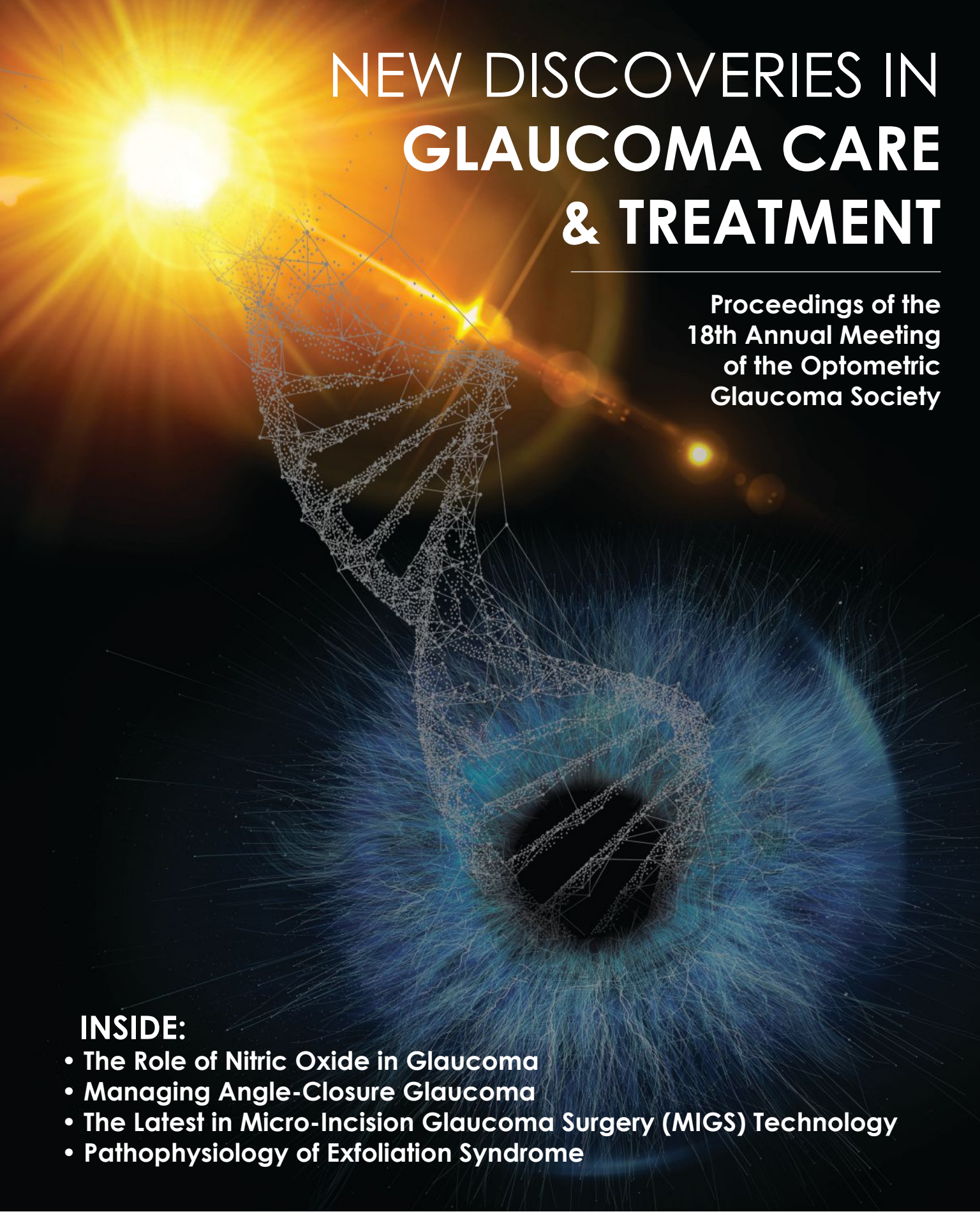

NEW DISCOVERIES IN GLAUCOMA CARE & TREATMENT

Proceedings of the 18th Annual Meeting of the Optometric Glaucoma Society

INSIDE:

- The Role of Nitric Oxide in Glaucoma
- Managing Angle-Closure Glaucoma
- The Latest in Micro-Incision Glaucoma Surgery (MIGS) Technology
- Pathophysiology of Exfoliation Syndrome

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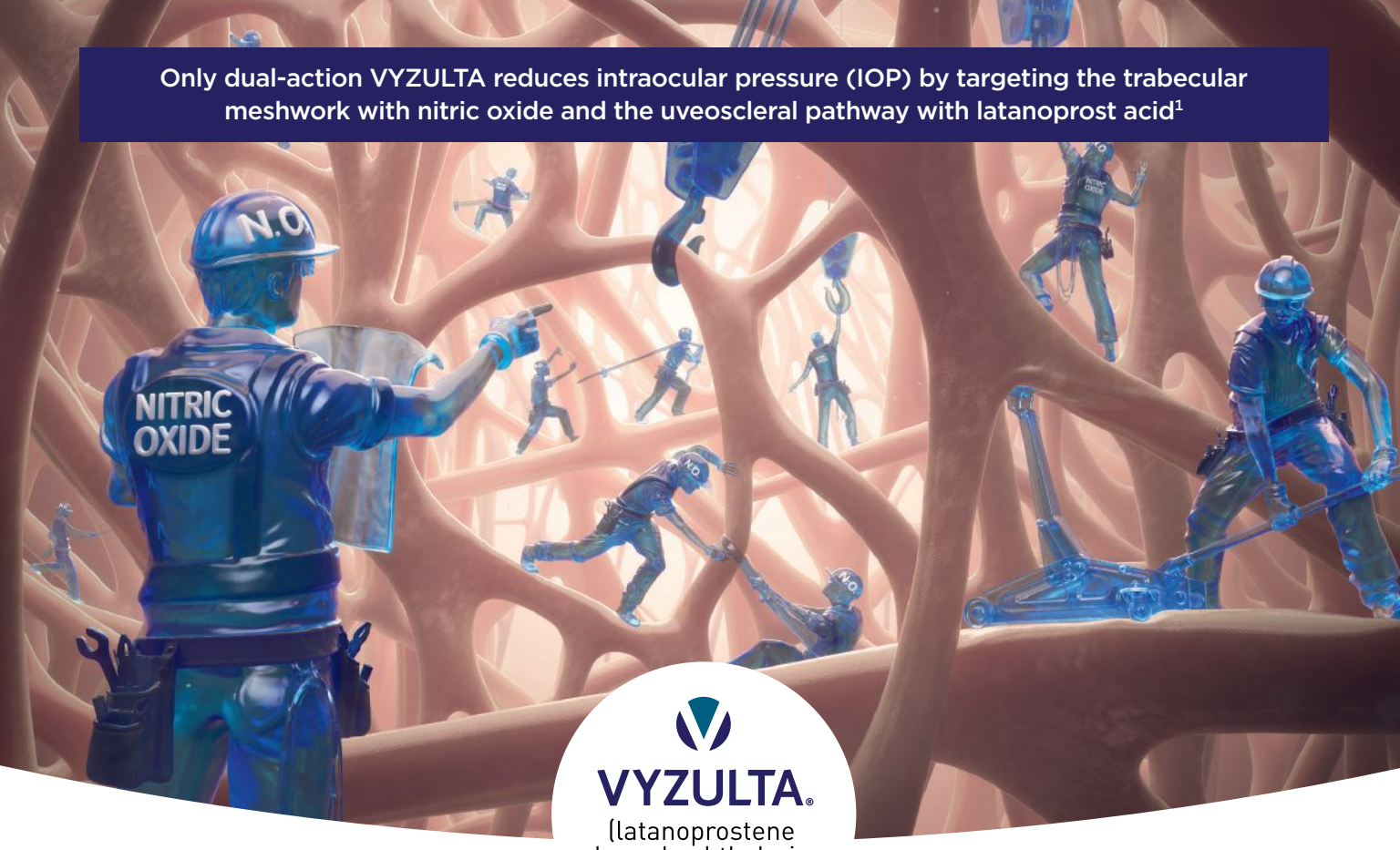
Supplement to
REVIEW OF OPTOMETRY
MARCH 2020



Only dual-action VYZULTA reduces intraocular pressure (IOP) by targeting the trabecular meshwork with nitric oxide and the uveoscleral pathway with latanoprost acid[1]

VYZULTA®
(latanoprostene bunod ophthalmic solution), 0.024%

EXPAND THE TRABECULAR MESHWORK WITH THE POWER OF NITRIC OXIDE[2-6]

VYZULTA achieved significant and sustained long-term IOP reductions vs Timolol 0.5% in pivotal trials[7]

P<0.001 vs baseline at all pre-specified visits over 12 months in a pooled analysis of APOLLO and LUNAR clinical trials (N=831)

VYZULTA demonstrated safety profile in clinical trials

Only 6 out of 811 patients discontinued due to ocular adverse events in APOLLO and LUNAR clinical trials[1,8,9]

Visit VYZULTANOW.com to see our efficacy results

INDICATION

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

IMPORTANT SAFETY INFORMATION

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

IMPORTANT SAFETY INFORMATION cont'd

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

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

References: 1. VYZULTA Prescribing Information. Bausch & Lomb Incorporated. **2.** Cavet ME. *J Ocul Pharmacol Ther*. 2018;34(1):52-60. DOI:10.1089/jop.2016.0188. **3.** Wareham LK. *Nitric Oxide*. 2018;77:75-87. DOI:10.1016/j.niox.2018.04.010. **4.** Stamer DW. *Curr Opin Ophthalmol*. 2012;23:135-143. DOI:10.1097/ICU.0b013e32834ff23e. **5.** Cavet ME. *Invest Ophthalmol Vis Sci*. 2015;56(6):4108-4116. **6.** Kaufman PL. *Exp Eye Research*. 2008;861:3-17. DOI:10.1016/j.exer.2007.10.007. **7.** Weinreb RN. *J Glaucoma*. 2018;27:7-15. **8.** Weinreb RN. *Ophthalmology*. 2016;123(5):965-973. **9.** Medeiros FA. *Am J Ophthalmol*. 2016;168:250-259.

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BRIEF SUMMARY OF PRESCRIBING INFORMATION

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

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

Initial U.S. Approval: 2017

1 INDICATIONS AND USAGE

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

4 CONTRAINDICATIONS

None

5 WARNINGS AND PRECAUTIONS

5.1 Pigmentation

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

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

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

5.2 Eyelash Changes

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

5.3 Intraocular Inflammation

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

5.4 Macular Edema

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

5.5 Bacterial Keratitis

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

5.6 Use with Contact Lens

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

6 ADVERSE REACTIONS

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

6.1 Clinical Trials Experience

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

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

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

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

The background risk of major birth defects and miscarriage for the indicated population is unknown. However, the background risk in the U.S. general population of major birth defects is 2 to 4%, and of miscarriage is 15 to 20%, of clinically recognized pregnancies.

Data

Animal Data

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

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

8.2 Lactation

Risk Summary

There are no data on the presence of VYZULTA in human milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered, along with the mother's clinical need for VYZULTA, and any potential adverse effects on the breastfed infant from VYZULTA.

8.4 Pediatric Use

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

8.5 Geriatric Use

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

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

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

13.2 Animal Toxicology and/or Pharmacology

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

U.S. Patent Numbers: 7,273,946; 7,629,345; 7,910,767; 8,058,467.

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INTRODUCTORY REMARKS

The 18th Annual Scientific Meeting of the Optometric Glaucoma Society (OGS), held Oct. 21-23, 2019, in Orlando, Fla., convened a distinguished group of researchers and clinicians in the field of glaucoma. These leaders engrossed practitioners with fresh insights on glaucoma characteristics, pathophysiology, and treatment—even covering ways genetics and *climatic factors* may play a role in glaucoma.

OGS Honoree Lecturer Louis Pasquale, MD, FARVO, dove deeply into biology to explain how endothelial cell dysfunction with impaired nitric oxide signaling is proving to be a pivotal secondary mechanism in primary open-angle glaucoma (POAG). Research is uncovering that nitric oxide signaling is not only involved in IOP regulation and optic nerve homeostasis, but that targeting the nitric oxide signaling pathway has provided structural neuroprotection in preclinical models—a significant revelation.

