer, macula, and other important structures in the eye is essential to managing the disease. Optical coherence tomography (OCT) and visual field (VF) testing are the two primary imaging technologies clinicians rely on for disease tracking. Rather than competing, however, the two complement and reinforce one another by providing information about retinal nerve fiber layer and optic nerve structure and function. This article describes the best clinical use of OCT, in our opinion, for detecting and managing glaucoma.

REPRODUCIBILITY IS KEY

OCT enables glaucoma specialists to measure the thickness and shape of the retina and the optic nerve, as well as other parts of the eye, with a high degree of accuracy and precision (Figure 1). Most commercial spectral-domain OCT devices have a viewing resolution of 5 to 7 µm in the axial direction, which allows them to discriminate between different layers of the retina and measure those layers with a high rate of reproducibility. Reproducibility is an important function of OCT imaging, because the ability to generate repeated, consistent images of the same area of the eye over months or years helps clinicians detect small structural changes over time.

Spectral-domain OCT remains the most popular form of the technology for ophthalmology, although some practitioners still use time-domain OCT, and swept-source OCT is in development. Although the speed of these machines varies, they operate on the same basic principles. Spectral-domain OCT can create a 3-dimensional map of the retina and the optic nerve, which can then be measured in individual layers, such as the retinal nerve fiber layer near the optic nerve head, or the retinal ganglion cell and adjacent layers in the macula (both useful for glaucoma detection and monitoring).

DETECTING EARLY DISEASE

We believe that one of OCT's greatest uses is in detecting glaucoma in its early stages. Patients with early glaucoma usually do not have any visual defect but will present with a reproducible or progressive abnormality in a shape and in an area of the eye that is characteristic for glaucoma. If the overall thickness of the nerve fiber layer on the Cirrus HD-OCT (Carl Zeiss Meditec) reads above 80 µm, then it is unlikely that the eye will have a VF defect associated with the nerve fiber layer abnormality.

> "The newest OCT devices are able to detect glaucoma earlier and with a higher degree of certainty than ever before, prior to the appearance of VF abnormalities."

Thus, the newest OCT devices are able to detect glaucoma earlier and with a higher degree of certainty than ever before, prior to the appearance of VF abnormalities. The earlier we can detect the disease, the less aggressively we have to treat it. A Humphrey 24-2 VF test (Carl Zeiss Meditec), for example, requires a 15% to 20% loss of the mean retinal nerve fiber layer thickness before it can detect visual defects. A Humphrey 10-2 test may show the abnormalities earlier, but this only evaluates the central 10º.

MEASURING FOR PROGRESSION

OCT can measure the thickness of the retinal nerve fiber layer in quadrants, clock hours, or points to help clinicians identify locations of glaucomatous abnormality. We can assess whether or not change over time is statistically significant. In fact, by measuring the correspondence between optic nerve structure and function, OCT can confirm the existence of a progressive event or abnormality seen on VF testing. Although historically, studies have suggested that multiple VF tests are necessary to prove the existence of such VF changes, we have found that conducting one structure/function correspondence test with OCT and a VF test gives a high degree of certainty that the progression is true, particularly for moderate disease to the early stages of advanced glaucoma. However, once the nerve fiber layer thins to a certain point—approximately 50 or 55 µm on the Cirrus device—most OCT units are unable to detect further thinning. This is called a *floor effect*.

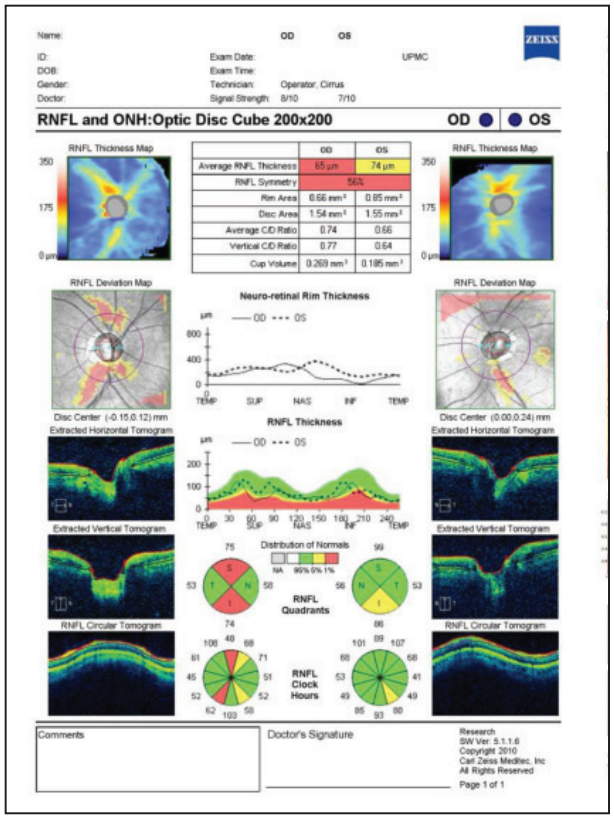

Figure 1. Today's OCT technology offers high-precision imaging, as in the case of this thin inferior and superior RNFL (OD) with the Cirrus HD-OCT (Carl Zeiss Meditec).

Many of OCT's quantitative parameters pertaining to the nerve fiber layer are related to the circle that is centered on the optic nerve. Although the information from that central circle is useful, we would also encourage glaucoma specialists to evaluate the data outside of the circle. We like to look at the deviation map to determine the shape and location of abnormalities and changes that I might otherwise miss with the circumpapillary scan, in case the abnormality has not yet reached that area.

Also, it is worth mentioning that some eyes with early-stage glaucoma may show a change on the VF test before the clinician can actually see a VF defect. The eye's sensitivity to light may be decreasing, but the nerve fiber layer's thickness still lies within the normal range. Such changes are measureable with the standard progression software available on most OCT devices.

SWEPT-SOURCE OCT

Swept-source OCT sweeps light through a number of wavelengths in an interferometer, similar in some ways to both spectral-domain and time-domain OCT. For swept-source OCT, a photo detector (as is used with time-domain OCT) instead of a camera or spectrometer (required with spectral-domain OCT) is used. In this way, swept-source OCT avoids some of the challenges of spectral-domain OCT, such as the SD-OCT's decrease in sensitivity and resolution with increasing distance from the zero delay. The central wavelength with spectral domain is approximately 850 nm, compared to 1 µm with swept source. A longer wavelength penetrates deeper into the tissue and enables clinicians to more easily view structures such as the choroid or the lamina cribrosa, but the axial resolution is not quite as good as with most commercial spectral-domain OCT devices.

SUGGESTED PROTOCOL

As a researcher, I (Dr. Schuman) am involved in several ongoing studies, so I am continually using a variety of devices with patients. If I were practicing clinically, I would routinely use spectral domain OCT on eyes I suspect of any glaucomatous abnormality. I also believe it is worthwhile to perform a baseline VF test on every new glaucoma or glaucoma suspect patient. If a glaucoma suspect's eyes look normal on OCT and VF, then I would test him or her again at 6 months. If there were still no change at that visit, I would ask to see the patient a year later. If there were still no change, I would have him or her return every 2 years.

