Supplement to

July/August 2015

Glaucoma TODAY

Glaucoma Disease Diagnosis and Management Update

A review of the latest developments in the field.

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Glaucoma Disease Diagnosis and Management Update

BY STEVEN D. VOLD, MD

Both the diagnosis and management of glaucoma continue to evolve at a rapid rate. Advancements in diagnostic testing allow clinicians to both diagnose glaucoma at earlier stages as well as more accurately detect glaucoma progression. Our understanding of how potential glaucoma risk factors, such as IOP fluctuation and corneal hysteresis actually impact disease progression, is also coming into clearer view. Intraocular IOP sensors and corneal biomechanical measurements are quickly becoming significant additions to the glaucoma diagnostic technology library.

The glaucoma treatment paradigm has also been impacted by a variety of advances in medical therapy as well. These include the availability of additional fixed-combination agents, preservative-free medication alternatives, improved laser technologies, and more minimally invasive glaucoma procedures. The use of generic medications now plays a much more prominent role in medical glaucoma treatment than in the past, as well. How generic medications impact glaucoma patient care is yet to be fully elucidated. Glaucoma medication side effect profiles and increasing medication costs also influence clinical decision-making, patient medical compliance, and ultimately glaucoma outcomes.

In this supplement, several key leaders in our field share their impressions as to where we are now as well as future directions in glaucomatous disease diagnosis and management. ■

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ADD SIMBRINZA® Suspension to a PGA for Even Lower IOP[1]*

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

SIMBRINZA® Suspension

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.

Prescribe SIMBRINZA® Suspension as adjunctive therapy to a PGA for appropriate patients

SIMBRINZA® Suspension should be taken at least five (5) minutes apart from other topical ophthalmic drugs

Learn more at myalcon.com/simbrinza

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

Reference: 1. Data on file, 2014.

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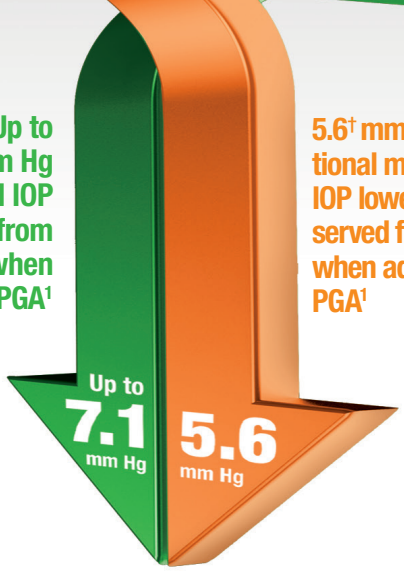
Up to 7.1 mm Hg additional IOP reduction from baseline when added to a PGA[1]

5.6† mm Hg additional mean diurnal IOP lowering observed from baseline when added to a PGA[1]



		IOP Time Points (mm Hg)†‡			
Treatment Arm		8 AM	10 AM	3 PM	5 PM
PGA + SIMBRINZA® Suspension (N=83)	Baseline§	24.5	22.9	21.7	21.6
	Week 6	19.4	15.8	17.2	15.6
PGA + Vehicle (N=92)	Baseline§	24.3	22.6	21.3	21.2
	Week 6	21.5	20.3	20.0	20.1

‡Least squares means at each Week 6 time point. Treatment differences (mm Hg) and *P*-values at Week 6 time points between treatment groups were: -2.14, *P*=0.0002; -4.56, *P*<0.0001; -2.84, *P*<0.0001; -4.42, *P*<0.0001.
§Baseline (PGA Monotherapy).

		Mean Diurnal IOP (mm Hg)‖
Treatment Arm		
PGA + SIMBRINZA® Suspension (N=83)	Baseline¶	22.7
	Week 6	17.1
PGA + Vehicle (N=92)	Baseline¶	22.4
	Week 6	20.5

‖Treatment difference (mm Hg) and *P*-value at Week 6 was -3.4, *P*<0.0001.
¶Baseline (PGA Monotherapy).

Study Design: A prospective, randomized, multicenter, double-blind, parallel-group study of 189 patients with open-angle glaucoma and/or ocular hypertension receiving treatment with a PGA. PGA treatment consisted of either travoprost, latanoprost, or bimatoprost. Patients in the study were randomized to adjunctive treatment with SIMBRINZA® Suspension (N=88) or vehicle (N=94). The primary efficacy endpoint was mean diurnal IOP (IOP averaged over all daily time points) at Week 6 between treatment groups. Key secondary endpoints included IOP at Week 6 for each daily time point (8 AM, 10 AM, 3 PM, and 5 PM) and mean diurnal IOP change from baseline to Week 6 between treatment groups.[1]

*PGA study-group treatment consisted of either travoprost, latanoprost, or bimatoprost.
†Treatment difference (mm Hg) and *P*-value at Week 6 was -3.7, *P*<0.0001.

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

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.

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The Role of Visual Field in Assessing Glaucoma

Information gleaned from visual field testing is additive in assessing patients' glaucoma and risk for progression.

BY STEVEN R. SARKISIAN JR, MD

Like most of the prognostic and diagnostic information we gather in the clinic to assess the status of a glaucoma suspect or patient, visual field (VF) data is best utilized in the context of all the data points collected. Properly understanding where a patient is on the continuum of the glaucoma spectrum involves the ocular and systemic history, optic nerve findings, results of visual field testing and other imaging (if warranted), a complete eye examination, and measurement of the IOP. In truth, not one of these is necessarily more important than another.