Shan Lin, MD, opened our eyes in the President's Lecture to angle-closure glaucoma's (ACG's) disturbing epidemiologic trends in individuals of Asian descent, emphasizing the importance of gonioscopy to see the angle. He discussed advancing imaging techniques and the challenge of selecting surgical interventions for patients over the short- and long-term. Sometimes, Dr. Lin said, taking no action is the right choice if pressure is controlled and the patient is happy with the status quo.

Although no surgery yields perfect results or comes risk-free, Constance O. Okeke, MD, MSCE, hit home why micro-incision glaucoma surgery (MIGS) fills an important need in glaucoma care. Though more effective glaucoma medications are available today, Dr. Okeke said that many patients just want to reduce the number of topical drugs they are using. She catalogued the major MIGS devices available by their mechanisms of action, and outlined postoperative care considerations for patients who undergo these procedures.

Dr. Pasquale returned with evidence that exfoliation syndrome is more than just a cause of open-angle glaucoma, it truly is a panocular disease. Studies are finding that the condition is not exclusive to Scandinavian populations and that it lacks a strong polygenetic underpinning. Rather, climatic exposures may hold powerful clues to the etiology of the condition. Believe it or not, solar reflectivity occurring in young adulthood could be the possible X-factor for exfoliation syndrome pathophysiology. Who knew?

This supplement, developed by *Review of Optometry*, was made possible with generous support from Bausch + Lomb.

Please visit the OGS website (www.optometricglaucomasociety.org) and consider signing up for our free, quarterly e-journal to keep up with the group's latest happenings, and developments in glaucoma diagnosis, treatment and management.

Murray Fingeret, OD
Founding Member & Past President, Optometric Glaucoma Society; President, Optometric Glaucoma Foundation

OGS Honoree Lecture

The Role of Nitric Oxide in Glaucoma

Louis R. Pasquale, MD, FARVO

Collectively, primary open-angle glaucoma (POAG) and primary-angle closure glaucoma (PACG) will constitute more than 100 million cases by the year 2040.[1] This staggering number is in part because people are living longer and the diseases are strongly age-related. So we need to get a better handle on understanding these conditions in order to effectively target treatments for them.

Looking at how we characterize POAG and PACG, the word "primary" in both monikers suggests there's no secondary causes for these glaucomas. As a point of fact, there must be many secondary factors for these complex diseases. And, indeed, there are many hypothesized secondary mechanisms for POAG. However, I don't think that patients fall into discrete buckets of pathophysiology; they likely have blends of pathophysiological states.

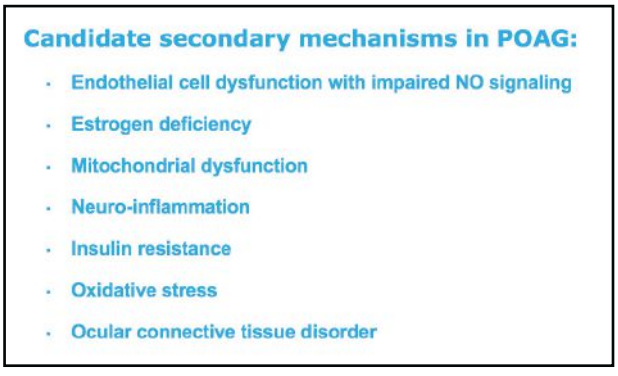

FIGURE 1. CANDIDATE SECONDARY MECHANISMS IN POAG.
Many secondary factors may be at play in primary open-angle glaucoma. *Images: Louis Pasquale, MD, FARVO*

The following discussion will focus on one reported secondary mechanism for POAG—endothelial cell dysfunction with impaired nitric oxide signaling—an area of research where I and others have concentrated a great deal of resources.

CASE OF PRESUMED NITRIC OXIDE-DEFICIENT GLAUCOMA

To better understand the role of nitric oxide signaling in glaucoma, it helps to examine a case study. I will focus on one patient whose thorough medical history provided my team with new clues about how microvascular issues occurring in other areas of the body may hold significance for glaucoma.

This 46-year-old Asian female with POAG came to me with visual acuity of 20/20 and maximum intraocular pressure (IOP) of 16 mmHg in both eyes. Her central corneal thickness (CCT) was 540 µm, the slit-lamp exam showed no signs of pigment dispersion syndrome, and her angles were open. Images of the optic nerves revealed nerve fiber layer defect in the right eye, with a superior nasal step visual field defect.

The medical history in this case was particularly significant. The woman had chronic fatigue, cold hands and feet, and difficulty sleeping at night. She also had very low body mass index and very low blood pressure, and her primary care doctor told her she had "autonomic dysfunction."

Interestingly, some of her fingernails were discolored and deformed, and a dermatologist had prescribed her a medication for a fungal infection. However, I knew that 46-year-old women didn't get fungal infections in their fingers on average. So my research team took a closer look using nailfold capillary microscopy—a method first described in the rheumatology literature to evaluate patients with Raynaud Syndrome, and classify and stratify people at risk of developing significant connective tissue diseases such as rheumatoid arthritis.

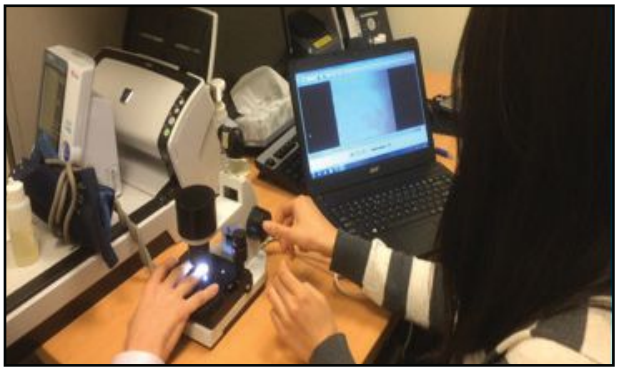

FIGURE 2. NAILFOLD CAPILLARY CONNECTION.
In the case of my 46-year-old Asian female POAG patient, some of the patient's fingernails were discolored and deformed, leading my research team to get a closer look with nailfold capillary microscopy to investigate a possible glaucoma connection.

In this case, the microscope was useful in illuminating capillary and red blood cells—which also move through the optic nerve—and morphological changes. Microscopy revealed regions without capillaries in the patient's nailfold bed. Since I have long suspected glaucoma to be a polygenetic disease involving some vascular genes, I expected that changes seen in the nailfold would be representative of changes occurring at the optic nerve head. After a thorough ophthalmic exam, it was clear the patient had about 18 hemorrhages in the extracellular space, and she exhibited several avascular zones.

My team went on to study this phenomenon in POAG patients with similar nailfold bed issues. In one study of 199 POAG patients and 124 controls, we examined the fourth and fifth digits of the subjects' nondominant hands with nailfold capillary video microscopy.[2] Masked graders evaluated videos for hemorrhages, dilated capillary loops >50 µm, and avascular zones >100 µm. We obtained multivariable odds ratios and 95% confidence intervals for POAG by logistic regression analyses, as well as corresponding estimates of severity based on the Hodapp-Anderson-Parrish scale.

Our group found that 80 percent of POAG subjects, regardless of their IOPs, had at least one hemorrhage in their fingernail per 100 capillaries, while just 30 percent of controls did.[2] The frequency of microvascular abnormalities wasn't associated with disease severity however ($p \geq 0.43$). We speculated that vascular abnormalities in the optic nerve, similar to those found in the nail bed, could render an individual susceptible to glaucomatous damage since POAG was a risk factor for having

nail bed hemorrhages.

NITRIC OXIDE & THE MICROVASCULATURE

Nitric oxide is important in the microvasculature for many reasons. At a basic level, nitric oxide is needed to keep the capillaries open, specifically at points of high shear stress in vascular beds. To better grasp its complex biological role, it's helpful to gain insights into discoveries about how nitric oxide functions.

Nitric oxide is a lightweight, colorless gas with a molar mass of 30g/mol. In 1998, Dr. Robert Furchgott, with two colleagues, won the Nobel Prize in Medicine for discovering that nitric oxide was the signaling molecule liberated from endothelial cells to mediate smooth muscle cell relaxation.

Leading up to that honor, Dr. Furchgott's lab was experimenting on *ex vivo* rabbit aortic rings at a time when evidence existed that endothelial cells exposed to acetylcholine would yield vasorelaxation. During one of the experiments, a technician exposed blood vessels to acetylcholine, and the vessels didn't dilate. The experiment failed because the technician had mechanically denuded the ring's vascular endothelium. Dr. Furchgott realized then that the signaling molecule had to be generated inside endothelial cells. This breakthrough eventually led to his team's discovery of nitric oxide's unique role as a signaling molecule in the cardiovascular system.

WHAT THE LITERATURE SAYS

A great deal of evidence suggests that nitric oxide signaling is important in glaucoma. In various studies, POAG patients demonstrate the following physiological characteristics: impaired retinal vascular autoregulation;[3] blunted brachial artery vasodilation in response to acetylcholine;[4] nailfold capillary morphological and hemodynamic abnormalities;[2,5] and reduced flow-mediated vasodilation.[6,7]

In experiments I conducted with Gil Feke in the early 2000s, we used Doppler velocimetry via a Canon Laser Blood Flowmeter to examine the retinal arteriole near the optic disc, and measured patients sitting and laying down. That simple positional maneuver uncovered an immense vascular dysregulation in the optic nerves of OAG patients that occurred across the IOP spectrum. In one study, OAG patients revealed significant (p=0.031) associations between baseline ocular perfusion pressure and a lack of autoregulated retinal blood flow response to posture change, compared with healthy controls.[3]

Research conducted by Colm O'Brien's team in 1999 assessed vascular endothelial function in individuals with normal pressure glaucoma (NTG).[4] In an intervention study, the group administered incremental doses of acetylcholine (an endothelial-dependent vasodilator) and found that the controls had a dose-dependent increase in forearm blood flow, which was blunted in untreated NTG patients.[4] The findings suggested a problem with endothelium-mediated vasodilatation in NTG initiated by acetylcholine and leading to the production of NOS3.[4]

Building on my earlier analyses of nailfold morphology, I was also involved with studies analyzing the hemodynamics of nailfold segment capillary beds in POAG.[2,5] Blood flow, it turned out, moved rapidly in normal patients, while it traveled dramatically slower in POAG. Imagine that the red blood cells were cars on a road, and it was as if the normal patients' cells were transiting on the Autobahn while the POAG patient's cells were moving along New York City's 5th Avenue at rush hour.

Other scientists evaluated peripheral vascular endothelial function in NTG and POAG subjects using noninvasive, endothelium-dependent, flow-mediated vasodilation (FMD) and ultrasonographic imaging of the brachial artery.[6] All individuals underwent blood sampling for biochemistry, lipid profile, and high sensitivity C-reactive protein analysis. Both sets of glaucoma subjects had impaired endothelium-dependent FMD, and the NTG group had lower FMD than the POAG subjects.[6]

Another set of investigators studied vascular endothelial function in individuals with ocular hypertension (OHT) or POAG, and controls by measuring endothelium-dependent FMD of the brachial artery and circulating endothelial progenitor cells (EPCs).[7] Subjects underwent a complete ophthalmological exam, biochemistry study, cardiovascular assessment, brachial artery ultrasound, and EPC count with flow cytometry. OHT and POAG subjects without cardiovascular risk factors had severely reduced circulating EPCs and FMD—indicating endothelial dysfunction and increased risk of cardiovascular events.[7]

From my perspective, this research looking at a blood vessels outside of the eye demonstrates a presumed impairment in nitric oxide signaling. I strongly believe these reported blood flow disruptions are also occurring at the optic nerve head, until proven otherwise.

NO SIGNALING HYPOTHESIS

An ongoing debate has persisted in the field of glaucoma about whether vascular or mechanical processes are primarily mediating the damage leading to glaucoma. I tend to look "upstream" for a mediator leading to both kinds of injury—trabecular meshwork dysfunction and vascular dysregulation rendering the optic nerve more vulnerable to a slightly elevated IOP. Such a marker would be an ideal target for disease.