CONCLUSIONS

As described previously, it is important to perform both VF and OCT testing to assess both structure and function of the eye and to look for corresponding changes between these two metrics. Glaucoma has a spectrum of disease. Early on, we can track its progression using OCT alone. At a certain point, we need both OCT and VF testing to track it, and we get the highest degree of certainty of the disease's status when changes in structure and function correspond with one another. Advanced glaucoma is best followed by VF testing; at this point, OCT is not particularly helpful. ■

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Fixed-Combination Therapy Is Fast and Effective

Combined medications aggressively lower IOP.

BY ROBERT NOECKER, MD, MBA

Convenience and efficacy are among the benefits that make fixed-combination pharmacologic therapy a go-to option for me when managing glaucoma in my patients. *Fixed combinations*—the term refers to a solution of two glaucoma medications in one bottle—make it relatively easy for me to be aggressive about lowering IOP. I prefer an aggressive strategy because generally, reducing IOP earlier in the disease process allows patients to retain vision longer. This tenet of glaucoma management remains important to specialists and patients alike.

CLINICAL USE OF FIXED-COMBINATIONS

Fixed-combination treatments have been available for decades, and glaucoma specialists are increasingly comfortable prescribing them. Over time, it has become clear that patients' adherence to therapy is affected by the number of eye drop bottles in the treatment regimen.[1] Based on this knowledge, I tend to use fixed-combination therapy either as an alternative to prostaglandin analogue (PGA) therapy or in addition to it. Although it is common practice to use fixed-combination glaucoma drugs in conjunction with PGAs, the question remains whether to introduce the fixed-combination therapy first or whether to employ it as a second-line choice after gauging the effect of a PGA.

AVAILABLE OPTIONS AND BENEFITS

Three fixed-combination glaucoma drops are currently available in the United States: Cosopt (Akorn), which is a combination of timolol and dorzolimide; Combigan (Allergan), which is a combination of timolol and brimonidine; and the newest option, Simbrinza (Alcon), which is a combination of brinzolamide and brimonidine.

Compared with individual medications, fixed-combination therapies are easier for patients to use and less costly to purchase. One of the biggest problems in glaucoma treatment is the variability associated with patients' having to instill various drops several times throughout the day. For the regimen to be effective, the patient must take the right drops at the prescribed times, and he or she has to space administration appropriately to avoid washing one drop out of the eye by instilling another. It is not uncommon for patients to put the second drop in right after the first one, which can diminish the efficacy of the first drop. Anecdotal experience suggests that patients prefer to administer their drops at the same time.

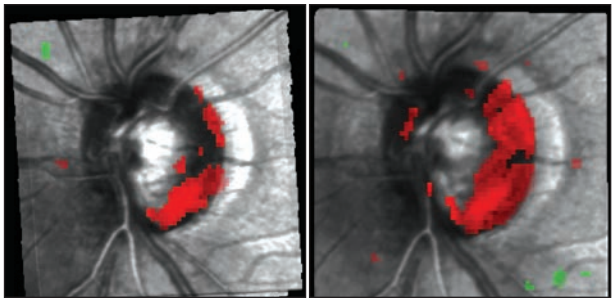

Figure 1. Images taken with the Heidelberg Retinal Tomograph (HRT; Heidelberg Engineering GmbH) demonstrate progressive loss of the optic nerve in patient who was inadequately treated for glaucoma. The increasing red areas indicate a change from baseline imaging.

Cost can also be a barrier when patients have several prescriptions to purchase. Ultimately, the fewer bottles they have, the fewer challenges they face, and the more likely they are to succeed with the prescribed regimen.

DOSING

Fixed-combination drops provide a simpler dosing regimen for glaucoma patients, which I believe boosts adherence and therefore efficacy. Twice-daily dosing, which is available with Combigan and Cosopt and supported by the literature,[2] is easier for patients to maintain. In my experience, twice-a-day dosing with Simbrinza is also effective, although the product label calls for dosing three times a day. I think it is unrealistic to expect busy patients to instill drops more than twice a day.

Twice-daily dosing is about the maximum prescription for a β-blocker[3,4] and possibly less than ideal for an α–agonist or carbonic anhydrase inhibitors.[5] This highlights another benefit of combination therapy: oftentimes, the strengths of one component make up for the weakness of the other.

LIMITATIONS OF FIXED-COMBINATION THERAPY

If a patient is intolerant of or develops a side effect to one of the combination's components, he or she cannot use that fixed-combination drug. For instance, a patient with a brimonidine allergy cannot use Combigan or Simbrinza. Similarly, a patient who is intolerant of β-blockers must avoid fixed combinations that include that component.

Another criticism of fixed-combination therapy is that, if one of the components is not working as effectively as expected, it is difficult to identify which one, if the target IOP is achieved. This is more of a theoretical argument, however, as long as the IOP is effectively reduced.

MY TREATMENT ROUTINE

The data on fixed-combination products suggest their efficacy is comparable to that of PGAs.[6,7] If a patient's IOP does not respond sufficiently to a PGA or he or she developed side effects from it, then a combination product is the next treatment I try. The only downside is that the patient will have to instill the product twice daily instead of once. If the switch is effective, however, I think more frequent dosing is an acceptable trade-off. The upside of the combination products is that they deliver the efficacy of a PGA without the tolerability issues associated with that class of medication such as red eye, skin changes, and eyelash growth.

The greatest source of disagreement among clinicians with respect to fixed-combination therapy is which patients may benefit most from it. Combination products are probably not necessary in individuals with mildly elevated IOP, for whom there is plenty of time to slowly bring the pressure into a safe and healthy range. On the other hand, when a patient is at risk of losing sight to glaucoma and quick and substantial IOP lowering is in order, a combination drug is an excellent choice. Too often, patients present at my practice after being marginally treated elsewhere for far too long. By then, the damage has been done, and it is obvious that the individual would have benefited greatly from more aggressive treatment years earlier. Thus, I think that medically lowering a patient's IOP too much is a lesser concern.

> "The data on fixed-combination products suggest their efficacy is comparable to that of PGAs."

I make every attempt to keep my treatment strategy simple. Ideally, patients only have to use a single drop from a single bottle, but sometimes, two bottles are necessary. Some patients are organized enough to deal with multiple bottles; others are not. When I see that a patient with several individual component drops is getting confused and missing doses, I immediately introduce a combination product to simplify the routine. This philosophy has evolved over the years as I have seen so many patients respond positively to fixed-combination drugs. Now that I know what to expect from these medications, they have become indispensable to my practice. ■

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Generics Versus Branded Medications: Efficacy and Tolerability Are Not the Only Concerns

BY MALIK Y. KAHOOK, MD

As the patents on many glaucoma medications are running out, generic formulations are coming on the market in greater numbers. Within the past couple of years, for example, several generic formulations of latanoprost have emerged. Thus, an ongoing discussion has developed within the glaucoma community about the efficacy of generics versus brand name formulations. Beyond our concerns as healthcare providers, we clinicians need a clear position regarding generic versus branded medications, so that we can reassure those patients who ask us to explain the difference.

PROCEED SLOWLY WHEN SWITCHING

Naturally, our patients want to know whether a generic glaucoma drug is going to be as effective as a branded one. My typical answer is, "yes." The majority of my patients who are taking a generic formulation have well-controlled IOP, similar to what I see with brand-name versions. Furthermore, my patients seem to tolerate generic drops fairly well; most of them demonstrate good efficacy as well as sufficient tolerability for these formulations.