ROLE OF VF TESTING

The great hope in glaucoma is that we will be able to predict exactly who will progress from ocular hypertension to glaucoma, and when a patient develops glaucoma, we will be able to know which patients require more urgent follow up due to their risk of progression. Sadly, however, that level of prognostic specificity is not possible with our current technology.

I tell my patients that the automated VF machine is measuring an island in a sea of darkness. The entire island does not just sink into the sea all at once when the glaucoma winds blow, but rather it erodes slowly over time. This is why glaucomatous damage sneaks up on people, and, therefore, why regular VF testing can be helpful to detect glaucoma progression before it becomes symptomatic if the glaucoma is diagnosed in a timely fashion.

TYPES OF VF TESTING

There are various forms of VF testing, some of which may be more appropriate for monitoring glaucoma than others. Confrontation VF testing is part of the basic eye examination and should be performed on all patients on a regular basis. Frequency doubling perimetry (FDT) is considered a screening test by most ophthalmologists and has not been generally adopted by glaucoma specialists as being the standard for following patients with well-defined VF defects over time. However, as FDT targets ganglion cells in the magnocellular pathway, the portion of the ganglion cell layer responsible for transmitting information about flicker and motion, this test may in fact be predictive of early glaucomatous changes.[1,2]

Automated perimetry, such as the Humphrey VF, is the generally accepted method of measuring the VF and monitoring for

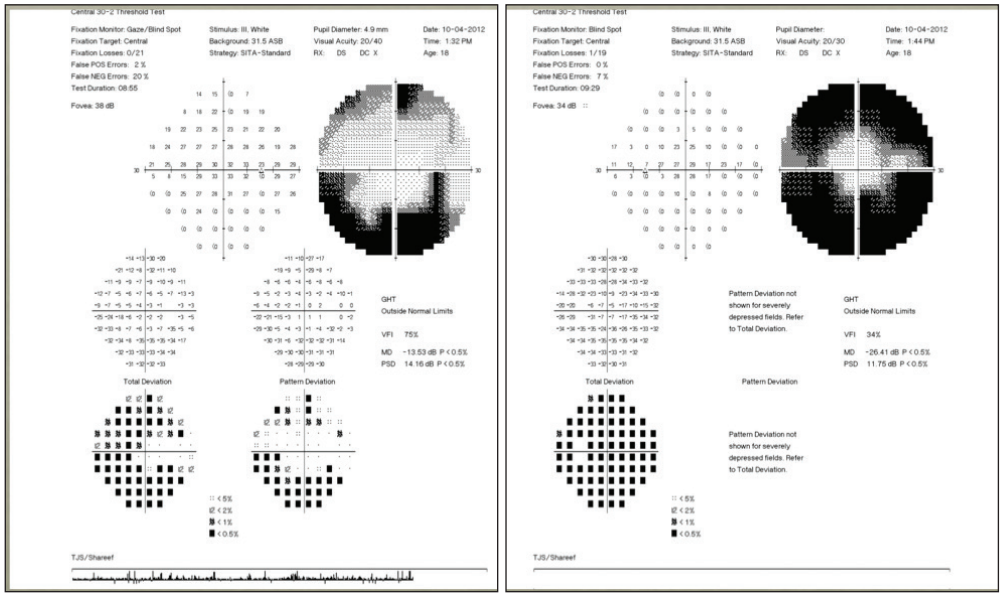

Photo courtesy of Shakeel Shareef, MD

Figure 1. A Humphrey 30-2 Swedish interactive thresholding algorithm standard visual field test of the patient's right and left eyes following her referral.

progression. Some patients are unable to fixate for the duration of the Humphrey test or are otherwise unable to complete the test, and so manual perimetry, such as Goldman Perimetry, may be required.

The most typical pattern of VF loss in patients with glaucoma is around the central 24° to 30° on standard automated perimetry (SAP), which makes sense given the loss of arcuate fibers of the retinal nerve fiber layer in the inferior hemifield that is hallmark of early glaucomatous progression. However, SAP is not specific to the involved ganglion subtypes of this region, and, thus, patients quite typically experience optic nerve damage prior to displaying visual field defect on SAP testing.

Given the lack of specificity in SAP, testing algorithms have been devised to amplify changes indicative of early glaucomatous progression—that is, testing that targets the cells most typically damaged by early glaucomatous changes. Notably, the Swedish Interactive Threshold Algorithm (SITA) used on the Humphrey perimeter maps the dimmest stimuli that will be detected 50% of the time in 54 points on the macula in the 24-2 VF test (and on 76 points in the 30-2 VF test) and determines threshold values for each location in relation to nearby points using a mathematical algorithm. This potentially delivers a precise and repeatable pattern on the VF test output. Such a testing algorithm can be combined with short-wavelength automated perimetry (SWAP) in select patients (ie, those who can fixate through the long duration of the test time and who do not have significant nuclear sclerosis) to detect early ganglion cell loss changes, perhaps even before optic nerve damage occurs.

SWAP testing takes advantage of the koniocellular pathway and has been shown to identify early glaucomatous changes.[3,4] However, it is prone to test-retest variability and is limited by media opacities. Additionally, the time required for fixation is long and intolerable to some patients, although its incorporation in Humphrey 24-2 testing shortens the test time and lessens the variability of outcomes.