In fact, the genomics literature has unearthed several promising glaucoma markers, including: nitric oxide synthase 3 (*NOS3* is part of a family of proteins catalyzing nitric oxide's production from L-arginine; it also refers to the gene *NOS3*); Caveolin (a family of proteins and components of caveolae membranes involved in

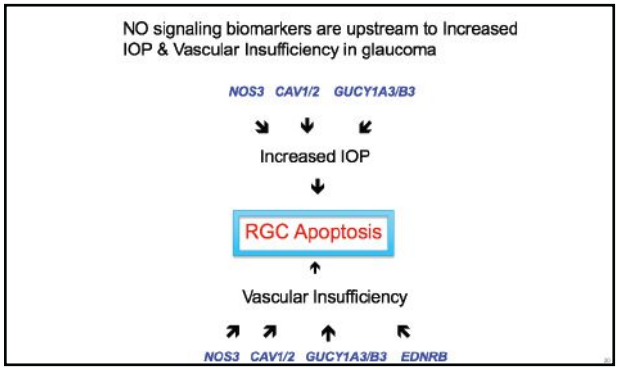

FIGURE 3. NITRIC OXIDE SIGNALING HYPOTHESIS.
Following reports of genetic markers involving both vascular and mechanical process mediating glaucoma damage, the nitric oxide glaucoma hypothesis put forth that upstream nitric oxide signaling biomarkers contributed to glaucoma by causing increased IOP and vascular insufficiency.

receptor-independent endocytosis; it includes gene members *CAV1* and *CAV2*); and soluble guanylate cyclase (sGC, an enzyme in the cardiopulmonary system that also serves as the intracellular receptor for nitric oxide). These three biomarkers have been associated with elevated IOP, vascular insufficiency, and retinal ganglion cell (RGC) apoptosis.

As a natural outgrowth of these discoveries, the nitric oxide glaucoma hypothesis put forth that upstream nitric oxide signaling biomarkers contribute to glaucoma by causing increased IOP and vascular insufficiency. With normal endothelial cell relaxation, endothelial cells communicate with nearby smooth muscle cells such as those lining the trabecular meshwork; the cells are relaxed, IOP and blood flow are normal, and the optic nerve is healthy, producing a normal visual field. Any impaired signaling between endothelial cells and underlying smooth muscle cells can lead to trabecular meshwork dysfunction, elevated IOP, concomitant vasoconstriction, and damage to the optic nerve, which can contribute to visual field loss.

A GENETIC LINK

The notion of a genetic component to glaucoma has only been reinforced with ongoing research. As of now, the three aforementioned genetic biomarkers are being evaluated more closely as part of genetic epidemiology studies. However, such research primarily involves associations; we don't know the functional significance of the common gene variants in relationship to POAG.

NOS3

The hormone estrogen has always been of interest to me because it upregulates the activity of NOS3. A gene environment interaction study, led by Jae Hee Kang at the Brigham and Women's Hospital, evaluated whether associations between *NOS3* gene variants and POAG risk depended on female reproductive factors, using 374 Nurses' Health Study cases and 1,085 controls.[8]

I was on this team collecting data on *NOS3* genotypes and post-menopausal hormone use. Among users of post-menopausal hormones, we found a reduced risk of POAG if the subject had a particular *NOS3* genotype.[8] This supported the idea that *NOS3* genotype and female reproductive health interactions were important in POAG pathogenesis. Some investigators have also found a relationship between *NOS3* gene variants and PACG or related traits such as anterior chamber depth.[9-11]

Another investigation looked at *NOS3* knockout mice—genetically modified mice that undergo inactivation of a gene, in this case *NOS3* and wild type, by replacement or disruption with an artificial piece of DNA.[12] The study demonstrated that the knockout mice had elevated IOP compared with age-matched controls (knockout mice, 18.2 mmHg vs. control mice, 13.9 mm Hg [n=30; $p<0.05$]).[12] Investigators speculated that this was the result of reduced pressure-dependent drainage. The mice also had a reduced aqueous humor outflow facility.[12]

The takeaway from these findings is that NOS3 gene variants were associated with OHT and development of glaucoma, pointing to genetic markers in the nitric oxide signaling pathway that correlated with mild to moderate trabecular meshwork dysfunction.

Caveolin

Other studies have evaluated the role of the Caveolin gene in glaucoma. Caveolin interacts with *NOS3*—located on adjacent vascular endothelial cells—to regulate the amount of nitric oxide produced.[13] Variants in the *CAV1/CAV2* region are expressed in the trabecular meshwork and RGCs involved in POAG pathogenesis.[13] Work led by Dr. Janey Wiggs at Harvard Medical School confirmed these findings—that specific haplotypes in the *CAV1/CAV2* intergenic region were associated with POAG in a US population. Moreover, associations with several *CAV1/CAV2* variants were particularly significantly in women.[14]

Dr. Wiggs' team, of which I was a part, went deeper to examine the relationship between the *CAV1/CAV2* region and POAG, and determined it was stronger in women with early paracentral visual field loss.[15] The data supported a role for *CAV1 or CAV2*, or both in POAG, and suggested that the caveolins particularly may affect POAG pathogenesis in women and individuals with early paracentral VF defects.

In mouse models, when investigators knocked out *CAV1*, IOPs became elevated compared with controls.[16] In addition, the mice developed OHT, outflow resistance increased, and outflow tissue cells were more susceptible to plasma membrane rupture, indicating that caveolae played a role in mechanoprotection.[16] Further, aqueous drainage was more sensitive to NOS inhibition, suggesting that excess nitric oxide partially counteracted outflow pathway dysfunction.[16]

Soluble Guanylate Cyclase (sGC)

Other scientists have evaluated the nitric oxide receptor sGC and its relationship to POAG. Our group, led by Dr. Manu Buys from Massachusetts General Hospital, studied mice knocked out for sGC, and found that the mice experienced retinal nerve fiber layer thinning and loss of optic nerve axons in the context of an open iridocorneal angle.[17] In addition, the knockout mice had retinal vascular dysfunction and modestly increased IOP—from 14±2 to 18±3 mmHg, which wasn't much but was age-related.[17] Moreover, an age-related decline in RGC counts was reported.[17] So we know that defective nitric oxide signaling triggered optic nerve degeneration.

These gene studies reinforce that vascular endothelial cells have *NOS3*, which generates nitric oxide. Nitric oxide diffuses into underlying smooth muscle and binds to sGC, mediating downstream effects that cause smooth muscle cell relaxation.

A "DRUGGABLE" PATHWAY

Research is revealing that the nitric oxide signaling pathway is a "druggable" one. Potential therapies may employ the use of arginase inhibitors, which reduce the supply of L-arginine needed by NOS to produce nitric oxide, or possibly some form of inhaled nitric oxide. Also being considered are sGC activators to synthesize and potentiate cyclic guanylate monophosphate (cGMP)—which relaxes vascular smooth muscles for vasodilation and increased blood flow.

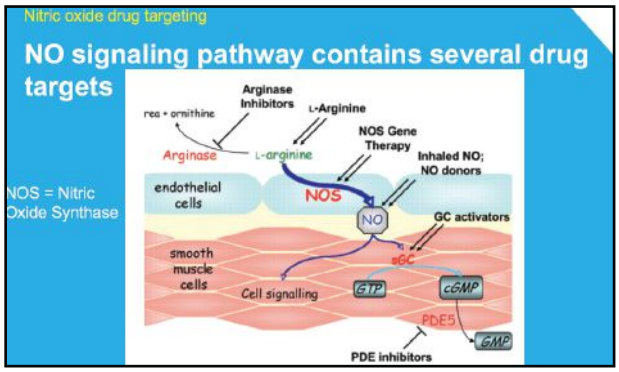

FIGURE 4. NO SIGNALING PATHWAY.
The nitric oxide signaling pathway contains several potential drug targets.

Most recently, Manu Buys had the idea of using phosphodiesterase (PDE) 5 inhibitors to enhance the nitric oxide-guanylyl cGMP (NO-GC-1-cGMP) pathway signaling.[18] Nitric oxide activates GC-1 to increase cGMP levels, which can be lowered by cGMP-specific PDE activity.[18] I was on the team investigating whether such a strategy could protect RGCs from glaucomatous degeneration. We administered tadalafil, a PDE5 inhibitor, orally in mouse models of POAG and PACG, and measured RGC viability at the soma and axon level. The tadalafil treatment increased plasma cGMP levels in both models, but didn't alter IOP or mean arterial pressure.[18] Notably, though, it prevented degeneration of RGC soma and axons in both models, and decreased necrotic and apoptotic cell death pathways in RGCs.[18]

To summarize, blocking PDE5 potentiated cGMP, which favorably affected nitric oxide signaling cascades as a way to maintain smooth muscle cell relaxation and protect RGCs from dying. The findings open the door to a therapy that could enhance signaling through this pathway, acting independently of IOP. Beneficially, tadalafil has a long half-life, crosses the blood brain barrier, and is very selective for a PDE5.

Yet, evidence of functional protection from the experimental therapy strategy is ongoing. We're not 100% sure how tadalafil was effective; we think its success was tied to nitric oxide signaling but more data will be needed to confirm this theory. Since tadalafil is an FDA-approved drug, we are evaluating the possibility of a large, randomized clinical trial. However, many steps would have to be taken in advance of such a study. Tadalafil is a very expensive erectile dysfunction drug, although it recently went off patent, and we have to address the issue of side effects. From a practical perspective, we need funding to do this kind of work. We may first look at initiating some shorter-outcome studies using optical coherence tomography angiography, nailfold capillary blood flow microscopy, and contrast sensitivity to verify more of the data.

As of now, we're confident that genetic determinants in the nitric oxide signaling pathway are associated with POAG and PACG. Animal models have confirmed that nitric oxide signaling molecules are involved in IOP regulation and optic nerve homeostasis. In preclinical glaucoma models, targeting the nitric oxide signaling pathway has afforded structural neuroprotection.

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President's Lecture
Managing Angle-Closure Glaucoma

Shan Lin, MD

Angle-closure glaucoma (ACG) is a form of glaucoma that generally is not well-understood. Though many of us doing research in this area of glaucoma thought we had a solid understanding about the pathophysiology of ACG, evolving findings continue to surprise us.

ACG is characterized by the increase of intraocular pressure as a result of acute or chronic blockage of aqueous humor outflow.

Its prevalence is increasing dramatically because of an aging population and the fact that the lens gets larger with age. In 2010, 15.7 million people were diagnosed with angle closure worldwide.[1] The number of primary ACG cases was projected to increase 18% globally between 2012 and 2022, according to one study.[2]

ACG's epidemiologic trend is quite disturbing. With 46% growth of the Asian population in the US alone between 2000 and 2010,[3] Asian patients were expected to represent 87% of all ACG cases across the globe by 2020[1]—a significant disparity in one type of glaucoma affecting a specific group of people. Not only is ACG the most prevalent form of glaucoma in Eastern Asian and Eskimo populations, it is also pervasive in India.[1]

Most of us who regularly treat ACG understand that this form of

glaucoma is more aggressive than primary open-angle glaucoma (POAG) and in some ways more complex. A case series I was involved with demonstrates the unique and unexpected aspects of ACG.

RARE CONDITION: A FAMILY AFFAIR

A number of years ago, I saw a 52-year-old female patient who needed to have an iris tumor ruled out due to a bump on her iris. Though this wasn't initially an angle closure case, I was the unofficial ultrasound biomicroscopy (UBM) expert in my department so I headed up the evaluation.

The patient's pressures were 14 mmHg OU, the slit-lamp exam revealed mild elevation of the peripheral iris at 7:30 OD, and the cup-to-disc ratios—0.7 OD, 0.6 OS. Gonioscopy revealed narrow angles—grade I to II OU—which were suspicious. UBM uncovered no tumors; however, multiple iridociliary cysts could be seen elevating the iris, ultimately causing angle closure.