It is not infrequent, however, for patients to have significant issues when switching between branded and non-branded drops. In my experience, a significant number of individuals who have switched to a generic therapeutic from a branded one for various reasons have experienced a slight increase in IOP, and several have experienced tolerability issues such as stinging and a foreign body sensation. My staff and I follow these patients closely and switch them back to branded medications if the IOP response is not sufficient or tolerability issues are persistent after 2 to 3 visits post switch to generic medications.

CONSISTENCY IS THE MAIN ISSUE

To me, however, efficacy and tolerability are not the major issues with generic drugs. I am most concerned about whether the formulations are consistent from refill to refill. For physicians, the primary benefit of prescribing branded combination drugs is knowing exactly what the patient is getting. Aside from consistency in the bottle's size, shape, and color, we are assured of a standardized formulation, no matter which pharmacy the patient uses.

> "I am most concerned about whether the formulations are consistent from refill to refill."

Patients can be easily confused by differences in bottle size, cap color, shape, and labeling. Most patients identify their bottle by color and shape and become very confused when their refills look different. The more medications an individual is on, the more confusing such changes become. Since half of all glaucoma patients are taking more than one medicine, this a significant issue for those under our care.

Even the color of bottle caps, which is supposed to remain consistent between the families of branded and generic formulations, can vary. I have seen differences in the cap color of some generic latanoprost formulations. The cap is supposed to be teal, but some of them are off-green and some are more blue-ish than green. Most recently, this happened with a generic formulation of timolol. β-blockers are supposed to have yellow caps, and when one came out with a white cap, patients were confused. This may sound like a mild issue, but medication identification is a cornerstone of compliance and safe dosing.

COMBINATION THERAPIES

Combination therapies are a newer pharmaceutical arena for patients to navigate. As yet, there is no generic formulation of Combigan (brimonidine tartrate/timolol maleate; Allergan) or Simbrinza (brinzolamide/brimonidine tartrate ophthalmic suspension; Alcon). Cosopt (dorzolamide hydrochloride-timolol maleate ophthalmic solution; Merck & Co.) does exist in generic formulations, and also now a nonpreserved formulation, and is made by multiple manufacturers. Here again, there are slight differences in the bottles from one manufacturer to another.

KNOW THE SOURCE OF GENERIC FORMULATIONS

I, along with Robert Noecker, MD, and other colleagues, participated in an examination of the nonbranded formulations of Cosopt and Xalatan (latanoprost ophthalmic solution; Pfizer) that are made overseas.[1] We found significant contamination of the bottles as well as decreased stability of the active ingredient at room temperature and at high temperatures with two of the nonbranded formulations that were manufactured in India. Patients obtain these formulations online and by mail order—methods that bypass FDA regulation. While nonbranded pharmaceuticals sold in this country have to get FDA approval, which may address several of these concerns, issues with bottle type and cap color persist.

CHECKING LABELS IS KEY

In order to make sure that my patients are receiving a quality product, I ask them to bring in their drops each visit so I can check the labeling and see what they are using. From visit to visit, I can see if they are switching from one generic to another, and I can ask them about any associated symptoms. Also, this check-up lets me verify that the patient is using the drops appropriately. If a patient tells me he or she has been using the drops for 2 weeks but the bottle is nearly empty, he or she may be missing the eye or instilling too many drops. Naturally, if the bottle is almost full, they are not getting enough of the needed medication.

It is not uncommon for a patient to come into the clinic with multiple medication bottles having switched the caps. Thus, he or she may be using the drops incorrectly based on the color of the cap, and this is another opportunity to educate the patient about how to follow the regimen. Again, with multiple generic formulations available on the market with differing bottle caps, I think it is important for ophthalmologists to ask their patients to bring in their drops at each visit to be reviewed by the physician or technician. ■

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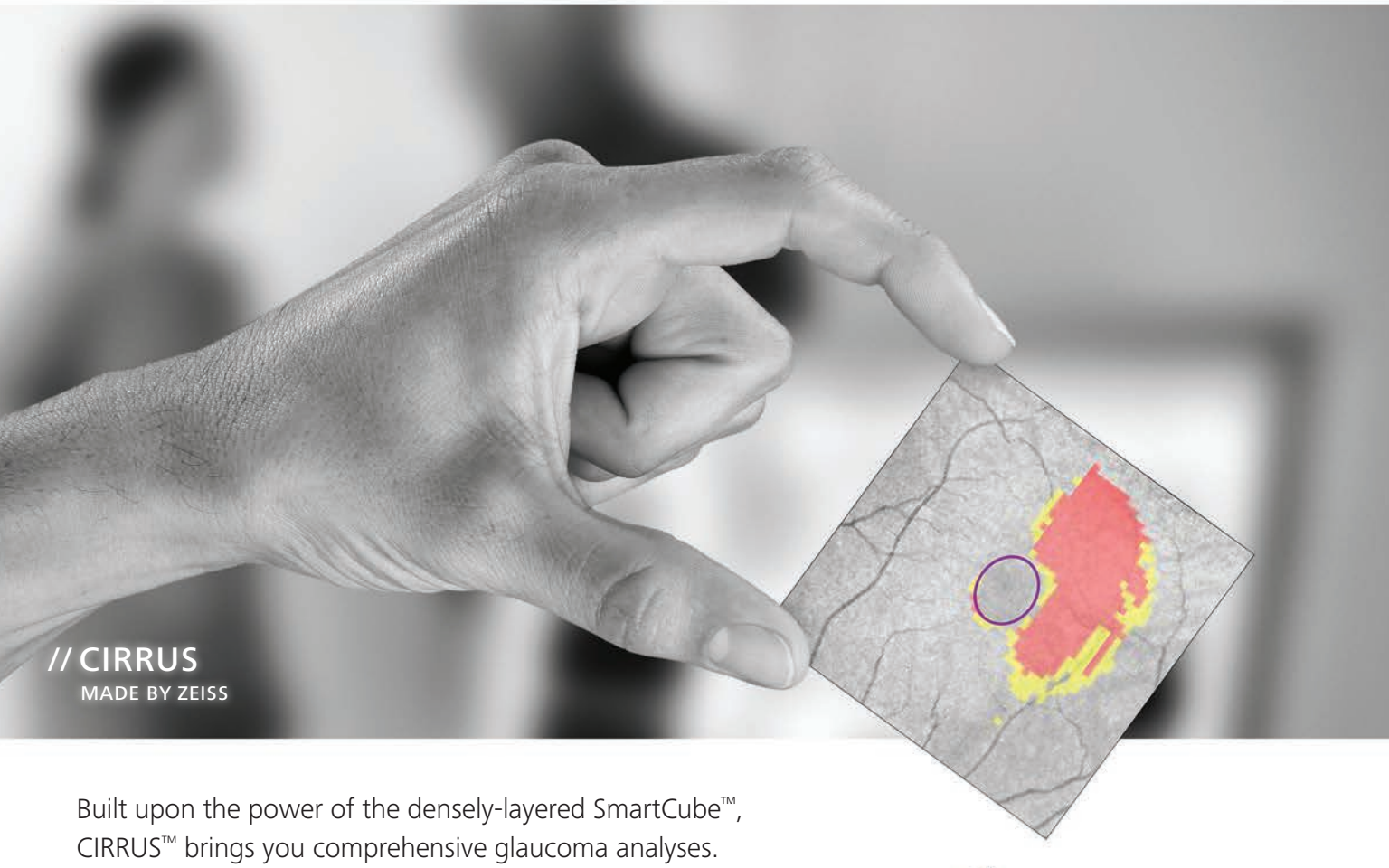

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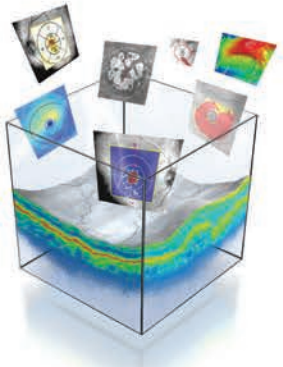

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Recent Advances in Glaucoma Filtration Surgery

The latest procedures and devices that are expanding surgical options.