INCORPORATING VF IN PRACTICE

With all of these various tests available, the question becomes how to incorporate them into practice. And, again, the answer is that it depends on the context. For patients referred to my practice with a SITA Fast VF test or a frequency doubling VF test, I will conduct a SITA standard Humphrey VF. I rarely use the SITA Fast in my practice, because it is not the best test to monitor progression over time. In reality, a SITA Standard HVF may only take an extra couple of minutes compared to a SITA Fast and if you perform a 24-2, rather than a 30-2, the timing is often equivalent.

If the patient has preperimetric glaucoma, I may consider getting a SITA-SWAP protocol Humphrey VF to detect for early loss if the optic nerve imaging shows early nerve fiber layer thinning. However, the ability to conduct the test will depend on the patient's ability to fixate.

For patients presenting with low vision, it may be necessary to increase the target size; however, in my experience, most of these patients are able to perform the Humphrey 10-2 test.

Recent studies tracking usage patterns of VF and other imaging devices, namely OCT, have shown that VF testing has unfortunately fallen out of favor.[5] It appears that some physicians are relying on advanced imaging alone, rather than both imaging and VF testing.

OCT on its own is not enough for the definitive diagnosis of glaucoma, although it can be crucial for monitoring over time. Imaging studies do play a significant role in diagnosing glaucoma, yet they should not be used in the absence of VF testing—the exception being patients in whom the Humphrey VF is normal. In such patients, it may be possible to repeat the Humphrey VF every couple of years if the OCT continues to be stable. Such cases may be rare, however, and I would truly only consider this in my most reliable and compliant glaucoma suspects and patients with ocular hypertension who have been stable for a reasonable period of time and who show up to all of their appointments.

CONCLUSION

Humphrey VF changes are fundamentally useful in managing glaucoma. If a patient has a confirmed, repeatable glaucoma-related VF defect that is progressing, this is a clear indicator for more advanced treatment. Alternatively, if the Humphrey VF is stable, it may be plausible to defer more advanced treatment, even if the IOP is borderline.

Unfortunately, you cannot rely on VF alone, and you must look at it in the context of the entire history and examination. Yet, VF testing remains a crucial and central component of composing a complete clinical picture of the individual glaucoma patient. ■

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The Role of Fixed-Combination Agents in Management of Glaucoma

Evolving treatment standards may include a more prominent role for combination agents as adjuvant therapy.

BY TONY REALINI, MD, MPH

Prostaglandin analogue (PGA) therapy is a first-line mainstay for treating patients with glaucoma. However, some patients will require adjunctive therapy to achieve the target IOP. A smaller subset of patients may not tolerate prostaglandins and may require a switch to a different class of medicines.

Fixed-combination agents are becoming a popular choice for adjunctive therapy to PGAs or as alternative therapy if PGA therapy is inappropriate, ineffective, or poorly tolerated. There are three fixed-combinations available in the United States: dorzolamide hydrochloride 2.0%/timolol 0.5% was approved by the US Food and Drug Administration (FDA) almost 20 years ago; brimonidine 0.2%/timolol 0.5% (Combigan, Allergan) has been in use for about 10 years; and, more recently, brinzolamide 1%/brimonidine 0.2% (Simbrinza, Alcon) was approved by the FDA.

THE ROLES OF FIXED-COMBINATION AGENTS

To gain regulatory approval, each of these products went through rigorous phase 3 clinical trials as monotherapy. Each has demonstrated efficacy and safety that generally mirrors concomitant dosing with constituent agents. However, each of these agents was approved after the introduction of PGAs. Thus, despite data supporting their first-line efficacy and safety, these fixed combinations have been uncommonly used as first-line therapy for glaucoma.

Instead, they are typically used as adjunctive therapy. Historically, clinicians have followed the adage: start low and go slow. This axiom dictates that we should add one drug at a time, so as to best assess the incremental additivity of efficacy and clearly attribute new safety issues to the newly added single agent.

This paradigm is now in transition. The reality is that adding a single agent—whether it is a β-blocker, a carbonic anhydrase inhibitor (CAI), or brimonidine—to a PGA generally provides only 2 mm Hg to 4 mm Hg of additional IOP reduction, on average. It is true that some patients will have greater IOP reductions than the average, but others will have even less. If PGA therapy provides IOP reduction to within 2 mm Hg to 4 mm Hg of the target IOP, a single agent adjunct is an entirely reasonable strategy.

> Fixed-combination agents are becoming a popular choice for adjunctive therapy to PGAs or as alternative therapy if PGA therapy is inappropriate, ineffective, or poorly tolerated.
>
> —*Tony Realini, MD, MPH*

But if PGA therapy falls far short of achieving target IOP, adding a single agent may not be the most effective next step.

Fixed-Combinations as First Adjunct

For a patient in whom the IOP is inadequately controlled on PGA monotherapy, a fixed-combination may be the appropriate first adjunct. A series of industry-sponsored phase 4 clinical trials have demonstrated that, when added to a PGA, the various fixed-combinations provide an average of 5 to 8 mmHg of additional IOP reduction. This exceeds the expected benefit of single-agent therapy and may provide adequate IOP control using a two-bottle, three-drop regimen.