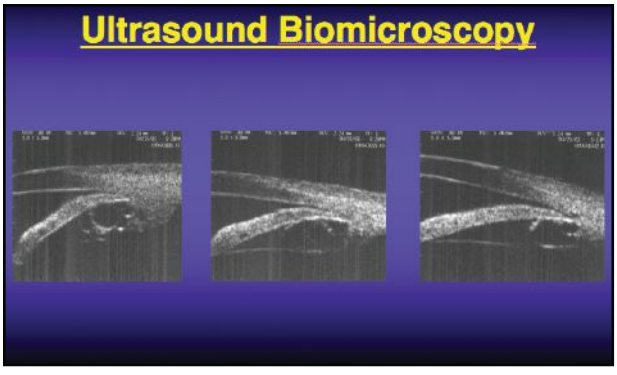


FIGURE 1. IRIDOCILIARY CYSTS ON UBM
In a 52-year-old female referred for a possible iris tumor, UBM revealed multiple iridociliary cysts elevating the iris and causing angle closure. *Images: Shan Lin, MD*

The patient referred other family members for evaluation of possible glaucoma. Her 49-year-old sister came in with complaints of pressure and aching around the eyes at night, and a previous diagnosis of narrow-angle glaucoma in the left eye; she was on a prostaglandin analog to reduce pressure in the left eye. UBM confirmed angle closure with multiple iris cysts. A middle-aged brother presented with relatively severe glaucoma not previously diagnosed and multiple iris cysts on UBM. I also saw the patient's 72-year-old mother, previously diagnosed with chronic ACG in both eyes, who had undergone cataract extraction and iridotomies in both eyes but was still on timolol 0.5% OU BID and pilocarpine 2% OU QID. So the treating physician recognized problems with the angles despite the earlier surgeries.

Gonioscopy revealed OD segmental angle narrowing and OS narrow angle temporally, and optic nerve cupping was occurring in both eyes. Although visual field defects weren't severe, signs were indicating moderate glaucoma was present. UBM showed evidence of segmental angle narrowing and iris cysts, similar to those seen in the woman's children. So despite a cataract extraction with a posterior chamber intraocular lens to open the angle, the angle didn't open in the setting of iris cysts.

As it turned out, the iris cysts found in these family members were part of an inherited syndrome. This rare condition, first reported in 1893 by Treacher Collins, was later associated with narrow-angle glaucoma in 1958 by Chandler and Braconier. It is characterized by autosomal dominant inheritance, and classified as primary or secondary, depending on cyst origin.

Though the case series centered around what was traditionally considered an uncommon condition, new imaging techniques show that it may not be so rare and point to the complexity of ACG's pathophysiology, suggesting that we don't know as much about angle closure as we initially thought.

GONIOSCOPY OVERVIEW

All glaucoma patients require gonioscopy, but the exam is particularly important in ACG—to visualize the anatomical angle formed between the cornea and iris, any neovascularization, or possible tumors. In all cases of gonioscopy, it's essential to perform it in the dark to minimize the amount of light going through the pupil. When lights are off, the angle tends to close up.

Indirect gonioscopy, which is commonly used in clinical offices, uses light passing from the chamber angle to a goniolens, reflected by an internal mirror, to view anterior chamber angle structures. Illumination and magnification are provided by a slit lamp, and the patient can be upright during the exam.

I prefer dynamic pressure gonioscopy in which the lens is able to be pressed onto the eye such that the corneal pressure displaces the iris to widen a narrow or closed anterior chamber angle.[4] The maneuver exposes additional anatomic markers and angle structures, and helps establish the presence of peripheral anterior synechiae (PAS)[4]—adhesions of the peripheral iris to angle structures—or if pupillary block is a mechanism. The caveat with dynamic gonioscopy is to make sure it is done intentionally, since inadvertently performing the maneuver may open up what is actually a narrow angle and lead to misdiagnosis.

Direct, or Koeppe, gonioscopy may be the most effective type of gonioscopy since a steeply convex lens reduces or eliminates any internal reflection for a better view of the iridocorneal angle.[4] The Koeppe lens, a 50-diopter lens, is placed on the eye of a recumbent patient using saline, and the examiner views the angle through a handheld binocular microscope.[4] Unfortunately, the exam is time-consuming to perform so it's infrequently used.

A number of grading systems are available to evaluate gonioscopy findings, but I tend to rely on two of them.

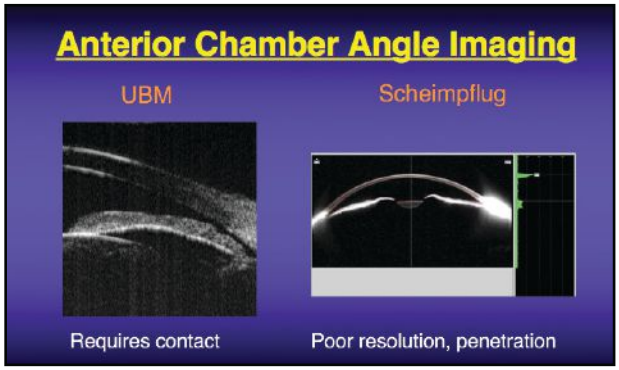
With the Van Herick system, a user places a narrow slit beam perpendicular to the most peripheral part of the cornea, and adjusts the oculars for an angle view of about 60 degrees from the light beam.[5] The anterior chamber depth is graded in comparison to the corneal thickness: If it's thicker than the cornea, the angle is a wide-open grade 4; one-quarter corneal thickness is considered a narrow grade 2; less than a quarter thickness is a very narrow grade 1; "slit" is dangerously narrow; and no space between the cornea and the iris is a closed angle.[5]

The Shaffer system (named after Dr. Robert N. Shaffer, the founding member of our group at the Glaucoma Center of San Francisco) approximates the angle where the iris inserts into the

trabecular meshwork.[5] If the angle is greater than 20 degrees, it's considered at little or no risk of closure; angles from zero to 20 degrees are graded capable of closure.[5] More specifically, a 10-degree angle is grade 1, a 20-degree angle is grade 2, and a 25-degree angle or greater is grade 3 or 4.

IMAGING ACG PATIENTS

Various technologies exist to image the angle, including UBM, Scheimpflug analysis, and anterior segment optical coherence tomography (AS-OCT). Each has benefits and disadvantages.



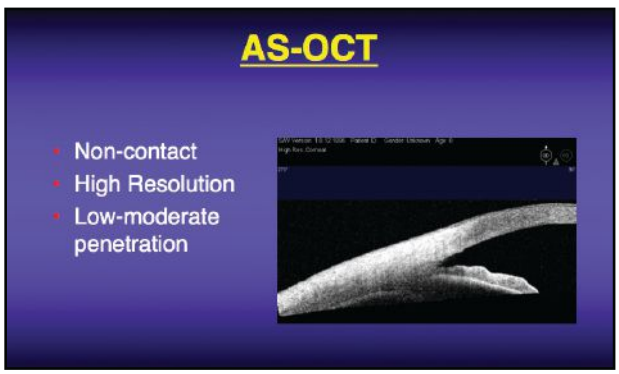


FIGURE 2 AND 3. ANTERIOR CHAMBER ANGLE IMAGING
UBM is adept at visualizing structures behind the iris, but requires a water-bath immersion and contact with the patient; Scheimpflug technology generates three-dimensional images without need for contact but has poor resolution; and AS-OCT is a noninvasive imaging technique with high resolution, but low to moderate penetration of structures.

UBM excels in its ability to visualize structures behind the iris, including the ciliary body and lens.[6] First introduced by Foster and Pavlin in the early 1990s as a way to obtain cross-sections of the eye at microscopic resolution, UBM primarily is used for imaging the anterior segment.[6] Compared with regular ultrasound modalities such as A- or B-scan, UBM uses a much higher frequency transducer, resulting in resolutions up to 20 µm axially and 50 µm laterally, with tissue penetration of 4 to 5 mm.[6] Of the three commonly used imaging techniques, UBM falls in the middle for resolution, with a frequency range depending on the probe being employed.

Disadvantages include the need for a water-bath immersion, direct eye contact, and an experienced operator; and the modality's longer image acquisition times.[6] Overall, UBM is relatively time-consuming and can be somewhat uncomfortable for the patient. Traditionally, the clinician applies water-soluble gel to the eye and moves a probe around in the gel—introducing the possibility of scratching the eye. Even with newer probes that have the water/gel bath embedded in a casing of the probe, contact with the eye is needed for the sound waves to transmit for imaging.

Clinically, UBM is useful in patients at high risk for plateau iris—anterior chamber angle narrowing due to insertion of the iris anteriorly on the ciliary body (or displacement of the ciliary body anteriorly), resulting in a mechanical obstruction of the trabecular meshwork. The condition is often diagnosed in patients under age 50 who have narrow angles despite having had properly performed peripheral iridotomies.[7] UBM also can reveal patients with occluded angles impacted by pupillary block, as evidenced by tented irises. In addition, it can help assess for adequate angle opening post-iridotomy as well as other causes of angle closure such as iris cysts or tumors.

Scheimpflug analysis generates three-dimensional images of the anterior segment including anterior and posterior surface topography of the cornea.[8] With the Pentacam (Oculus), a rotating Scheimpflug camera takes up to two seconds to generate a complete image, from which a model can be created; any eye movement is detected by a second camera and corrected for.[8] The Galilei (Ziemer) dual Scheimpflug camera incorporates Placido disc technology to improve curvature information on the central cornea.[8]

Scheimpflug analysis has the benefit of not requiring eye contact. However, optical light reflects from the camera positioned perpendicular to a slit beam and causes glare at the angle, so this imaging technique has the worst resolution of the three commonly used imaging techniques.

AS-OCT is a noninvasive imaging technique using near-infrared light to provide cross-sectional images based on tissue reflectance.[6] Its application in the anterior segment was first reported in 1994, and it recently has been used for anatomic and structural measurements—with axial resolution of 5 to 10 µm, lateral resolution of 15 to 25 µm, and tissue penetration of 3 to 6 mm.[6,9] Other advantages are its non-contact design and fast acquisition speeds, and that it doesn't require experienced operators.[6]

Though AS-OCT yields the highest resolution images of the three commonly used imaging technologies, it has low to moderate penetration compared with UBM. So, unfortunately, this limitation can lead to missing conditions. For example, it can't visualize iris cysts, and it isn't always able to detect plateau iris.

Within the AS-OCT arena, Fourier-domain (FD) OCT is coming into practice, offering faster speeds and higher resolution. The technique extracts spectral information by distributing optical frequencies onto a detector stripe so a full-depth scan can be acquired in a single exposure.[10] The technology provides a very high-resolution view of the trabecular meshwork and Schlemm's canal area to assess for angle closure and evaluate the effects of medications on the structures.

Also available is swept-source OCT, a variation of FD-OCT, with a light source wavelength centered at ~1 µm that sweeps across a narrow band of wavelengths with each scan.[11] An improvement over spectral-domain OCT (SD-OCT), which uses a broadband light source, the technology can achieve exceptionally

high imaging speeds and generate 100,000 A-scans per second.[11] SS-OCT creates three-dimensional images of the anterior segment that can be used to assess PAS, for example.

My team looked at whether UBM or AS-OCT offered a more representative picture of the true angle.[12] We found that UBM led to overcalling of angle closure more often than AS-OCT. This could have been due to patient positioning and the need to touch the eye with UBM, or because UBM has lower resolution than AS-OCT.

My algorithm for angle assessment begins with Van Herick analysis. I look at the slit angle to discern whether it's wide open or narrow. Then, dynamic gonioscopy aids me in determining how many quadrants are occludable. With any potential narrowing, I turn to AS-OCT. I don't do UBM in every patient but will use it after an iridotomy if the angle is still narrow, to search for other causes.

COMMON ANGLE-CLOSURE SCENARIOS

It is widely understood that pupillary block—occurring when aqueous humor flow to the anterior chamber becomes functionally obstructed between the pupillary portion of the iris and the lens—is the number one cause of angle closure in adults. Pupillary block can result in retention of fluid in the posterior chamber and anterior bowing of the peripheral iris, or iris bombe, and trabecular meshwork obstruction. Both UBM and AS-OCT detect these conditions well.

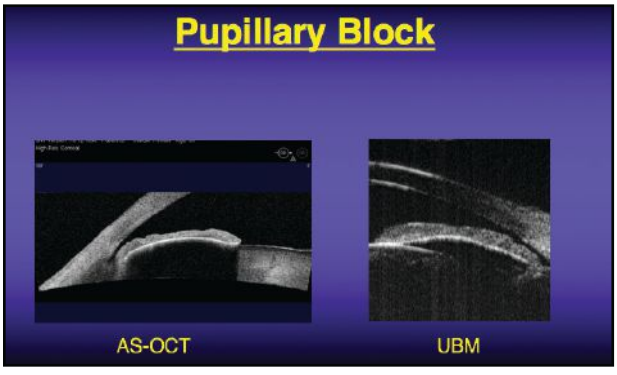


FIGURE 4. PUPILLARY BLOCK
Pupillary block is the number one cause of angle closure in adults. It can result in anterior bowing of the peripheral iris, or iris bombe, and obstruction of the trabecular meshwork. Both UBM and AS-OCT detect these conditions well.