BY STEVEN R. SARKISIAN JR, MD

Glaucoma specialists have new minimally invasive tools in their armamentarium to stabilize IOP and reduce the impact of glaucoma surgery. This article discusses the devices that have changed the paradigm of care in my glaucoma practice.

THE EX-PRESS MINI GLAUCOMA SHUNT

The EX-PRESS Glaucoma Filtration Device (Alcon; Figure 1), which has more than 10 years of implantation experience under the scleral flap, allows for safer filtration surgery compared with trabeculectomy.[1] A recent multicenter prospective study of the EX-PRESS demonstrated significantly faster visual recovery from filtration surgery compared with trabeculectomy.[1] In my practice, trabeculectomy is no longer the gold standard of glaucoma surgery.

THE OLOGEN COLLAGEN MATRIX

A primary challenge with glaucoma filtration surgery is the risky use of antimetabolites, which are chemicals originally designed for chemotherapy. By interfering with wound healing, antimetabolites have greatly improved the success rate of glaucoma surgery over the past 30 years. If overused, however, these drugs can cause wound leaks, endophthalmitis, and hypotony. Most surgeons use mitomycin-C (MMC), although some now use 5-Fluorouracil (Mitosol; Mobius) off-label.

The Ologen Collagen Matrix Implant (Optous) is an artificial porcine extracellular matrix implant (Figure 2). Approved by the FDA in August 2009, Ologen modifies ocular wound healing without major side effects. It acts as a spacer over the scleral flap to tamponade the flow of fluid, and it also prevents subconjunctival scarring by encouraging fibroblasts to regrow through pores in its matrix. The device biodegrades in 90 to 180 days.

In my opinion, there is no question that antimetabolites improve the success rate of glaucoma surgery. Should specialists compare Ologen to MMC and possibly discontinue using the latter? A former fellow and I compared the EX-PRESS device with MMC versus the Ologen.[2] We randomized 50 patients to receive either the Ologen or MMC during bleb filtration surgery. The final IOP at 1 year was in the low teens for both groups, and there was no statistical

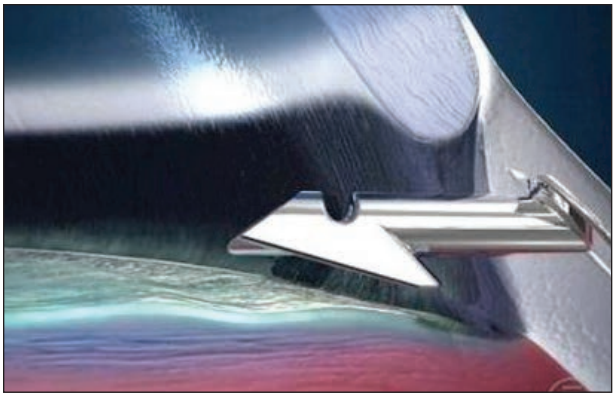

Figure 1. The EX-PRESS device (with a scleral flap).

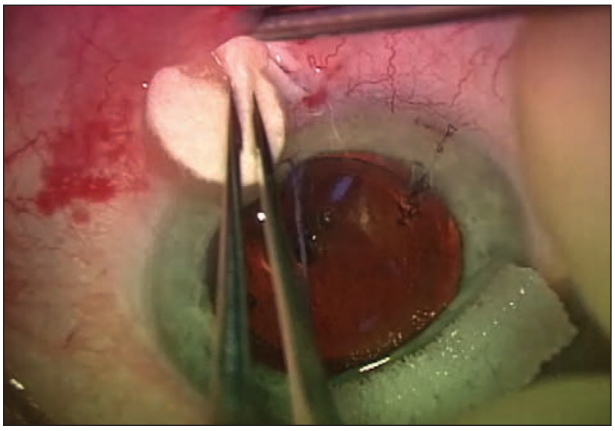

Figure 2. The bleb of the Ologen implant is low and diffuse as the collagen matrix starts to biodegrade at 3 months.

significance between the two groups. There are some small studies in which the Ologen produced a higher IOP than MMC, but these studies were retrospective and underpowered, and many of them used the older version of the Ologen, which was manufactured with a different type of collagen than the atelocollagen the brand currently uses.

The learning curve for the Ologen involves using fewer sutures and tying them more loosely.[3] Unlike MMC blebs that tend to be thin and avascular and therefore prone to leaks, Ologen blebs are thicker and gently vascular. They rest a little higher than MMC blebs, but they carry a lower risk of infection while maintaining IOP at a similar level to MMC.[2]

Figure 3. The Mitosol standardized MMC product.

MITOSOL AND SUBCONJUNCTIVAL MMC

The advent of Mitosol was another important development for treating glaucoma. Previously, clinicians acquired MMC from compounding pharmacies for off-label applications, and there were some reports of drug shortages, delivery delays, and differences in the concentrations of mixed batches. Mitosol is a standardized MMC product with FDA labeling (Figure 3). Its components come prepackaged so that technicians can mix it up before surgery, ensuring the concentration and freshness of each batch. I now use Mitosol exclusively instead of compounding, and I have found it to be very predictable.

Many doctors have switched from using sponges soaked with MMC to injecting it directly into the subconjunctiva. The advantages of MMC injections are lower diffuse blebs, more diffuse wound modulation, and significantly less time intraoperatively, because the surgeon does not have to wait for MMC to soak into the subconjunctiva via a sponge. Since adopting this approach several years ago, I have been very pleased with the low diffuse appearance of my blebs, and I have had no adverse complications. My rates of hypotony and bleb leakage have not increased. My standard filtration surgery includes the EX-PRESS with the Ologen for routine glaucoma patients. I use Mitosol for patients with very thick tenons or those at a very high risk for failure, because the Ologen cannot be titrated. I can also increase the concentration as necessary.

MIGS AND ECP

I am performing less filtration surgery than ever before, thanks to endoscopic cyclophotocoagulation (ECP) and microinvasive glaucoma surgery (MIGS). Although I have performed ECP for almost a decade, adding it after phacoemulsification usually only decreases patients' medication load by one. The iStent Trabecular Micro Bypass (Glaukos) is the only FDA-approved MIGS device. I combine ECP (E2 Microprobe Laser and Endoscopy System; Endo Optiks) and the iStent in a procedure called *ICE*, or iStent, cataract surgery, endoscopic cyclophotocoagulation. This three-in-one procedure is safe because it uses no bleb and it combines two MIGS procedures, one that decreases aqueous production (ECP), and one that increases aqueous outflow (the iStent). This approach is the surgical equivalent to having a patient on an aqueous suppressant plus a prostaglandin analog. β-blockers, carbonic anhydrase inhibitors, and α-agonists are aqueous suppressants, and prostaglandin analogs increase aqueous outflow. The benefit of the surgical option over the pharmacologic one, however, is that the former combines nicely with phacoemulsification.