There are sound arguments against adding two drugs at once. We cannot know for certain that a single agent would not have been enough unless we try it. Incrementally adding constituents is a reasonable alternative but requires several extra office visits. We run the

risk of exposing patients to the side effects of drugs they may not need. We also cannot be certain which agent may be responsible for any new side effects that appear after adding a fixed-combination. However, we are well familiar with the adverse event profiles of all the constituents and can usually infer the causative component when a safety issue arises. Also, some fixed-combinations are only available as branded products and are more expensive than their generic constituents.

Ultimately, the decision to use a fixed-combination as a first adjunct, versus stepwise addition of constituent agents, should be made on an individual patient basis considering all of these issues. If the incremental approach is used and the need for two adjuncts is established, strong consideration should be given to dosing the two adjuncts as a fixed-combination, as there are numerous important benefits of fixed-combination therapy over concomitant dosing.

PROS AND CONS OF COMBINATION AGENTS

There are many advantages to fixed-combinations over concurrent administration of constituent drugs and some disadvantages that clinicians should be aware of before incorporating them into practice.

Some studies support an improved rate of adherence with therapy when the fixed-combination is used. Adherence decreases as the therapeutic regimen becomes more complex,[1-3] and fixed-combination agents can help simplify a multi-bottle, multi-drop regimen.

Likewise, fixed-combinations may avoid problems associated with use of multiple drops, such as the potential washout effect if a second drop is instilled too soon after a first drop.[4] Also, patients may be more likely to regularly refill the prescriptions when on a regimen that includes a fixed-combination.[5] There are potential cost savings for patients using fixed-combination agents, especially for those with drug coverage (ie, one copayment versus two). However, patients without insurance or those without prescription drug coverage may realize cost savings from two concomitant generics versus a branded fixed-combination.

There are some downsides to using fixed-combination agents that physicians should be aware of. Namely, it is not possible to titrate the concentration, frequency, or timing of dosage of the constituents in a fixed-combination. For instance, some patients may need adjunctive β-blockers once daily, but with dorzolamide/timolol or brimonidine/timolol, double that dose is required if the fixed-combination is prescribed twice daily, as its label indicates.

SELECTING A FIXED-COMBINATION

Once the decision is made to add a fixed-combination to the IOP-lowering regimen, the attributes of the various fixed-combinations should drive the selection process. In terms of efficacy, the three combinations available in the US are roughly comparable in efficacy when added to a PGA—although there are relatively few studies to inform us, so the characterization of their adjunctive efficacy and safety profiles remains incomplete.

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Cost is another matter. Some of these combinations are now available in generic formulations while others remain branded products. If cost is a factor—as it is for the uninsured, those without pharmacy benefits, or those in the Medicare doughnut hole—generic options may be the best choice.

Safety issues can also drive the selection process. Two of the three combinations contain the β-blocker timolol. There is nothing inherently wrong with β-blockers. Indeed, prior to the PGA era, β-blockers formed the cornerstone of glaucoma therapy. However, of the many glaucoma drugs available, β-blockers have the most serious potential side effects and the most contraindications, of which symptomatic bradycardia, second-degree AV block, and reactive airway disease head the list. Theoretical contraindications, such as diabetes, depression, and erectile dysfunction, have not been established in clinical study as potential safety issues, nor have they been observed at clinically meaningful rates, even in studies of systemic β-blocker therapy.

In addition to the safety issues discussed above, the use of β-blockers for IOP reduction may pose efficacy issues as well. The frustrating truth is that, at least in most US studies, β-blockers provide minimal additional IOP reduction when added to PGAs. For this reason, there are no fixed-combination agents containing both a PGA and a β-blocker in the United States (there are three such products available in ex-US markets).

Another issue is the use of systemic β-blockers. Glaucoma patients are generally older and are usually taking several medications to control concomitant chronic conditions. Use of oral β-blockers for control of systemic hypertension is common in this population. In these patients, topical β-blockers—and fixed-combinations

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IOP Fluctuation and Risk of Glaucoma: Is There a Link?

Autonomous IOP monitoring devices under development may improve our understanding of this important question.

BY MALIK Y. KAHOOK, MD

The effect of IOP fluctuation on the risk of developing glaucoma and/or glaucoma progression has been studied for years. To this point, however, we do not have definitive answers as to what defines a significant fluctuation, whether it is in fact relevant to the disease process, and, if it is, how we can adjust our interventions to decrease the amplitude of IOP peak and trough.

IOP fluctuations are generally understood to occur in the short-, intermediate-, and long-term. Short-term fluctuations are those that occur during various activities such as sitting or lying down, blinking, or other physical activities. Intermediate-term fluctuations occur during any given day (diurnal and nocturnal) and are the result of the sum of various short-term fluctuations as well as longer-term changes in the habitual position (ie, standing, sitting, supine), along with inherent differences in aqueous production and outflow (ie, the circadian rhythm of aqueous flow) that are present in all patients. Long-term fluctuations are those that occur between visits and are influenced by various factors, such as disease progression (ie, deterioration in outflow facility with higher IOP) and changes in therapy (ie, added medications leading to lower average IOP) among other factors. What is more difficult to answer is the actual influence of all of these fluctuations on disease presence and progression.