Research is also finding that plateau iris is not as rare as we thought. In a study of Indian eyes that had undergone laser peripheral iridotomies (LPIs) for narrow angles, 60 percent were still narrow after the procedures.[13] This was primarily due to plateau iris, as shown on UBM.[13]

And iris cysts, though not overly prevalent, are not uncommon in younger patients.[14] Bob Ritch's team did UBM on ACG patients 40 years and younger to evaluate causes, and iris cysts came in second place after plateau iris.[14] The etiology of angle closure in younger individuals correlated more with structural/developmental ocular anomalies than pupillary block.[14] This suggested that such eyes should be monitored post-LPIs for recurrent angle closure and the need for further laser or incisional surgical intervention.[14]

ANATOMIC RISK FACTORS FOR ACG

Various anatomic risk factors predispose individuals to having ACG. They include anterior chamber depth and width,[15,16] lens vault[17,18], iris volume,[19] anterior chamber area, and angle/iris changes from light to dark.[19,20]

A series of collaborative studies I was involved in assessed central corneal thickness and related factors in about 500 Chinese and Caucasian subjects.[20-25] The team looked at a Chinese-American population in San Francisco, and Chinese individuals in Beijing University in Northern China and in Zhongshan Ophthalmic Center, a tertiary hospital in Southern China. One outcome that we evaluated was whether there were regional differences among the Chinese subjects. Though this wasn't borne out, we did find a basis for the discrepancy between Chinese and Caucasian populations that might explain why ACG is so prevalent in Asian populations.

For one thing, Chinese subjects had a smaller anterior chamber depth[23] even with comparative axial length (distance between the corneal anterior surface and fovea), and smaller anterior chamber width and volume,[24] compared with Caucasian subjects. Further, their irises exhibited greater dynamic changes from light to dark, leading to more iris thickening.[25] Moreover, their angle recess and trabecular-iris space areas were smaller than those in Caucasian subjects, and Chinese subjects had had greater dark-to-light shifts.[21]

Both static and anatomic and dynamic factors were at play in all of the subjects, but the bottom line was the ocular anatomies of people of Chinese descent predisposed them to greater angle closure and a more crowded anterior segment.

TREATMENT OPTIONS

Various interventions exist to address ACG. They include older procedures and some newer strategies.

Laser peripheral iridotomy (LPI) uses a focused beam of light to create a hole on the iris rim to increase aqueous humor flow between anterior and posterior chambers. This opening may decrease eye pressure and prevent the sudden buildup of pressure that occurs during an acute ACG attack. From my perspective, the primary purpose of LPI should be to treat pupillary block. My recommendation for LPI is based on 180 degrees or more of a grade 0 to 1 angle, meaning at least two of four quadrants are occludable by assessment.

A recent study raised the question of whether we should be performing LPI at all. Researchers looked at the efficacy and safety of performing LPI prophylaxis for potential PACG patients in a Chinese population.[26] The randomized, controlled trial enrolled bilateral PAC suspects 50 to 70 years of age at the Zhongshan Ophthalmic Center.[26] Eligible participants received LPI in one randomly selected eye, with the other eye remaining untreated.[26] The primary outcome in the intent-to-treat analysis was incident PAC disease as a composite endpoint of IOP elevation, PAS, or acute angle closure during 72 months of follow-up.[26] A total of 889 individuals were included.

The team found that diagnosis of PACG was very low among PAC suspects and that LPI had a modest, albeit significant, prophylactic effect.[26] Incidence of the primary outcome was 4.19 per 1,000 eye-years in treated eyes compared with 7.97 per 1,000 eye-years in untreated eyes (hazard ratio: 0.53; 95% CI, 0.30 to 0.92; p=0.024).[26] Researchers wrote that, due to the low inci-

dence rate of outcomes that had no immediate threat to vision, the benefit of prophylactic LPI was limited, so they didn't recommend widespread prophylactic LPI for PAC suspects.[26]

I have more patients with occludable angles than angle closure, and the decision to do LPI in these patients is often dependent on other circumstances and features. In the aforementioned study, the conclusions were drawn on very few attacks of acute angle closure, and some outcomes were in part due to dilation of the patients' eyes during examination. The study's recommendation to not perform widespread prophylactic LPIs makes sense from a population standpoint, but I still recommend LPIs to patients with occludable angles. However, I now review this study's findings with patients and let them help decide whether they want to go forward with the procedure. My rationale in recommending LPI is that, from my perspective, it's such a low-risk procedure that if it were my eye, I'd prefer to treat the narrow angle to prevent potential progression to angle closure and/or glaucoma.

Some general guidelines regarding LPI include that I perform the procedure at the horizontal position, usually the temporal iris. I was taught to do LPI in a superior position, but a prism affect from the tear film bends light into the iridotomy and causes the patient to have photopsias. I also avoid doing LPI in the setting of a "zipped-up" angle; that is not just an occludable angle, but also ≥180 degrees of PAS. Otherwise, IOP spikes can occur and induce more angle closure, leading to future surgery for uncontrolled pressure.

In some post-LPI cases, it's been determined that a much larger hole would have been more beneficial to the patient. One German study reported that post-LPI patients who had small LPIs but still had appositionally closed or narrow anterior chamber angles had benefit to their angles with repeat LPIs to increase the size of the holes.[27]

Laser iridoplasty involves burning the peripheral iris to contract the peripheral iris stroma and create space between the anterior iris surface and trabecular meshwork.[28] The procedure can open the angle and remove residual appositional closure caused by plateau iris syndrome post-laser iridotomy.[29] Studies show it has benefits for opening angle parameters,[30-32] diurnal IOP,[30] darkroom prone provocative testing,[33] and preventing angle closure attacks.[34] Yet, risks include the potential for IOP spikes and development of more PAS, and few studies have evaluated the procedure's long-term benefits for glaucoma progression.

Endoscopic cyclophotocoagulation, also known as endocyloplasty (ECPL) when used for treating angle closure, involves lasering the ciliary body so it shrinks posteriorly and opens the angle in ACG due to plateau iris. The procedure is usually conducted in tandem with cataract surgery. One study found that patients receiving both ECPL and cataract surgery had greater opening of the angle than those who only had cataract surgery.[35]

Cataract surgery/phacoemulsification was found in a 2015 review to be a beneficial glaucoma treatment with the potential to provide substantial IOP lowering and medication reduction for ACG patients.[36] Research has shown that it's almost a cure for acute angle closure to help prevent IOP elevation later on. In four studies, acute PACG patients had an overall 71% reduction in presenting IOP and rarely required long-term glaucoma medications when phacoemulsification was performed soon after medical IOP reduction.[36] Furthermore, trabeculectomy after phacoemulsification was uncommon in glaucoma subjects.[36]

Clear lens extraction's use as a therapy for ACG patients has sparked some discussions about whether we should be taking out the lenses of patients without cataracts. My team completed a case series on five patients with acute or chronic ACG who had lenses removed with better than 20/40 vision but uncontrolled preoperative IOP despite maximal topical medications.[37] After clear lens extraction, three cases had good IOP control (<22 mmHg) without the need for topical medications; one case had better controlled IOP, although topical medications were required; and the last case did not reach the desired IOP despite restarting maximum topical therapy, so the individual went on to get a trabeculectomy.[37] Given that four out of five cases were classified as successes, we concluded that therapeutic clear lens extraction may have a role in certain ACG cases.[37]

The EAGLE study, a randomized study, compared the effectiveness of clear lens extraction with LPI and medications in newly diagnosed PACG or PAC (with IOP 30 mmHg or greater) subjects 50 years or older without cataracts.[38] No serious adverse events were reported in either group, but researchers found that removing the lens was more efficacious and cost-effective long-term than LPI and medications; vision, visual acuity, pressure, and the angle all improved with clear lens extraction; and individuals who had their lenses out had less need for additional glaucoma surgeries (including lens extraction) than those who had LPI (one vs. 24).

My approach to therapy is that LPI is still generally my first choice for ACG patients. Laser iridoplasty remains controversial, and I've leaned away from the procedure. Overall, I believe that cataract surgery and clear lens extraction are justified in ACG. However, I don't do them if pressure is controlled and the patient is happy with the status quo. They should not be performed in people who are ACG suspects, which has been misinterpreted in the past. And it's a difficult decision as to whether you do them in individuals who don't have glaucoma but have PAC with high pressures.

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› VYZULTA increases aqueous humor outflow by targeting the **uveoscleral pathway** with latanoprost acid and the **trabecular meshwork** with nitric oxide[1,6]

PROVEN EFFICACY:

› VYZULTA decreased mean IOP up to **9.1 mmHg** from baseline in clinical trials of up to 12 months[6]

DEMONSTRATED SAFETY:

› **6%** of patients in pivotal trials reported **hyperemia**[6]

› **6 out of 811** patients on VYZULTA in pivotal trials **discontinued** treatment[1]

INDICATION

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

IMPORTANT SAFETY INFORMATION

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

IMPORTANT SAFETY INFORMATION (CONTINUED)

- Contact lenses should be removed prior to the administration of VYZULTA and may be reinserted 15 minutes after administration
- Most common ocular adverse reactions with incidence ≥2% are conjunctival hyperemia (6%), eye irritation (4%), eye pain (3%), and instillation site pain (2%)

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

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

IOP=intraocular pressure

BAUSCH + LOMB

VYZULTA®
(latanoprostene bunod ophthalmic solution), 0.024%

BRIEF SUMMARY OF PRESCRIBING INFORMATION

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

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

Initial U.S. Approval: 2017

1 INDICATIONS AND USAGE

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

4 CONTRAINDICATIONS

None

5 WARNINGS AND PRECAUTIONS

5.1 Pigmentation

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

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

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

5.2 Eyelash Changes

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

5.3 Intraocular Inflammation

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

5.4 Macular Edema

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

5.5 Bacterial Keratitis

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

5.6 Use with Contact Lens

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

6 ADVERSE REACTIONS

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

6.1 Clinical Trials Experience

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

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

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

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

The background risk of major birth defects and miscarriage for the indicated population is unknown. However, the background risk in the U.S. general population of major birth defects is 2 to 4%, and of miscarriage is 15 to 20%, of clinically recognized pregnancies.

Data

Animal Data

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

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

8.2 Lactation

Risk Summary

There are no data on the presence of VYZULTA in human milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered, along with the mother's clinical need for VYZULTA, and any potential adverse effects on the breastfed infant from VYZULTA.

8.4 Pediatric Use

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

8.5 Geriatric Use

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

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

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

13.2 Animal Toxicology and/or Pharmacology

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

U.S. Patent Numbers: 7,273,946; 7,629,345; 7,910,767; 8,058,467.

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The Latest in Micro-Incision Glaucoma Surgery (MIGS) Technology

Constance O. Okeke, MD, MSCE

Though no surgical intervention yields perfect results or comes without risks, micro-incision glaucoma surgery (MIGS) fills an important need for many glaucoma patients. In a medical landscape where patients were once only offered traditional surgeries that could lower pressure but were associated with significant postoperative complications, it's a relief to have other tools at our disposal. All of us want to do good for our patients, not harm, so that's part of the reason why MIGS matters so much.

Of the reported 3.6 million cataract surgeries performed annually in the US, 20% of those are on patients with comorbid glaucoma.[1,2] That means about 700,000 individuals may benefit from having MIGS combined with their cataract surgery. Research has shown that cataract surgery alone often is not enough to maintain long-term intraocular pressure (IOP) control.[3]

If given the option, many glaucoma patients would choose less of a daily medication burden if there was some other method to reduce their IOP. At our clinic, we asked nearly 70 glaucoma patients in evaluation for cataract surgery who were taking glaucoma medications if they would be interested in having a procedure done in conjunction with their cataract surgery to potentially lower the number of daily drops they were taking. Eighty-six percent were interested or extremely interested.

We have to give our patients the MIGS choice. To do that, we need to be aware of available options and understand how each of those technologies works to lower IOP. The following are some of the latest devices in use today, categorized by their mechanisms of action.

TRABECULAR MESHWORK REMOVAL

A number of MIGS target the trabecular meshwork (TM)—an area of high resistance in the juxtacanalicular tissues. Devices in this category remove sections of tissue from the TM and Schlemm's canal to create direct aqueous humor access to the collector channels. So it's paramount to look on gonioscopy for markers—starting with Schwalbe's line and proceeding through the TM, scleral spur, and ciliary body band.