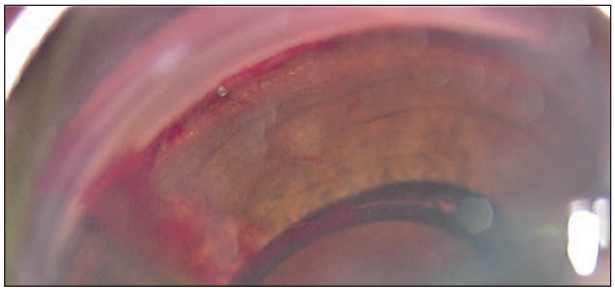

Figure 4. The iStent viewed with the endoprobe.

With ICE, I perform fewer filtration surgeries. I am also examining the efficacy of ICE with a group of other investigators; we presented our long-term data at the Annual Meeting of the American Society of Cataract and Refractive Surgery and the European Society of Cataract and Refractive Surgery in 2014.[4] ECP is an excellent procedure; I do not think surgeons should stop performing it in favor of using the iStent. ECP has indications that the iStent does not have, namely in patients with narrow-angle glaucoma.

CONCLUSIONS

Glaucoma surgeons are constantly seeking to raise the standard of care. Our armamentarium and practice patterns will continue to expand and shift as more devices gain FDA approval and early adopters push them into clinical use. The technologies I have described are making a positive impact on my practice, and I look forward to continued research into their applications and efficacy. ■

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Two Objectives, One Surgery

Using cataract surgery to lower IOP in glaucoma patients.

BY REAY BROWN, MD

When glaucoma patients develop cataract, performing cataract surgery can help to manage their glaucoma. Historically, however, surgeons often have delayed cataract surgery in glaucoma patients because of a fear of greater operative risk. Although it is true that glaucomatous eyes are more likely to have smaller pupils, shallower chambers, and greater postoperative intraocular pressure (IOP) spikes, most cataract surgery performed in glaucoma patients is routine. Furthermore, a growing body of evidence supports the benefits of cataract surgery in reducing the IOP in most types of glaucoma—especially in angle closure.

CATARACT SURGERY AS A TREATMENT FOR OPEN-ANGLE GLAUCOMA

The 2008 article by Poley et al on the long-term effects of phacoemulsification/IOL implantation on normotensive and hypertensive eyes[1] placed the treatment of glaucoma with cataract surgery squarely in the spotlight. Although many previous studies had shown an IOP reduction following cataract surgery, the magnitude was small and considered clinically insignificant. The insight of Poley et al was to stratify the patients by their preoperative IOP, which showed that the pressure reduction was proportional to the preoperative IOP. This is the effect we want in glaucoma treatment—the patients

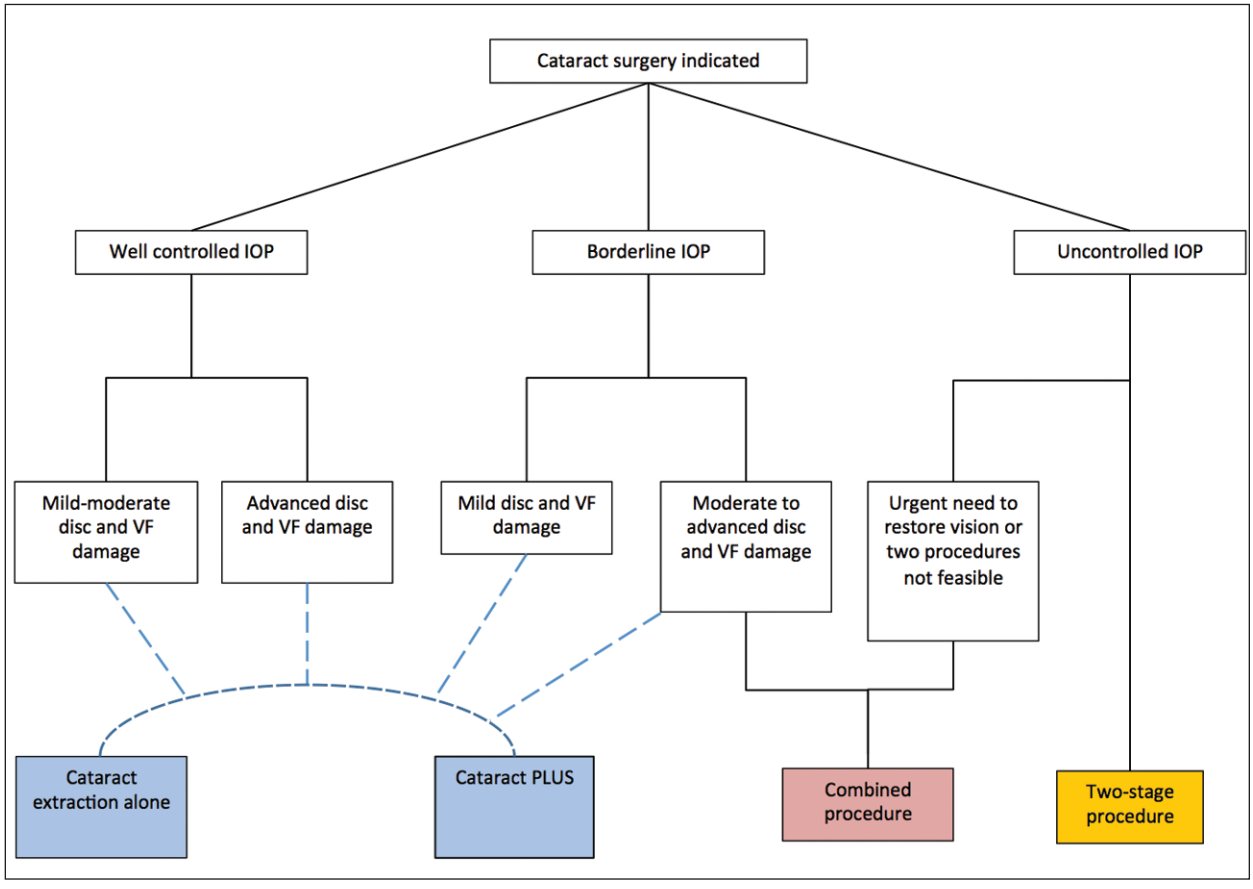

Figure 1. Surgical options for eyes with cataract and glaucoma. (Reprinted from: Brown RH, Zhong L, Lynch MG. Lens-based glaucoma surgery: Using cataract surgery to reduce intraocular pressure. *J Cataract Refract Surg*. 2014;40(8):1255-1262, with permission from Elsevier.)