One difficulty with assessing and quantifying fluctuations is that inter-visit differences rely on data points spread months apart in the average patient visiting glaucoma clinics. Using these snapshot IOPs to determine whether fluctuations exist is unreasonable. Until there are long-term IOP tracking devices, much of what is discussed in regard to IOP fluctuation is academic with little practical application.

BACKGROUND: A NEED FOR BETTER DATA

As with many things in glaucoma, the effect of IOP fluctuations and its implications is not at all straightforward. However, several major clinical trials have attempted to answer questions about the effects of fluctuations.

An analysis of patients enrolled in the Advanced Glaucoma Intervention Study (AGIS) suggested that IOP fluctuation was predictive of worsening of visual fields, but, interestingly, only among patients with low mean IOP at the time of study enrollment.[1] Patients enrolled in the study who fell within the study's upper tercile of mean IOP did not exhibit a statistically significant increased risk of visual field worsening based on whether there was inter-visit fluctuations in IOP. Based on about 7 years of follow up, the AGIS investigators found that increasing age and greater IOP fluctuation increased the odds of visual field progression; the latter persisted as a risk factor among patients who both did and did not undergo cataract extraction.[2]

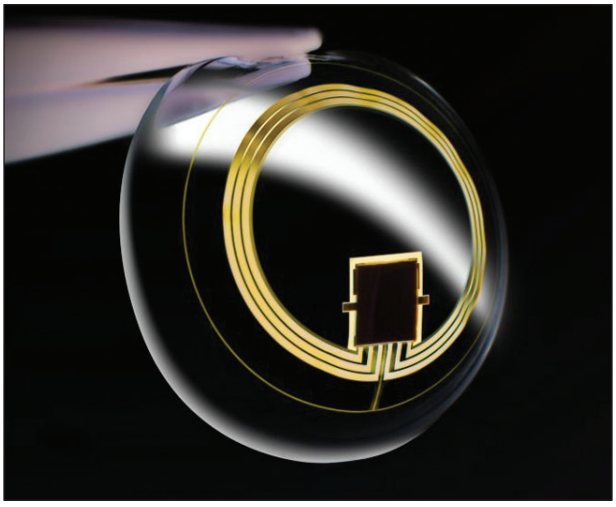

Figure 1. Autonomous IOP gauges, such as the one introduced by Sensimed, which functions as a strain gauge to continuously measure IOP fluctuation over a 24-hour period, will be crucial in better understanding the effects of pressure fluctuation on developing glaucoma or disease progression.

At the opposite end of the spectrum, investigators in the Early Manifest Glaucoma Treatment study[3] and the European Glaucoma Prevention Study (EGPS)[4] found no correlation between inter-visit IOP fluctuation and risk of glaucoma progression. An analysis of patients enrolled in

the Diagnostic Innovations in Glaucoma Study (DIGS)[5] found no correlation between IOP variability and risk of developing glaucoma. An analysis of both the OHTS and EGPS studies performed by researchers not affiliated with either study suggested that variability in IOP after enrollment and randomization were more likely to develop primary open-angle glaucoma.[6]

Published retrospective and population studies,[7-9] as well as studies using at-home monitoring performed by patients, suggest a link between IOP fluctuation and risk of glaucoma. However, the methodology of these studies and/or small number of enrollees limits the ability to draw definitive conclusions from their findings.

The sum total of all these data is that the correlation between IOP fluctuation and risk of progressing from ocular hypertension or to worsen glaucoma is inconclusive. There may be several reasons why. First, patient populations are not the same from study to study. Some of these studies enrolled patients with early glaucoma while others involved patients with later stages of the disease. If the outcomes of the AGIS study are to be believed, patients with lower IOP who experience fluctuations may be more prone to progression. Second, different instruments and methods were used to determine IOP in the studies—and in some cases, the conclusions rely on patients checking their pressure at home. A third (and very important) point is that the definition of IOP fluctuation is different from study to study. Some of these studies looked at diurnal fluctuation while others looked at long-term, inter-visit variation in IOP readings. Also very important, some studies failed to take into account the influence of added medications or laser/surgical intervention during the follow-up period and how this might have influenced the amplitude of IOP fluctuation.

TOWARD BETTER DATA

Twenty-four-hour IOP sleep studies have been proposed as a way to better understand IOP fluctuation. However, one issue with sleep studies is that once patients are placed in the very controlled environment of the study, the applicability of the findings to real-world scenarios may be limited. In other words, patients are likely not going through their normal daily routines that may include exercise, climbing stairs, running from meeting to meeting, or drinking coffee, and, therefore, we cannot extrapolate directly from the artificial environment of a well-controlled sleep lab.

What is needed to better understand the effects of 24-hour changes in IOP is a measuring device that would be independent of both the patient and investigator in measuring pressure throughout the day. Several companies are working on such a device. One proposed device was introduced by Sensimed and utilizes a noninvasive contact lens with a strain gauge (Figure 1). This device measures architectural changes at the limbus that may occur secondary to pressure changes; thus, it is not a direct measure of IOP change, per se, but rather a gauge of curvature change as a function of pressure fluctuation.

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There are also a number of companies studying implantable devices that are either coupled with an intraocular lens or might be implanted inside the eye or in the sclera. These devices are, for the most part, in the preclinical phase or the early clinical phase of validation to see if they actually correlate with gold standard pressure measurement, which is still Goldmann applanation—which is to say, we do not have a good understanding of how reliable their output will be.

BUT THEN WHAT?