MIGS in this category include: the Trabectome (MicroSurgical Technology [MST]); OMNI Surgical System (formerly Trab 360 and Visco 360; Sight Sciences); Kahook Dual Blade (New World Medical); Gonioscopy-Assisted Transluminal Trabeculotomy (GATT), an ab interno refinement of an ab externo procedure; and the Gonio-

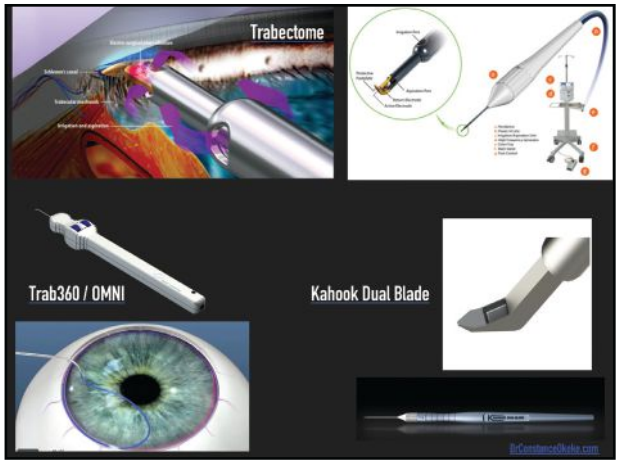

FIGURE 1 AND 2. MECHANISM OF ACTION: TM REMOVAL
The trabecular meshwork (TM)—an area of high resistance in the juxtacanalicular tissues—is the target for a number of MIGS procedures.
Images: Constance O. Okeke, MD, MSCE

tome (MST).

The Trabectome, an electrosurgical ablation system, is unique from other MIGS because it incorporates fluidics and electrocautery capabilities. The fluidics keep the anterior chamber irrigated and well-formed during gonioscopy, and help maintain a clear view for surgeons, while tissue edges can be cauterized as the TM is unroofed. During the procedure, I use the Trabectome handpiece to pierce the TM tissue and remove some viscoelastic material. Once in Schlemm's canal, I enter one passageway, stop and turn, and then go the other way. Usually I do about four to five clock hours with this technique, and depress a pedal to do the cautery. Typically some level of intraoperative bleeding is common and indicates that heme is refluxing through the collector channel—a sign that the surgeon is in the right area.

The Goniotome offers a newer procedure in this category requiring less of a capital expenditure than the Trabectome, with added flexibility. A one-piece disposable unit with blades on either side, the Goniotome has a wider tip for clean edges, and it can be connected to a cataract machine with irrigation to help maintain a good chamber. In addition, the Kahook Dual Blade is a single-unit device whose blade includes a ramp to lift tissues for a clean cut. The surgeon can use viscoelastic material to expand the anterior chamber before advancing the device in one direction and then the other. As the dual blade moves forward, it removes a leaflet of TM to grant better access to the collector channels.

After these procedures are completed, the slit-lamp exam and gonioscopy should reveal a sheen where TM tissue was removed; this light, whiteish area is the outer wall of Schlemm's canal. In addition, the newly formed cleft should be free of peripheral anterior synechiae (PAS). These markers are a good indication that the procedure was structurally successful.

TRABECULAR MESHWORK BYPASS

Other MIGS devices create a TM bypass. These devices increase outflow by implanting a stent that serves as a stable conduit in Schlemm's canal to keep the area open and patent, and to circumvent part of the TM.

The iStent Trabecular Micro-Bypass Stent (Glaukos), a first-generation device, utilizes a tiny snorkel-like mechanism embedded near a collector channel to make way for direct aqueous humor flow access. The newer design, the iStent inject, includes two mushroom-like stents that achieve a similar result, but times two—creating two patent bypass pathways yielding multidirectional flow through Schlemm's canal. The device is indicated for use in conjunction with cataract surgery to reduce IOP in adult patients with mild-to-moderate primary open-angle glaucoma (POAG).

With two iStents, research has shown the possibility for increased access to collector channels, and greater pressure reduction and flow. In one study, IOP decreased by more than 8 mmHg, a 37% drop, which was approximately two to four times greater than the reduction expected with cataract surgery alone.[4] At 36 months, 92.7% of eyes decreased the number of medications from preoperative regimens.[4] Over 36 months postoperatively, mean IOP was maintained at ≤15 mmHg, and mean medication burden was 0.9 or fewer medications.[4]

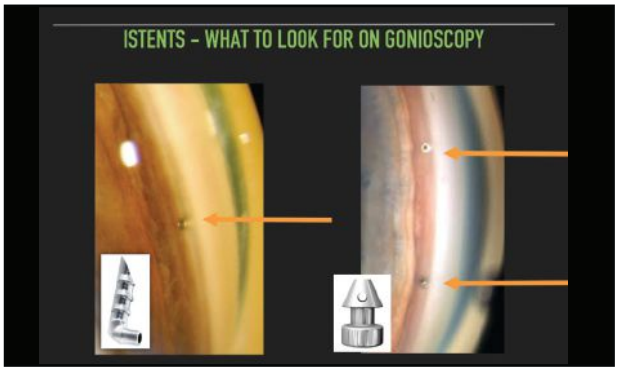

FIGURE 3. GONIOSCOPY EVALUATION FOR ISTENTS
Looking post-procedure at the traditional iStent on gonioscopy, only the snorkel tip in Schlemm's canal should be visible, with the rest of the device obscured under TM tissue; with the iStent inject, two circular areas signify that the devices are in good position in the TM.

Given that aqueous humor outflow is segmental and not evenly distributed, one obstacle in the field is we don't have the diagnostic imaging capabilities to pinpoint the exact area of resistance. Since research tells us the TM is a known location, we remove some of the tissue or bypass it, but there could be other areas that we may miss with stent-based MIGS.

The Hydrus Microstent (Ivantis) dilates Schlemm's canal and remains in the eye as a bypass to keep material patent and increase aqueous humor flow, for a kind of dual action. A 90-degree scaf-

folding span promotes consistent access to the collector channels and eliminates the need for stent targeting. The surgeon pierces the TM and moves into Schlemm's canal before using a handpiece to dial the Hydrus stent forward, and scaffold the canal for three or four clock hours. The device is released into the dilated space to create a stable conduit of fluid flow.

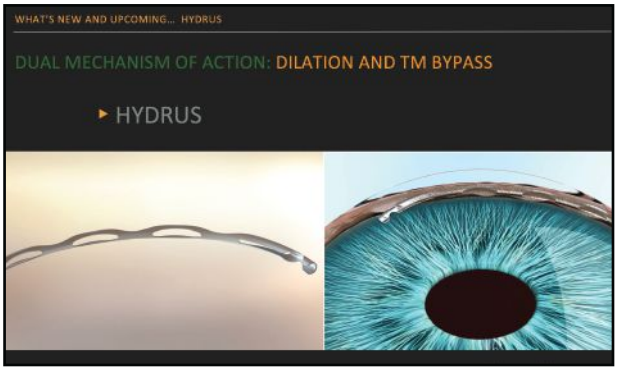

FIGURE 4. ELIMINATING NEED FOR STENT TARGETING
With the Hydrus Microstent (Ivantis), a 90-degree scaffolding span promotes consistent access to the collector channels and eliminates the need for stent targeting. Post-procedure on gonioscopy, the clinician should see gleams of material beneath lacy-appearing TM tissues.

DILATE, FLUSH SCHLEMM'S CANAL

Some MIGS procedures dilate or use viscoelastic material to flush the outflow system. They increase aqueous humor outflow by releasing viscoelastic material behind the TM to expand Schlemm's canal and the distal collector channels. Included in this category are the Ab-Interno Canaloplasty (ABIC; Ellex), performed with the iTrack surgical system; and the Visco 360 Viscosurgical System, now incorporated within the OMNI Surgical System (Sight Sciences), discussed in the next section.

ABIC re-establishes the eye's natural outflow system by accessing, catheterizing, and viscodilating the TM, Schlemm's canal, and the distal outflow system. It breaks up microadhesions, and flushes the natural outflow and collector channel ostia. Specifically, the surgeon feeds a catheter through the TM into Schlemm's canal 360 degrees around the canal to try to remove any adhesions. At the same time, viscoelastic material is being released, expanding Schlemm's canal and the collector channels, and evacuating through the TM. So multiple mechanisms are flushing the aqueous system. Before the procedure, the eye may appear slightly hyperemic, but once the case is closed, the eye is often white and quiet, sometimes dramatically so.

DUAL ACTION: DILATION & TM REMOVAL

The OMNI Surgical System combines two MIGS procedures that can be done in conjunction with cataract surgery using the same corneal incision or as stand-alone procedures. The device offers 360-degree viscodilation (former Visco 360), as viscoelastic material injected through Schlemm's canal, and also acts as a goniotomy via a catheter (former Trab 360) that is pulled through the TM.

For the viscodilation mechanism, under gonioscopic visualization, the surgeon uses the cannula to pierce the TM and Schlemm's canal, advancing the microcatheter around the canal. Upon retraction of the microcatheter, a fixed volume of viscoelastic is dispensed, leaving a wider opening into the canal and collector channels. Though the system offers the capability to unroof the TM for 360 degrees, I like to leave some "real estate" in the event that tissue is needed in the future. Typically, I do between 90 and 180 degrees of the goniotomy procedure.

SHUNTING THROUGH THE SUPRACHOROIDAL SPACE

Other MIGS procedures mimic the action of prostaglandin analogs by shunting through the suprachoroidal space using uveoscleral access. Via a stent, they increase aqueous humor fluid egress from the anterior chamber to the uveoscleral pathway. One device no longer on the market, but which was previously implanted is the CyPass Micro-Stent (Alcon). The device was pulled from the market after some patients experienced loss of endothelial cells, which can be associated with corneal damage, vision loss, and other complications.[5] In patients who currently have it implanted, we document its position and monitor endothelial cell counts. I have not had to explant any of these devices yet. Unfortunately, I have a number of patients who have done really well with this device so hopefully similar devices, which are now being evaluated in clinical trials, will be approved in the future.

The Xen Gel Stent (Allergan) is considered a less invasive glaucoma surgical (LIGS) procedure—a cross between a MIGS and traditional glaucoma surgery. Though the surgeon creates a bleb and employs mitomycin C, the procedure is less invasive than a trabeculectomy or tube shunt. After piercing the scleral wall, the surgeon advances a hard, tube-like gelatin stent through the anterior chamber beneath the conjunctival tissue. A lever is depressed to secure the stent, which becomes soft and flexible once in place. The stent is similar to a candle wick that enables aqueous humor fluid to percolate and create a kind of defuse, rather than ischemic, bleb, after which mitomycin C is employed to help prevent bleb failure.

AQUEOUS FLUID REDUCTION

Some MIGS decrease outflow by reducing aqueous humor production so less fluid has to exit the outflow system. Endocyclophotocoagulation can be performed to ablate the ciliary body, followed by endoscopic laser at the incision site. This strategy is designed to reduce aqueous production, thereby lowering eye pressure.

CONSIDERING A VARIETY OF MIGS

It's essential to keep an open mind when deciding upon MIGS since some patients have issues that preclude certain procedures. These factors could be pathologic in nature (e.g., downstream resistance in the discrete canalicular system), physiologic (e.g., variability in collector channel location), or anatomic (e.g., TM abnormality due to PAS from prior procedures or uveitis). For

example, if a patient has a large amount of PAS formation, I might use the Trabectome hand piece to perform a gonio-synechialysis to open the angle, and then perform goniotomy with the Trabectome along with a cataract removal to open the TM and secure access to outflow channels.

Practical considerations tied to insurance coverage also can come into play. A patient may be a candidate for two or three procedures, but I might only be able to do one because that's what insurance covers; not every patient can or will pay out of pocket for what you feel is the best intervention. Also, some MIGS have to be done in conjunction with cataract surgery (e.g., the Hydrus, iStent, and iStent inject). Moreover, some facilities don't want to accept certain procedures.