"When a glaucoma patient needs cataract surgery, there are three choices: cataract surgery alone, cataract surgery "plus" a microincisional glaucoma surgery (MIGS) procedure, and cataract surgery combined with a trabeculectomy. "

with the higher IOPs experience the greatest pressure reduction. Patients in the study with a preoperative IOP of 23 mm Hg or higher had a mean pressure reduction of 6.5 mm Hg. Such a substantial reduction in pressure following cataract surgery has led to the concept of "lens-based" glaucoma surgery.[2]

When a glaucoma patient needs cataract surgery, there are three choices: cataract surgery alone, cataract surgery "plus" a microincisional glaucoma surgery (MIGS) procedure, and cataract surgery combined with a trabeculectomy. The accompanying flowchart (Figure 1) shows a decision tree for planning which operation to use. If the pressure is not too elevated, I have favored either cataract surgery by itself or cataract surgery plus a MIGS procedure. In most cases, I will implant an iStent Trabecular Micro-Bypass Stent (Glaukos) along with the cataract surgery. This does not increase the risk of the cataract operation, but it may improve the IOP-lowering effect, so it seems like a good option. See the article in the August edition of the *Journal of Cataract & Refractive Surgery*[2] for an in-depth description of my decision tree for cataract surgery in glaucoma patients.

Cataract surgery can be particularly helpful in patients with either open or closed angles on maximal medical therapy who have IOPs that are still unacceptable. If the IOP is not markedly high, cataract surgery—perhaps in conjunction with an iStent if the angle is open[3]—can be enough to reach an acceptable pressure. The benefits of this approach may lead me to recommend surgery a little sooner than I would if the IOP were not elevated. However, it is important to be realistic. Cataract surgery alone will not reduce every raised IOP to a normal level; some patients still need a trabeculectomy to achieve an acceptable IOP.

ANGLE-CLOSURE GLAUCOMA

Cataract surgery can be beneficial in all phases of angle-closure glaucoma. Removing the lens following an acute attack has been shown to be more effective than laser iridotomy in controlling subsequent pressures and preventing future IOP spikes.[4] In chronic angle-closure patients with uncontrolled IOP, performing cataract surgery alone is nearly as effective as a phacotrabeculectomy in controlling pressure, and much safer.[5] Many studies have shown that cataract surgery can deepen the anterior chambers of shallow angle closure eyes to nearly normal depths.[2] This may be the mechanism of the benefit of cataract surgery in improving IOP.

IS CLEAR LENS EXTRACTION A REASONABLE OPTION?

Since the favorable effects of lens removal should not depend on the presence of a lens opacity, some surgeons have suggested clear lens extraction as a treatment for angle closure. I recently published a paper in which clear lens extraction was performed as an alternative to trabeculectomy in three eyes with angle closure and elevated IOP despite maximal medical therapy (all three were on multiple medications).[6] Lens removal achieved a dramatic improvement in pressure, and two of the three patients are free of all medications 6 years after surgery. The success of lens removal in angle closure has led to the undertaking of an international study to help determine the best way to use lens removal to help patients with angle closure.

CONCLUSION

Cataract surgery is a great option to help lower IOP in glaucoma patients. This approach can truly improve the lives of glaucoma patients, lowering their IOP and reducing their medication load. Patient selection is critical, however. Some glaucoma patients will still need a trabeculectomy or a tube-shunt to achieve a satisfactory IOP. In angle closure, cataract surgery can be effective, even in cases of markedly elevated pressures. In open-angle glaucoma, cataract surgery—perhaps in combination with an iStent—is most successful in patients with pressures that are either medically controlled or only modestly elevated. Lens-based glaucoma surgery is an opportunity to help our glaucoma patients see more clearly and reduce their future risk from pressure damage. ■

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BRIEF SUMMARY OF PRESCRIBING INFORMATION

INDICATIONS AND USAGE

SIMBRINZA® (brinzolamide/brimonidine tartrate ophthalmic suspension) 1%/0.2% is a fixed combination of a carbonic anhydrase inhibitor and an alpha 2 adrenergic receptor agonist indicated for the reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension.

DOSAGE AND ADMINISTRATION

The recommended dose is one drop of SIMBRINZA® Suspension in the affected eye(s) three times daily. Shake well before use. SIMBRINZA® Suspension 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.

DOSAGE FORMS AND STRENGTHS

Suspension containing 10 mg/mL brinzolamide and 2 mg/mL brimonidine tartrate.

CONTRAINDICATIONS

Hypersensitivity - SIMBRINZA® Suspension is contraindicated in patients who are hypersensitive to any component of this product.

Neonates and Infants (under the age of 2 years) - SIMBRINZA® Suspension is contraindicated in neonates and infants (under the age of 2 years*) see Use in Specific Populations*

WARNINGS AND PRECAUTIONS

Sulfonamide Hypersensitivity Reactions - SIMBRINZA® Suspension contains brinzolamide, a sulfonamide, and although administered topically is absorbed systemically. Therefore, the same types of adverse reactions that are attributable to sulfonamides may occur with topical administration of SIMBRINZA® Suspension. Fatalities have occurred due to severe reactions to sulfonamides including Stevens-Johnson syndrome, toxic epidermal necrolysis, fulminant hepatic necrosis, agranulocytosis, aplastic anemia, and other blood dyscrasias. Sensitization may recur when a sulfonamide is re-administered irrespective of the route of administration. If signs of serious reactions or hypersensitivity occur, discontinue the use of this preparation *[see Patient Counseling Information]*

Corneal Endothelium - Carbonic anhydrase activity has been observed in both the cytoplasm and around the plasma membranes of the corneal endothelium. There is an increased potential for developing corneal edema in patients with low endothelial cell counts. Caution should be used when prescribing SIMBRINZA® Suspension to this group of patients.

Severe Renal Impairment - SIMBRINZA® Suspension has not been specifically studied in patients with severe renal impairment (CrCl < 30 mL/min). Since brinzolamide and its metabolite are excreted predominantly by the kidney, SIMBRINZA® Suspension is not recommended in such patients.

Acute Angle-Closure Glaucoma - The management of patients with acute angle-closure glaucoma requires therapeutic interventions in addition to ocular hypotensive agents. SIMBRINZA® Suspension has not been studied in patients with acute angle-closure glaucoma.

Contact Lens Wear - The preservative in SIMBRINZA® Suspension, benzalkonium chloride, may be absorbed by soft contact lenses. Contact lenses should be removed during instillation of SIMBRINZA® Suspension but may be reinserted 15 minutes after instillation *[see Patient Counseling Information]*.

Severe Cardiovascular Disease - Brimonidine tartrate, a component of SIMBRINZA® Suspension, has a less than 5% mean decrease in blood pressure 2 hours after dosing in clinical studies; caution should be exercised in treating patients with severe cardiovascular disease.

Severe Hepatic Impairment - Because brimonidine tartrate, a component of SIMBRINZA® Suspension, has not been studied in patients with hepatic impairment, caution should be exercised in such patients.

Potentiation of Vascular Insufficiency - Brimonidine tartrate, a component of SIMBRINZA® Suspension, may potentiate syndromes associated with vascular insufficiency. SIMBRINZA® Suspension should be used with caution in patients with depression, cerebral or coronary insufficiency, Raynaud's phenomenon, orthostatic hypotension, or thromboangiitis obliterans.

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 have 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]*.

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

SIMBRINZA® Suspension - In two clinical trials of 3 months duration 435 patients were treated with SIMBRINZA® Suspension, and 915 were treated with the two individual components. The most frequently reported adverse reactions in patients treated with SIMBRINZA® Suspension occurring in approximately 3 to 5% of patients in descending order of incidence were blurred vision, eye irritation, dysgeusia (bad taste), dry mouth, and eye allergy. Rates of adverse reactions reported with the individual components were comparable. Treatment discontinuation, mainly due to adverse reactions, was reported in 11% of SIMBRINZA® Suspension patients.