The prospect of definitively measuring IOP fluctuations over a 24-hour period and how the data might correlate to developing glaucoma or disease progression is interesting academically. But how will we apply the newfound data in a practical manner to help our patients?

There are a number of ongoing studies looking at different medication classes, laser, and the various surgeries that can be performed and how they might flatten the IOP curve during the 24-hour period. Right now we know that some medication classes might be more effective than others at controlling night-time pressure: prostaglandin analogs work well at night, relatively speaking, whereas β-blockers appear to not work very well at night.[10] We know that laser trabeculoplasty appears to flatten the diurnal/nocturnal curve, but we do not know much about surgical interventions such as trabeculectomy and glaucoma drainage devices and what they actually do for pressure over a 24-hour period.[11]

I anticipate that sometime in the next 5 years we will have reliable devices for measuring 24-hour IOP fluctuations. With that, we should see an explosion in research to tease out whether fluctuations matter, and if so, how best to flatten the diurnal/nocturnal curve. However, for now and into the immediate future, there are simply too many

unanswered questions about the role of IOP fluctuation in the development or progression of glaucoma for us to substantially change our current clinical practices. ■

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that contain β-blockers—lower IOP les effectively than in patients not using oral β-blockers.[6]

Thus, for patients with contraindications to β-blocker therapy or those on systemic β-blockers, a fixed-combination that does not contain a β-blocker might be a reasonable choice.

CONCLUSION

Fixed-combination agents provide a reasonable choice for adjunctive therapy in patients requiring additional IOP lowering. In clinical practice, fixed-combinations may improve therapeutic compliance and offer additional advantages. However, they also have limitations, including the inability to titrate dosages of the individual components. When selecting a fixed-combination product, attributes of both the patient and the drug should be considered in order to optimize the efficacy and safety of the medical regimen. ■

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The Knowns and Unknowns of Generic Medications

Are the unknowns about generic medications enough to give us pause in using them for routine therapy?

BY NATHAN M. RADCLIFFE, MD

In 2015, doctors and glaucoma patients are navigating a pharmaceutical market that is becoming increasingly focused on generic medications. However, physicians and patients—in fact, market consumers—do not have as much information on generic medications as we would like, because a big part of what makes generic medications inexpensive is the fact that the companies manufacturing the medications do not typically perform human clinical trials with those medications. Therefore, doctors and patients are left to make treatment decisions regarding generic medications in a way that balances costs, patient safety, and efficacy. Yet, generic medications are not always as cheap as one might expect. A recent analysis by the *Wall Street Journal* noted that generic drug costs are in fact "skyrocketing," with some medications costing 17,000% more than they had in the past.[1]

Further complicating the matter is that payer formularies shift frequently. For example, generic fixed combination medications may be placed on a third tier or higher while branded fixed combinations or prostaglandin analogs may have better positioning. Additionally, some of the more recently available generic prostaglandin analogs (eg, travoprost 0.004% and bimatoprost 0.03%) may not be listed on formularies or may not be available at some pharmacies. Thus, it is often unclear which generic alternatives are truly available and how they will be priced.

When considering generics versus brand-name medications, we can categorize the issues into known and unknown factors.

WHAT WE KNOW

We know that in the late 1990s, problems with the formulations of generic nonsteroidal anti-inflammatory drugs (NSAID) caused problems.[2] Generic diclofenac was implicated in almost 200 cases of corneal melting and was eventually recalled. This case continues to serve as a cautionary tale that unexpected problems can arise from generic formulations.

According to standards from the US Food and Drug Administration (FDA), generic medications must be formulated similarly to the innovator (branded) product, and the concentrations of active ingredients must fall within 10% of the innovator product. But several recent studies demonstrate that important differences can still exist. Kahook and colleagues[3] studied the ability of generic dorzolamide-timolol and latanoprost to withstand thermal challenges compared to the brand-name counterpart. The study demonstrated that some formulations of generic latanoprost did not contain the required amount of the drug, falling more than 10% below the recommended levels. After a thermal stress, bottles of generic latanoprost fell even further below the benchmark, whereas the branded product demonstrated superior stability. Finally, several bottles of generic medications had higher levels of particulate matter than the brand name medication.

Similarly, a study by Canadian researchers found that generic medications differed from their brand name counterparts in terms of bottle volume, viscosity, surface tension, and bottle tip.[4] The important point here is that a generic bottle that has more or fewer drops might technically meet FDA requirements for bioequivalence, but in the hands of the patient, the medication could run out sooner, could deliver less medication, could waste more drops, or might be more prone to spillage. These differences could leave patients without their eye drops, which could lead to vision loss.

In several cases, the generic formulations of pressure-lowering molecules have been replaced by alternative formulations that have demonstrated a better safety profile, such as a lower risk of allergy or hyperemia. For example, generic brimonidine 0.2%, generic bimatoprost 0.03%, and travoprost 0.004% with benzalkonium chloride have been discontinued by the innovator companies in favor of alternate formulations that were felt to provide better safety profiles or that were more suitable to patients' needs. Thus, in some cases, generic alternatives that are suggested by the pharmacist or the insurance plan will not have the same safety or efficacy profile. For example, Myers and colleagues[5] were able to demonstrate that patients who were switched from generic latanoprost to branded Lumigan 0.01% (Allergan) achieved a significant

intraocular pressure reduction. The amount of pressure reduction achieved from the switch was roughly 4 mmHg, which is also the amount of pressure reduction one might expect from adding a second medication to latanoprost. This is concerning, because generic latanoprost is often suggested as a formulary alternative to latanoprost.