CASE: USING MULTIPLE MIGS

I have seen benefits to using multiple MIGS before turning to invasive surgery in some patients. One case, a 79-year old male with uncontrolled open-angle glaucoma OD, did fairly well with a Trabectome and cataract surgery OU for several years, but needed supplemental management. The OS eye was not a candidate due to reduced vision as a result of corneal decompensation from a previous trabeculectomy surgery and having had multiple retinal surgeries. So the patient underwent selective laser trabeculoplasty (SLT) OD, but pressure started to rise again postoperatively—up to 27 mmHg, even after medical treatments were added. Changes on OCT revealed progression.

My team thought about repeating the SLT or adding medications, but the patient was already using several drops, and this was before we had access to newer, more effective drugs. We were limited in the MIGS we could offer, having not learned some of them yet. We considered traditional glaucoma surgery, which the patient was hesitant about due to complications with his previous trabeculectomy. So we chose to do an ABIC with iTrack. The patient came through the surgery well. Target pressure was around 15 mmHg, and pressure came down significantly on postop day one, and was maintained in the mid-to-low teens over the next several months on one medication.

This is an example of how following MIGS with more MIGS may be an option before having to turn to traditional glaucoma surgeries with their potential risks.

POSTOPERATIVE CARE

When following MIGS patients, it's important to keep some postoperative considerations in mind.

On postop day one, vision can be slightly blurred, as mild bleeding often occurs in the anterior chamber during surgery. The cornea typically will be clear, and during the anterior chamber evaluation, anywhere from trace to one to two plus cells may be seen. I tend to see more microhyphema with goniotomy procedures, which produce more reflex bleeding. At times, scattered hyphema, a small clot, or even a layered hyphema will be present.

I institute the same patient restrictions as for cataract surgery, adding instructions for no heavy lifting or stooping for three days and to use a shield for the same period of time. Blood thinners can be reinstituted after about three days, although that can change with greater ocular bleeding and depending on how quickly the patient needs to get back on the blood thinner.

I typically put the patient on a steroid, a non-steroidal anti-inflammatory eyedrop (NSAID), and a topical antibiotic. If a patient has a propensity for PAS formation and is phakic post-goniosynechialysis, for example, I add pilocarpine for at least three to four weeks to help keep the angle tissues apart. For known steroid responders, I use lower-dose steroids such as Lotemax SM (loteprednol etabonate ophthalmic gel 0.38%) or Inveltys (loteprednol etabonate ophthalmic suspension 1%) to try and reduce the chance of pressure spikes. I temporarily stop prostaglandin analogs to avoid a slowing of the inflammatory process immediately after surgery, but continue with other glaucoma medications.

For routine follow-up, I have the patient back postop day one, postop seven to ten days, and postop three to four weeks. The main postoperative issue to be concerned about is elevated intraocular pressure. This could be the result of a steroid response, PAS formation, an occluded stent tip, or microhyphema so gonioscopy is key to determining the cause of IOP elevation. I'll typically burp the wound until day ten or beyond to see if there is a drop in pressure, and possibly add drops, while trying to stabilize the patient. I assess for early PAS formation, and if signs are apparent, I start pilocarpine to prevent further PAS formation. I also check for stent tip occlusion with associated MIGS.

Typically, any evidence of layering hyphema will clear. I can count on one hand the number of times I've had to do anterior chamber washouts for hyphemas to clear, but it's important to watch at-risk patients closely for PAS formation. With prolonged inflammation or IOP elevation, ocular surface dryness can become an issue. In these cases, artificial tears and similar products should be encouraged, to keep the surface well-lubricated. Once the anterior chamber is quiet, I will dial back the steroids and possibly take the patient off of them altogether, while potentially using NSAIDs at a higher dosage to avoid a rebound of inflammation.

TAKING ACTION

The first step to putting MIGS into practice is to seek out the right candidates. These patients have mild-to-moderate OAG with some degree of nerve reserve with visual fields and OCT findings that correlate. These are individuals for whom you're seeking a 20 to 30% pressure drop, or a reduction of one or more medications. These could be patients with pressures in the mid-teen range. Your MIGS candidates may have tried several topical medications and require cataract surgery. Or they may have undergone laser treatments but need further IOP reduction. Pseudoexfoliative or pigment dispersion syndrome cases tend do well with goniotomy procedures. And patients with pristine angles who have had failed trabeculectomies or tube shunts

could see good outcomes with MIGS procedures.

Individuals to avoid are those with significant primary angle closure or chronic uveitis because the cause of inflammation in the synechiae eye is likely to come back. If a person has a narrow angle, and the synechiae eye is appositional, that patient can do okay if the apposition isn't too high and hasn't been there too long. Individuals with active neovascularization or angle neovascularization caused by PAS should be avoided. Plateau iris, angle recession, or traumatic patients with glaucoma, and those with severely opacified corneas are not good prospects because you can't treat glaucoma if you can't see the angle in detail.

Once ideal patients are identified, the next step is to find and partner with surgeons who do MIGS. Some device representatives may be aware of doctors in the area who perform the associated procedures. However, it's key to remain "MIGS general" when making referrals, with the goal of providing patients with a variety of options. The most important step is to start referring MIGS candidates, and begin seeing greater patient and practice success.

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Exfoliation Syndrome

Pathophysiology of Exfoliation Syndrome

Louis R. Pasquale, MD, FARVO

As someone who seeks to uncover the root causes of disease, the pathophysiology of exfoliation syndrome—a condition involving the production of abnormal fibrillar extracellular material that accumulates in ocular tissues[1]—is something I've been fascinated with since I was a first-year resident.

The short answer is that we still don't know what's causing this condition, but research is revealing that climatic factors and the environment may play a major role. It should be emphasized that exfoliation syndrome is not just a cause of open-angle glaucoma (OAG), it truly is a panocular disease for many of the reasons explained below.

RISK FACTORS & ASSOCIATIONS

Studies are showing that glaucoma occurs more commonly in eyes exhibiting exfoliation syndrome than in those without it.[1] Furthermore, glaucoma derived from exfoliation syndrome tends to have a more serious clinical course and worse prognosis than primary OAG.[1]

Research also has revealed a higher risk of cataract formation and dense nuclear cataracts associated with exfoliation syndrome.[2,3] In patients with bilateral cases of exfoliation syndrome, we have found that the eye with more exfoliation material typically has the denser cataract. Situating itself on the zonule, the material triggers enzymatic activity that eats away at the zonular fibers over time, causing spontaneous zonulysis to occur.

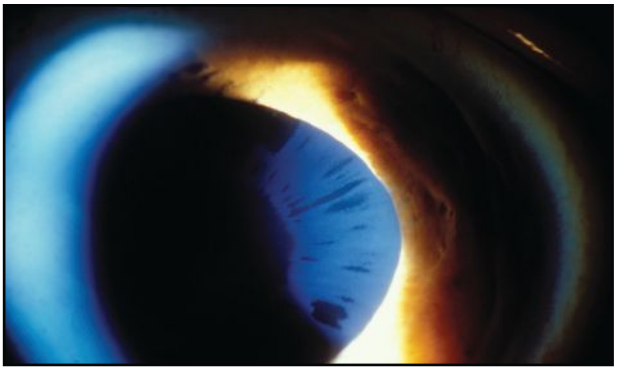

FIGURE 1. SPONTANEOUS ZONULYSIS.
Situating itself on the zonule, exfoliation material triggers enzymatic activity that eats away at the zonular fibers over time, causing spontaneous zonulysis to occur.
Images: Louis Pasquale, MD, FARVO

Patients with exfoliation syndrome are at greater risk of complications during cataract extraction.[3,4] Research has shown that their eyes dilate less well and have increased incidence of capsular rupture and vitreous loss, possibly due to zonular fragility and dehiscence.[2]

Furthermore, patients with exfoliation syndrome may be more prone to developing angle-closure glaucoma (ACG).[1] The development of ACG in exfoliation syndrome is a multifactorial process partially related to zonulysis, which can cause the lens to rotate forward. In addition, the lens grows thicker over time, exacerbating appositional angle closure.

Individuals with exfoliation syndrome also may be more vulnerable to retinal vein occlusion (RVO).[1,5] In one study, exfoliation syndrome and central RVO were strongly associated, and exfoliation syndrome was a potential independent risk factor for CRVO.[5] Exfoliation syndrome often is correlated with higher intraocular pressure (IOP)[1], which can impact on retinal venous outflow, increasing the proclivity for RVO.

Some exfoliation syndrome patients even present with a so-called "pseudouveitis."[6] They may have cells and flare with disruption of the blood-aqueous barrier, which can signal a bonafide cause of uveitis. Unfortunately, most patients I have managed with pseudouveitis haven't responded well to treatment with anti-inflammatory corticosteroids or

immunosuppressive drugs.

A MISNOMER

Some confusion has existed over the years about terminology used to reference the condition that I call "exfoliation syndrome." The syndrome, which many researchers and clinicians refer to as "pseudoexfoliation," is characterized by fibrillar deposits in the anterior segment of the eye.[7] The deposits have been found on and in the subconjunctival tissue, pupillary margin, ciliary epithelium; lens epithelium and capsule; iris pigment epithelium, stroma, and blood vessels; trabecular meshwork (TM), cornea, the zonule, and orbital soft tissues.[7]

Dr. Georgiana Dvorak-Theobald first shed light on the nomenclature of exfoliation syndrome in 1954 when she contributed a seminal paper in the *American Journal of Ophthalmology* describing the pathophysiology of "true exfoliation"[8]—a condition historically associated with glassblowers involving the splitting or delamination of the lens capsule."[9]

Dr. Dvorak-Theobald wrote at the time that although lens capsular delamination, or "true exfoliation," had been recognized for many years, case studies described in the paper pointed to another form of capsular change, which, in its "superficial characteristics" was so similar to true exfoliation of the lens capsule that it had been mistaken for it.[8] She proposed to call the second form of capsular change "pseudo-," or "false," exfoliation of the lens capsule, characterized by deposits or accretions of an unknown material on the lens capsule, ciliary body, and zonules.[8]

While Dr. Dvorak-Theobald used the term "pseudoexfoliation" for the latter condition, there's nothing "pseudo" about it. If you look at affected lens epithelial cells on electron microscopy, you'll see surface invaginations with electron-dense material that appear to exude perpendicular to the capsular surface. That's why I believe it is a true exfoliation syndrome. Personally, I think a better name for what Dr. Dvorak-Theobald described as "true exfoliation syndrome" would be "lens capsular schisis."

One can imagine the confusion in reporting the rare cases of patients exhibiting both conditions. A 63-year old Saudi male patient, described in the Oct. 14, 2014, edition of *Saudi Journal of Ophthalmology*, was diagnosed with unilateral "true exfoliation" and "pseudoexfoliation," confirmed histologically.[10] His OS lens exhibited dense cataract and exfoliation deposits, and delamination of the anterior lens capsule; the OD lens exhibited mature cataract with no exfoliation deposits. The researchers determined that exposure to high levels of infrared radiation in the desert may have played a part in capsular delamination, given that the nomadic male spent prolonged periods of time in the extreme environment.[10]

CASE SPARKS A QUEST

A 92-year-old female patient I previously followed propelled me to look more closely into the cause of exfoliation syndrome. Eleven years before the woman came to see me, she had had cataract surgery and posterior chamber lens (PCL) implantation in both eyes. Now, exfoliation material was developing on her IOL, and IOP was elevated, so I decided to do a trabeculectomy OD. I would have preferred a less invasive way to get the pressure down, but MIGS were still relatively new then.

I completed the procedure, and on post-op day seven, the

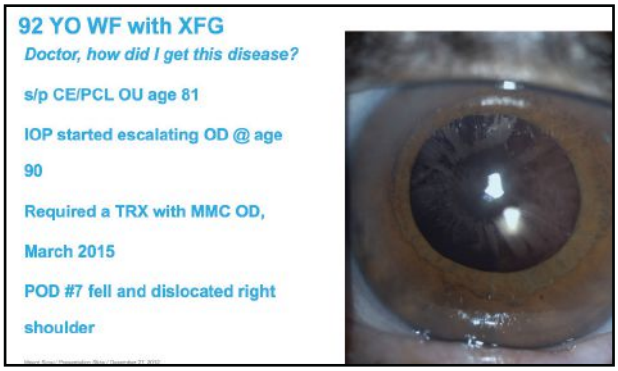

FIGURE 2. CASE OF EXFOLIATION SYNDROME.
A 92-year-old female patient I followed while on staff at Harvard Medical School propelled me to look more closely into the origin of exfoliation syndrome.

woman fell and dislocated her shoulder. My team was extremely concerned about her bleb, but it was fine. However, my patient asked me, "Doctor, how did this [exfoliation syndrome] happen to me?" So I launched into a mechanistic explanation about how the material accumulates in the anterior segment of the eye, and due to irido-lenticular contact, the material and pigment get released, which clog the drain and create TM dysfunction. I showed her the material in Schlemm's canal on histopathology and explained that, over time, this material can close the canal. So though we refer to this condition as a kind of OAG, it's really a form of ACG, I continued. My patient looked at me and said, "You didn't answer my question."