Other adverse reactions that have been reported with the individual components during clinical trials are listed below.

Brinzolamide 1% - In clinical studies of brinzolamide ophthalmic suspension 1%, the most frequently reported adverse reactions reported in 5 to 10% of patients were blurred vision and bitter, sour or unusual taste. Adverse reactions occurring in 1 to 5% of patients were blepharitis, dermatitis, dry eye, foreign body sensation, headache, hyperemia, ocular discharge, ocular discomfort, ocular keratitis, ocular pain, ocular pruritus and rhinitis.

The following adverse reactions were reported at an incidence below 1%: allergic reactions, alopecia, chest pain, conjunctivitis, diarrhea, diplopia, dizziness, dry mouth, dyspnea, dyspepsia, eye fatigue, hypertonia, keratoconjunctivitis, keratopathy, kidney pain, lid margin crusting or sticky sensation, nausea, pharyngitis, tearing and urticaria.

Brimonidine Tartrate 0.2% - In clinical studies of brimonidine tartrate 0.2%, adverse reactions occurring in approximately 10 to 30% of the subjects, in descending order of incidence, included oral dryness, ocular hyperemia, burning and stinging, headache, blurring, foreign body sensation, fatigue/drowsiness, conjunctival follicles, ocular allergic reactions, and ocular pruritus.

Reactions occurring in approximately 3 to 9% of the subjects, in descending order included corneal staining/erosion, photophobia, eyelid erythema, ocular ache/pain, ocular dryness, tearing, upper respiratory symptoms, eyelid edema, conjunctival edema, dizziness, blepharitis, ocular irritation, gastrointestinal symptoms, asthenia, conjunctival blanching, abnormal vision and muscular pain.

The following adverse reactions were reported in less than 3% of the patients: lid crusting, conjunctival hemorrhage, abnormal taste, insomnia, conjunctival discharge, depression, hypertension, anxiety, palpitations/arrhythmias, nasal dryness and syncope.

Postmarketing Experience - The following reactions have been identified during postmarketing use of brimonidine tartrate ophthalmic solutions in clinical practice. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. The reactions, which have been chosen for inclusion due to either their seriousness, frequency of reporting, possible causal connection to brimonidine tartrate ophthalmic solutions, or a combination of these factors, include: bradycardia, hypersensitivity, iritis, keratoconjunctivitis sicca, miosis, nausea, skin reactions (including erythema, eyelid pruritus, rash, and vasodilation), and tachycardia.

Apnea, bradycardia, coma, hypotension, hypothermia, hypotonia, lethargy, pallor, respiratory depression, and somnolence have been reported in infants receiving brimonidine tartrate ophthalmic solutions *[see Contraindications]*.

DRUG INTERACTIONS

Oral Carbonic Anhydrase Inhibitors - There is a potential for an additive effect on the known systemic effects of carbonic anhydrase inhibition in patients receiving an oral carbonic anhydrase inhibitor and brinzolamide ophthalmic suspension 1%, a component of SIMBRINZA® Suspension. The concomitant administration of SIMBRINZA® Suspension and oral carbonic anhydrase inhibitors is not recommended.

High-Dose Salicylate Therapy - Carbonic anhydrase inhibitors may produce acid-base and electrolyte alterations. These alterations were not reported in the clinical trials with brinzolamide ophthalmic suspension 1%. However, in patients treated with oral carbonic anhydrase inhibitors, rare instances of acid-base alterations have occurred with high-dose salicylate therapy. Therefore, the potential for such drug interactions should be considered in patients receiving SIMBRINZA® Suspension.

CNS Depressants - Although specific drug interaction studies have not been conducted with SIMBRINZA® Suspension, the possibility of an additive or potentiating effect with CNS depressants (alcohol, opiates, barbiturates, sedatives, or anesthetics) should be considered.

Antihypertensives/Cardiac Glycosides - Because brimonidine tartrate, a component of SIMBRINZA® Suspension, may reduce blood pressure, caution in using drugs such as antihypertensives and/or cardiac glycosides with SIMBRINZA® Suspension is advised.

Tricyclic Antidepressants - Tricyclic antidepressants have been reported to blunt the hypotensive effect of systemic clonidine. It is not known whether the concurrent use of these agents with SIMBRINZA® Suspension in humans can lead to resulting interference with the IOP lowering effect. Caution is advised in patients taking tricyclic antidepressants which can affect the metabolism and uptake of circulating amines.

Monoamine Oxidase Inhibitors - Monoamine oxidase (MAO) inhibitors may theoretically interfere with the metabolism of brimonidine tartrate and potentially result in an increased systemic side-effect such as hypotension. Caution is advised in patients taking MAO inhibitors which can affect the metabolism and uptake of circulating amines.

USE IN SPECIFIC POPULATIONS

Pregnancy - *Pregnancy Category C:* Developmental toxicity studies with brinzolamide in rabbits at oral doses of 1, 3, and 6 mg/kg/day (20, 60, and 120 times the recommended human ophthalmic dose) produced maternal toxicity at 6 mg/kg/day and a significant increase in the number of fetal variations, such as accessory skull bones, which was only slightly higher than the historic value at 1 and 6 mg/kg. In rats, statistically decreased body weights of fetuses from dams receiving oral doses of 18 mg/kg/day (180 times the recommended human ophthalmic dose) during gestation were proportional to the reduced maternal weight gain, with no statistically significant effects on organ or tissue development. Increases in unossified sternebrae, reduced ossification of the skull, and unossified hyoid that occurred at 6 and 18 mg/kg were not statistically significant. No treatment-related malformations were seen. Following oral administration of ^{14}C-brinzolamide to pregnant rats, radioactivity was found to cross the placenta and was present in the fetal tissues and blood.

Developmental toxicity studies performed in rats with oral doses of 0.66 mg brimonidine base/kg revealed no evidence of harm to the fetus. Dosing at this level resulted in a plasma drug concentration approximately 100 times higher than that seen in humans at the recommended human ophthalmic dose. In animal studies, brimonidine crossed the placenta and entered into the fetal circulation to a limited extent.

There are no adequate and well-controlled studies in pregnant women. SIMBRINZA® Suspension should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers - In a study of brinzolamide in lactating rats, decreases in body weight gain in offspring at an oral dose of 15 mg/kg/day (150 times the recommended human ophthalmic dose) were observed during lactation. No other effects were observed. However, following oral administration of ^{14}C-brinzolamide to lactating rats, radioactivity was found in milk at concentrations below those in the blood and plasma. In animal studies, brimonidine was excreted in breast milk.

It is not known whether brinzolamide and brimonidine tartrate are excreted in human milk following topical ocular administration. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from SIMBRINZA® (brinzolamide/brimonidine tartrate ophthalmic suspension) 1%/0.2%, 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 - The individual component, brinzolamide, has been studied in pediatric glaucoma patients 4 weeks to 5 years of age. The individual component, brimonidine tartrate, has been studied in pediatric patients 2 to 7 years old. Somnolence (50-83%) and decreased alertness was seen in patients 2 to 6 years old. SIMBRINZA® Suspension is contraindicated in children under the age of 2 years *[see Contraindications]*.