WHAT WE DO NOT KNOW

There are some issues regarding generic medications that have been identified as potential issues, but there is not yet enough information in the public sphere for us to ultimately decide. Cost is a great example of this. It is generally assumed that generic medications will be less expensive; however this is not only the case always the case, and the clinician is not able to tell in which circumstances savings will be large, small, or negligible. Without this information, it is impossible to balance the risks and benefits of a generic versus branded medication.

Another known issue that has unknown implications is the value of the brand itself. In our society, we tend to be enamored with brand name products. We want to wear brand name jeans, drink brand name soda, and populate brand name restaurants, and that is because we know what we are getting. In a marketplace driven by the principle of caveat emptor, predictability and reliability are important factors for consumers. It is likely that these same principles apply to the medications we put in our bodies. I think patients feel safer knowing that a drug has a track record of safety and efficacy. They prefer to know that the drugs we are prescribing have been studied in well-controlled clinical trials, because that supplies assurance of predictability and reliability.

It is known that patients have difficulty taking their medications—and confusion about which medication to take and when to take it is part of the problem. Part of the inherent value of a brand is the ability to recognize the product and to know its manufacturer and packaging is consistent over time. For example, it is implicitly the case that Cosopt (Merck) is an easier name to recognize then dorzolamide hydrochloride 2% timolol maleate 0.5% solution. In my clinical experience, the long title of the generic medication often leads patients to misreport the medication they are taking to their internist, often leaving off one of the two medications contained in the fixed combination product. This can result in the incorrect medication being refilled, and it also creates confusion, even with trained ophthalmic technicians. How much of a problem is caused by confusion regarding the names of generic medications, however, remains unknown.

Another unknown is how much disruption of care is caused each year when prescription plan formularies arbitrarily change the tiers of branded medications, forcing clinicians to change a patient's medication and disrupting their routine care. Although a change may save dollars paid out at the pharmacy, do increased office visits caused by these changes cancel out those costs?

Because patients may get confused about their medications, I believe the practice of starting a patient off on a generic medication and moving him or her to a brand if the first line generic is not effective is a suboptimal one, because this strategy may confuse the patient by exposing him or her to several medicines. I recall a patient who was briefly treated on dorzolamide 5 years earlier who only seemed to remember the bottle with "the orange cap." For many patients, care is best streamlined if we can keep them on one medicine during their whole career as a patient. To do that, you want to pick the best one to start with; if that is a brand medicine, you would ideally like to start with that, because switching medicines and formulations—especially if there are different dosing requirements or instructions—causes confusion that interferes with compliance and that might hurt outcomes.

CONCLUSIONS

When I am starting a patient on topical therapy, I tell him or her that I want to pick the best medication for their particular needs, but that I need a little help. The patient will often do a good job of explaining what is on his or her mind. Some will let me know they are under financial duress, while others will tell me that they want me to use the medicine that I think is the best. I will never force a patient to use a medicine that will cause financial stress, but if the patient asks for the medicine I have the most confidence in, I will suggest a brand medicine—because not only do I have my clinical experience to rely on, but there is a lot more literature on branded medicines confirming their safety and efficacy in treating glaucoma. Furthermore, the potential to offer samples or enroll patients in assistance programs gives them a path to affording the medicines I believe they need to stave off vision loss from glaucoma. ■

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Side Effect Profiles of Glaucoma Drug Classes

Because of the various classes of medications available for use, it is often possible to switch patients off of drugs they may not be able to tolerate.

BY ROBERT J. NOECKER, MD, MBA

The agents used for treatment of glaucoma are generally safe and well tolerated, although there are some side effects that glaucoma specialist should be aware of in order to have a proper informed conversation with patients. This article reviews some of the more common side effects associated with the various classes of medications used for treating glaucoma.

PROSTAGLANDIN ANALOGUES

Prostaglandin analogues (PGAs) are systemically very safe and they are highly effective as a front line medication for controlling elevated IOP. The ocular side effects associated with PGAs are the ones we are most often concerned about. By and large, side effects of PGAs are not medically dangerous or vision threatening; in most cases, patients may be able to tolerate the side effect to gain the benefit of the medication. However, because most of the side effects of PGAs have cosmetic sequelae, and they may limit their utility as a single eye drug, insofar as the cosmesis will be that much more apparent if only one eye is affected.

In particular, hyperemia (Figure 1) is the most common side effect associated with PGAs and it most commonly occurs after instillation of the first dose. A patient's response to hyperemia is variable and hard to predict, although the condition is usually self-limiting and reversible.

Another side effect commonly associated with PGAs is periocular changes, which can vary in degree from reddening of the skin around the eye to increased pigmentation (darkening of the skin around the eye) in some patients (Figure 2). These tend to be related to getting the drug on the skin, so washing the drug off may alleviate it.

PGAs may cause an increase in fat atrophy around the eye, and so there may be a more sunken appearance to the eye—again, most likely due to excessive eye drop instillation and drug getting on the area around the eye. Patients with less fat around their eyes tend to have a more dramatic response. The condition is reversible if PGAs are stopped.