She was absolutely right. She wanted to know how the material formed in the first place. If we understood that, perhaps we could prevent it from forming, or figure out how to disassemble and remove it. In some studies, when surgeons have tried to remove it from the TM, it has reaccumulated.[11] That's because we haven't gotten to the root cause of why the material is forming.

EPIDEMIOLOGY

Shortly thereafter, my team began researching the origin of this condition. We first tried to pinpoint who gets exfoliation syndrome. The findings were somewhat surprising—even counterintuitive to what many clinicians might think.

For one thing, the assumption that people of African descent don't get exfoliation syndrome—possibly stemming from the prevalence of the condition in Scandinavian populations—did not pan out. My team did a review of population-based studies looking at cases in sub-Saharan Africa, and though virtually none were reported in Ghana and Tanzania, a number were documented in nearby countries such as Nigeria and Ethiopia.[12] The rate ranged from 5.1 to 7.7% in patients >40 years, which is considerably higher than that reported in African Americans.[12] Confirming what many of us already knew, exfoliation syndrome was strongly associated with increasing age.[12]

We also evaluated the association between demographic and

geographic factors and exfoliation glaucoma, using data from the Nurses' Health Study and the Health Professionals Follow-up Study.[13] In this mainly white US cohort, increasing age, female gender, and living in the northern region of the US vs. the middle or southern regions were significant risk factors for exfoliation glaucoma; yet, Scandinavian heritage was not.[13]

So the notion that there's an ethnic predisposition to exfoliation syndrome is not entirely correct. Moreover, just because some reports have documented rates greater than 10%, in Scandinavian patients[14,15] and up to 20% to 25% in the Scandinavian countries of Iceland and Finland,[15,16] that doesn't mean ancestry is the risk factor.

As a way to dig deeper, researchers have turned to epidemiology to uncover clues about the preclinical phase of the condition—before the material forms—and to establish a timeline for development. They have analyzed potential genetic and environmental factors, and interactions that may be involved in the genesis of the exfoliation material.

GENETIC THEORY

Many of my genome-centric colleagues immediately gravitate to genetics to explain all disease processes. However, in the case of exfoliation syndrome, just a few genetic biomarkers have been discovered.

In 2007, researchers looked at 274 cases of exfoliation syndrome and identified one gene, *LOXL1*, which has become synonymous with this condition.[17] Another group went to a higher order of magnitude, and among 2,628 cases, found one additional gene beyond *LOXL1 (CACNA1A)* that was significantly associated with increased susceptibility to exfoliation syndrome.[18] Several investigators from this team took a step further to analyze almost 14,000 cases, and identified only seven gene variants of *LOXL1* and *CACNA1A*.[19]

Peter M. Visscher, a Dutch-born Australian geneticist, and professor and chair of quantitative genetics at the University of Queensland, has researched trait variation in various populations, and has applied statistical analysis to quantify the contribution of DNA polymorphisms to variations. He noticed that every time investigators double a sample size in an agnostic search for pathology-related genes, the number of genes found for polygenetic diseases (prompted by the combined action of genes) should also double.

However, that trend did not play out in genetic studies for exfoliation syndrome. Furthermore, *LOXL1* gene variants thus far have not been found to have a causative role in the condition's disease process. Consequently, one could argue that exfoliation syndrome is not a polygenetic disease.

For comparison's sake, in 2010, genetic researchers assessed 1,264 cases of POAG and found one associated gene.[20] A team in 2011 looked at fewer cases (590) and still identified an additional gene associated with POAG.[21] Assessing 7,017 cases in 2016, researchers uncovered 12 genes correlated with POAG,[22] and when a group in 2018 evaluated 12,315 cases, the number of related genes jumped to 47.[23]

That's the way a polygenetic disease behaves when taking an agnostic search of the genome to find common polymorphisms. Every time you increase the sample size, you find more genes associated with the disease. That's a distinct difference between exfoliation glaucoma and POAG that needs to be acknowledged.

CLIMATIC & ENVIRONMENTAL EXPOSURES

A number of climatic and environmental risk factors have been proposed for exfoliation syndrome. They include ocular solar exposure, dietary folate intake, coffee consumption, autoimmune factors, and slow viral or microbial infections. I would argue that findings point most strongly to ocular solar exposure as a risk factor.

One of the first researchers to identify ocular solar exposure as a possible contributor to exfoliation syndrome was Hugh Taylor. In the 1970s, Taylor studied a population of Aboriginal males and identified a 16 percent prevalence rate of exfoliation syndrome in individuals over the age of 60.[24] Men who had worked as stockmen, lived at lower latitudes, and been exposed to higher levels of global radiation had significantly higher rates of exfoliation syndrome than other individuals studied.[24] As a result, Taylor postulated that the condition may be an environmental disorder caused by solar radiation.[24] Interestingly, its prevalence in urban-dwelling Australians was shown in one paper to be low, with an overall rate of 0.98%.[25] Taking both of these findings into account, we can deduce that people who are spending more time outdoors are getting more exfoliation syndrome than those who aren't.

In a study I was involved in, led by Jae Hee Kang at the Channing Lab at Harvard Medical School and Brigham & Women's Hospital, we used data from the Nurses' Health Study and the Health Professionals Follow-up Study to evaluate the relationship between time spent outdoors at various life periods and risk of exfoliation glaucoma.[26] Although no association was observed with greater time spent outdoors in the age range of 25 to 35, or 36 to 59 years, the pooled multivariable-adjusted rate ratio for ≥11 hours per week spent outdoors between high school and age 24 was 2.00 compared with ≤5 hours per week (95% confidence interval=1.30, 3.08; p=.001).[26] Increased time spent outdoors in young adulthood yielded a higher risk of exfoliation glaucoma, supporting an etiologic role of early exposure to climatic factors.[26]

This would suggest that the critical time spent outdoors for exfoliation syndrome is between high school and early college. Though the condition is often considered an age-related disease starting between 65 and 70, it appears that this is just when the consequences of activities from youth are setting in.

This idea also is supported by data around the world. Ravi Thomas showed that outdoor activity was correlated with increased risk of exfoliation syndrome in a South Indian population.[27] The prevalence of exfoliation syndrome increased with age: 3.01% (95% CI, 2.45 to 3.80) in those 40 or older, and 6.28% (95% CI, 4.80 to 7.76) in those 60 or older. And it was significantly higher in people whose occupation involved outdoor activities (adjusted odds ratio [OR], 2.14; 95% CI, 1.10 to 4.16)[27]

A smaller study out of the Island of Rab in the North Adriatic Sea reported the frequency of exfoliation syndrome among farmers and fisherman, and found a 21% appearance of the condition (mean subject age, 65 to 80 years).[28] Investigators concluded that chronic exposure to sunlight led to the high rate of exfoliation syndrome within these groups.[28]

SOLAR REFLECTIVES

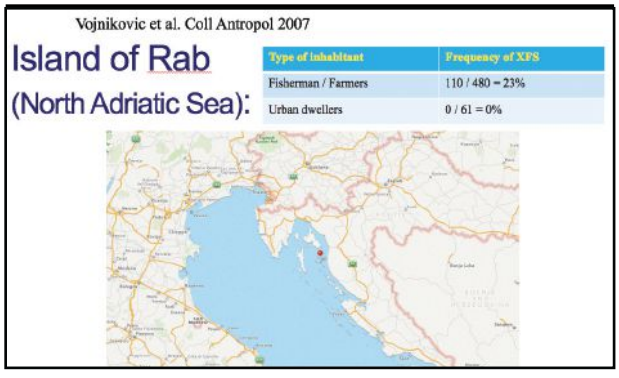

FIGURE 3. SUNLIGHT EXPOSURE IN ISLAND OF RAB
In a small study out of the Island of Rab finding a 21% appearance of exfoliation syndrome in farmers and fisherman, investigators concluded that chronic exposure to sunlight led to the high rate of exfoliation syndrome.[28]

My colleagues at Massachusetts Eye & Ear Infirmary in conjunction with Israeli investigators assessed the relationship between residential history, solar exposure, and exfoliation syndrome.[29] The main outcome measures were weighted lifetime average latitude of residence and average number of hours per week spent outdoors, as determined by validated questionnaires.

In multivariable analyses, each degree of weighted lifetime average residential latitude away from the equator was associated with 11% increased odds of exfoliation syndrome (pooled OR, 1.11; 95% CI, 1.05 to 1.17; p<.001).[29] Every hour per week spent outdoors during the summer, averaged over a lifetime, was associated with 4% increased odds of developing exfoliation syndrome (pooled OR, 1.04; 95% CI, 1.00 to 1.07; p=.03). For every 1% of average lifetime time spent wearing sunglasses in the summer between 10am and 4pm, odds decreased by 2% (OR, 0.98; 95% CI, 0.97 to 0.99; p<.001) in the US, but not in Israel (OR, 1.00; 95% CI, 0.99 to 1.01; p=.92; P for heterogeneity=.005).[29]

In the US, after controlling for environmental covariates, history of work over water or snow was correlated with increased odds of exfoliation syndrome (OR, 3.86; 95% CI, 1.36 to 10.9); in Israel, too few people were available for analysis.[29] Interestingly, we did not identify an association between brimmed hat wear and exfoliation syndrome (p>.57).[29] These findings suggested that ocular exposure due to light from reflective surfaces may be an important type of exposure in exfoliation syndrome etiology.[29]

This new idea about solar reflectivity being the possible X-factor for exfoliation syndrome pathophysiology started our research team heading in a new direction. The ongoing challenge is how to measure solar reflective impacts. Our goal is to estimate ocular ultraviolet exposure during times when individuals were most susceptible to this condition. We also are trying to evaluate high-risk geographies for ocular ultraviolet exposure—where a great deal of sunshine and reflective surfaces such as sand or snow offer a wealth of opportunities for the sun to bounce off surfaces and into the eye.

ONGOING RESEARCH & OBSTACLES

My team at New York Eye and Ear Infirmary of Mount Sinai is studying whether history of basal or squamous cells in the head and neck region—keratinocyte malignancies known to be ultraviolet-related—is a risk factor for exfoliation syndrome. While other factors may be at issue, data from the Nurses' Health Study and the Health Professionals Follow-up Study is revealing that individuals with these malignancies have a roughly 40% increased chance of developing exfoliation syndrome.

Conversely, we are finding that many patients with exfoliation syndrome have a history of dermatological malignancies. If, for example, a person had a basal cell carcinoma on one side of the face, we're assessing whether that corresponds with worse exfoliation syndrome. We think these malignancies may be the best biomarkers to assess ocular ultraviolet dosing at the present time.

For now, the ocular ultraviolet exposure theory of exfoliation syndrome has not resonated with the scientific community due to several confounding factors. First, exfoliation syndrome commonly is asymmetric, and no published scientific evidence can explain why one eye gets more exfoliation material than the other. In addition, we don't have an established animal model to confirm the solar reflectivity hypothesis. And though the ocular ultraviolet dose in young adulthood may be key, it's a difficult exposure to measure. Beyond that, exfoliation material can be found on intraocular surfaces not exposed to ultraviolet rays. And, finally, erythemal ultraviolet exposure is higher closer to the equator, but exfoliation syndrome is an extra-equatorial disease.

My latest idea for how exfoliation material forms comes from studying histopathological specimens of ciliary or lens epithelia. I believe these cells attempt to remove elastin stress fibers because lysosomal enzymes are unable to dissolve them. Those enzymes cause cell surface in-folding where the positively charged elastin fibers emanate. Highly electro-negative glycosaminoglycans then surround the material, initiating a nucleation or crystallization reaction. I believe that's how the exfoliation material starts. To better understand this process and further explore the ocular ultraviolet exposure theory, we will need additional research to provide illumination.

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