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

OVERDOSAGE

Although no human data are available, electrolyte imbalance, development of an acidotic state, and possible nervous system effects may occur following an oral overdose of brinzolamide. Serum electrolyte levels (particularly potassium) and blood pH levels should be monitored.

Very limited information exists on accidental ingestion of brimonidine in adults; the only adverse event reported to date has been hypotension. Symptoms of brimonidine overdose have been reported in neonates, infants, and children receiving brimonidine as part of medical treatment of congenital glaucoma or by accidental oral ingestion. Treatment of an oral overdose includes supportive and symptomatic therapy; a patent airway should be maintained.

PATIENT COUNSELING INFORMATION

Sulfonamide Reactions - Advise patients that if serious or unusual ocular or systemic reactions or signs of hypersensitivity occur, they should discontinue the use of the product and consult their physician.

Temporary Blurred Vision - Vision may be temporarily blurred following dosing with SIMBRINZA® Suspension. Care should be exercised in operating machinery or driving a motor vehicle.

Effect on Ability to Drive and Use Machinery - As with other drugs in this class, SIMBRINZA® Suspension may cause fatigue and/or drowsiness in some patients. Caution patients who engage in hazardous activities of the potential for a decrease in mental alertness.

Avoiding Contamination of the Product - Instruct patients that ocular solutions, if handled improperly or if the tip of the dispensing container contacts the eye or surrounding structures, can become contaminated by common bacteria known to cause ocular infections. Serious damage to the eye and subsequent loss of vision may result from using contaminated solutions *[see Warnings and Precautions]*. Always replace the cap after using. If solution changes color or becomes cloudy, do not use. Do not use the product after the expiration date marked on the bottle.

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

Concomitant Topical Ocular Therapy - If more than one topical ophthalmic drug is being used, the drugs should be administered at least five minutes apart.

Contact Lens Wear - The preservative in SIMBRINZA® Suspension, benzalkonium chloride, may be absorbed by soft contact lenses. Contact lenses should be removed during instillation of SIMBRINZA® Suspension, but may be reinserted 15 minutes after instillation.

U.S. Patent No:
6,316,441

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For the treatment of elevated IOP

UNLOCK TREATMENT POSSIBILITIES

SIMBRINZA® Suspension delivered 21-35% mean IOP reduction at Month 3[1-3]

- 1-3 mm Hg greater than either component[4]
- Efficacy proven in two pivotal Phase 3 randomized, multicenter, double-masked, parallel-group, 3-month, 3-arm, contribution-of-elements studies. Primary objective of studies was to compare IOP-lowering efficacy of SIMBRINZA® Suspension, brinzolamide, 1%, and brimonidine, 0.2%. IOP was measured at 8am, 10am, 3pm, and 5pm[1,2]
- The most frequently reported adverse reactions in a 6-month clinical trial in patients treated with SIMBRINZA® Suspension occurring in approximately 3-7% of patients were eye irritation, eye allergy, conjunctivitis, blurred vision, dysgeusia (bad taste, conjunctivitis allergic, eye pruritus, and dry mouth[5]
- Only available beta-blocker-free fixed combination[2,3]

INDICATIONS AND USAGE

SIMBRINZA® (brinzolamide/brimonidine tartrate ophthalmic suspension) 1%/0.2% is a fixed combination indicated in the reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension.

Dosage and Administration
The recommended dose is one drop of SIMBRINZA® Suspension in the affected eye(s) three times daily. Shake well before use. SIMBRINZA® Suspension 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.

IMPORTANT SAFETY INFORMATION

Contraindications
SIMBRINZA® Suspension is contraindicated in patients who are hypersensitive to any component of this product and neonates and infants under the age of 2 years.

Warnings and Precautions
Sulfonamide Hypersensitivity Reactions—Brinzolamide is a sulfonamide, and although administered topically, is absorbed systemically. Sulfonamide attributable adverse reactions may occur. Fatalities have occurred due to severe reactions to sulfonamides. Sensitization may recur when a sulfonamide is readministered irrespective of the route of administration.
If signs of serious reactions or hypersensitivity occur, discontinue the use of this preparation.

Corneal Endothelium—There is an increased potential for developing corneal edema in patients with low endothelial cell counts.

Severe Hepatic or Renal Impairment (CrCl <30 mL/min)—SIMBRINZA® Suspension has not been specifically studied in these patients and is not recommended.

Contact Lens Wear—The preservative in SIMBRINZA® Suspension, benzalkonium chloride, may be absorbed by soft contact lenses. Contact lenses should be removed during instillation of SIMBRINZA® Suspension but may be reinserted 15 minutes after instillation.

Severe Cardiovascular Disease—Brimonidine tartrate, a component of SIMBRINZA® Suspension, had a less than 5% mean decrease in blood pressure 2 hours after dosing in clinical studies; caution should be exercised in treating patients with severe cardiovascular disease.

Adverse Reactions
In two clinical trials of 3 months' duration with SIMBRINZA® Suspension, the most frequent reactions associated with its use occurring in approximately 3-5% of patients in descending order of incidence included: blurred vision, eye irritation, dysgeusia (bad taste), dry mouth, and eye allergy. Adverse reaction rates with SIMBRINZA® Suspension were comparable to those of the individual components. Treatment discontinuation, mainly due to adverse reactions, was reported in 11% of SIMBRINZA® Suspension patients.

Drug Interactions—Consider the following when prescribing SIMBRINZA® Suspension:
Concomitant administration with oral carbonic anhydrase inhibitors is not recommended due to the potential additive effect. Use with high-dose salicylate may result in acid-base and electrolyte alterations. Use with CNS depressants may result in an additive or potentiating effect. Use with antihypertensives/cardiac glycosides may result in additive or potentiating effect on lowering blood pressure. Use with tricyclic antidepressants may blunt the hypotensive effect of systemic clonidine and it is unknown if use with this class of drugs interferes with IOP lowering. Use with monoamine oxidase inhibitors may result in increased hypotension.

For additional information about SIMBRINZA® Suspension, please see Brief Summary of full Prescribing Information on adjacent page.

Learn more at myalcon.com/simbrinza

SIMBRINZA®
(brinzolamide/brimonidine tartrate ophthalmic suspension) 1%/0.2%

ONE BOTTLE. MANY POSSIBILITIES.

References: 1. Katz G, DuBiner H, Samples J, et al. Three-month randomized trial of fixed-combination brinzolamide, 1%, and brimonidine, 0.2% [published online ahead of print April 11, 2013]. *JAMA Ophthalmol.* doi:10.1001/jamaophthalmol.2013.188. **2.** Nguyen QH, McMenemy MG, Realini T, et al. Phase 3 randomized 3-month trial with an ongoing 3-month safety extension of fixed-combination brinzolamide 1%/brimonidine 0.2%. *J Ocul Pharmacol Ther.* 2013;29(3): 290-297. **3.** Data on file, 2013. **4.** SIMBRINZA® Suspension Package Insert. **5.** Whitson JT, Realini T, Nguyen QH, McMenemy MG, Goode SM. Six-month results from a Phase III randomized trial of fixed-combination brinzolamide 1% + brimonidine 0.2% versus brinzolamide or brimonidine monotherapy in glaucoma or ocular hypertension. *Clin Ophthalmol.* 2013;7:1053-1060.

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