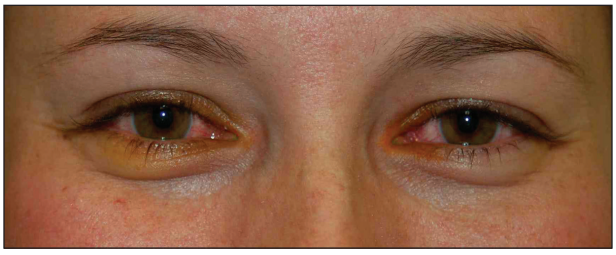

Figure 1. Hyperemia, as seen in this patient, is the most common side effect associated with PGAs.

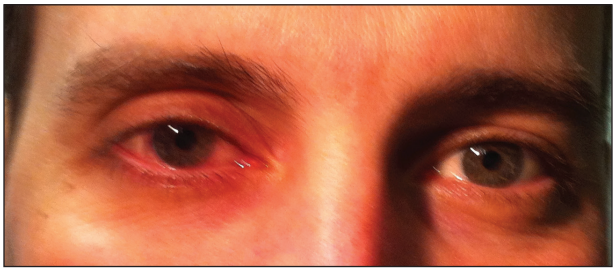

Figure 2. PGAs can cause reddening of the skin around the eye as seen in this patient.

One condition that may not be reversible is iris pigmentation, which although associated with all of the PGAs in the class, has been reported most frequently associated with latanoprost. Patients with hazel eyes are at highest risk, as an increase in melanosomes (which causes darkening of the iris appearance) will rarely be detectable in darker eyes. Patients with blue eyes are at lesser risk for iris pigmentation. Although not vision threatening, patients who are concerned about their hazel eye color should be advised of the risk of iris darkening.

PGAs have been associated with prolongation of inflammation. They do not cause inflammation de novo, but patients with inflammation, such as iritis or uveitis, can experience increased inflammation. Around the time of cataract surgery, there can be an increase in cell or flare postoperatively, which is treatable, but there is a risk of developing cystoid macular edema. As such, PGAs may not be vision threatening, but their use around the

time of cataract surgery can be additive in the risk of developing cystoid macular edema, which can be vision threatening if not detected and adequately addressed.

Another common issue with PGAs is eyelash growth, although this may be a desired effect in some patients. PGAs are used in some settings to intentionally spur eyelash growth; however, if the agent is used in only one eye, it will obviously be more detectable.

PGA INTOLERANCE: NEXT STEPS

Patients may be moved off of PGAs for a variety of reasons,[1-4] including lack of response to the initial therapy and/or because of intolerance of the side effects. Among patients in whom I started with a generic latanoprost and there was not adequate response, I would consider switching in the class to Lumigan (bimatoprost 0.01%, Allergan) or Travatan Z (travoprost 0.04%, Alcon) to get more efficacy. There are some patients who will not respond to any PGAs while others are more selective in their response. I believe it is worth the effort to attempt a switch before abandoning the class so that patients can stay on one bottle of therapy if possible.

My next level of intervention for patients after PGAs is to consider selective laser trabeculoplasty or to add additional medical therapy—either a single agent (α-agonist, carbonic anhydrase inhibitor [CAI], or β-blocker) or a fixed-combination agent. My experience has been that if a single agent (ie, the PGA) did not lower the pressure adequately, then the stakes have been raised and there is a need to get the pressure under control as quickly as possible. And so, I tend to add fixed-combination agents as adjunctive therapy, both for efficacy reasons, but also to simplify therapy and reduce exposure to multiple drops.

ADJUNCTIVE AGENT CLASSES

There are some known side effects with the classes of medications used for adjunctive therapy that are worth noting.

α-Agonist

Patients taking α-agonists, such as brimonidine, may develop an allergy to the medication over time. The active ingredient becomes oxidized, and patients begin to mount a local hypersensitivity and conjunctivitis. This tends to be dose-related and so does not typically occur after the first dose.

This class has also been associated with pupil changes in some patients; dry mouth (especially at high doses) if the drug becomes systemically absorbed and gets to back of throat; and changes in blood pressure (a rare side effect).

CAIs

CAIs are systemically safe, but dorzolamide 2% is acidic preparation and so it can cause some discomfort upon instillation. It can be affect the cornea and cause ocular surface changes. Brinzolamide (Azopt, Alcon) is a suspension, so blurred vision may occur, and a metallic taste in the mouth has also been reported by some patients.

β-Blocker

β-blockers have a fairly long list of known systemic effects, but they are well tolerated by the eye. The biggest concern with this class relates to respiratory and cardiac issues, namely bronchospasm, exacerbation of asthma, bradycardia, and exercise intolerance. There are also a number of infrequently occurring but potentially noteworthy side effects such as depression, decreased libido, and exacerbation of pre-existing heart problems.

CONCLUSION

The brand medications we use for treating glaucoma have all undergone rigorous testing to prove their safety and efficacy. Although generic medications are not subject to equivocal testing, they contain the same active ingredients as their brand comparators and, therefore, should not introduce any new side effects (although there is suggestion that certain generic formulation may be associated with higher rates of some side effects compared with their brand comparators). Nevertheless, because of the multiple classes of medication available for use, it is often possible to switch patients to other medications if they have a problem with tolerance. Laser trabeculoplasty remains a viable option for patients intolerant of medical therapy before the need for interventional surgery is entertained. ■

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