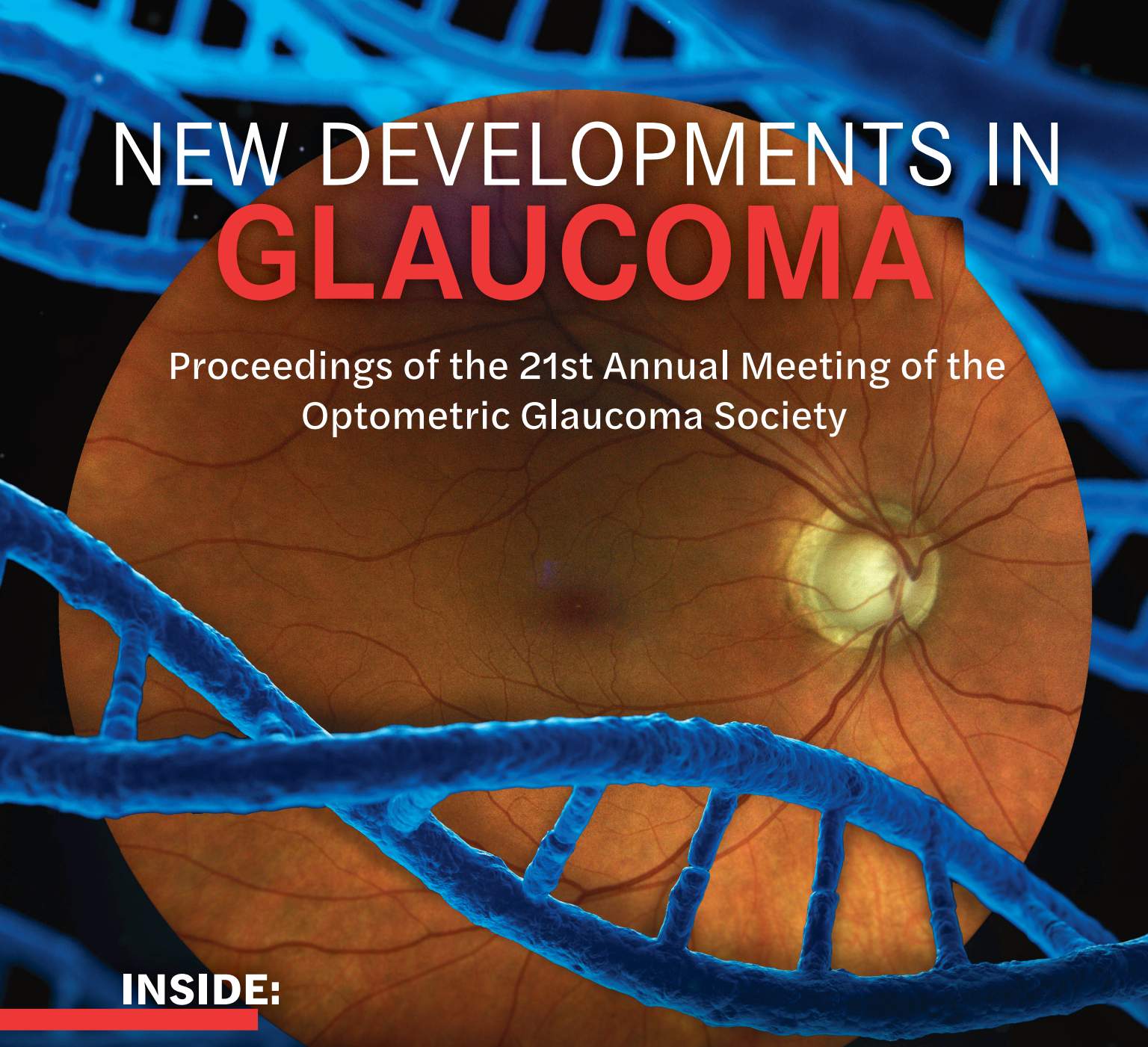
NEW DEVELOPMENTS IN GLAUCOMA

Proceedings of the 21st Annual Meeting of the Optometric Glaucoma Society



INSIDE:

- Advances in Glaucoma Genetics
- Fifty Years of Managing Structural and Functional Change in Glaucoma
- Unusual Structural Signs of Glaucoma and Progression

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SUPPLEMENT TO:
REVIEW of OPTOMETRY
March 2024

VYZULTA®
(latanoprostene bunod ophthalmic solution), 0.024%

GO FOR IOP CONTROL FROM THE START

Go for monotherapy with VYZULTA
to give your open-angle glaucoma or ocular hypertension patients:

SIGNIFICANTLY GREATER IOP REDUCTION
vs Xalatan (latanoprost) 0.005% and timolol 0.5%[1-3]*†

<1% EXCELLENT TOLERABILITY
Low incidence of hyperemia and <1% discontinuation due to any ocular AE[4,5]

BETTER MEDICARE PART D COVERAGE THAN EVER BEFORE
~75% coverage in Medicare Part D without a latanoprost failure necessary‡

*__APOLLO/LUNAR study design:__ Two Phase 3, randomized, multicenter, double-masked, parallel-group 3-month studies were conducted comparing the IOP-lowering effect of once-daily VYZULTA with that of twice-daily timolol 0.5% in patients with open-angle glaucoma or ocular hypertension: APOLLO (VYZULTA, n=284; timolol, n=133) and LUNAR (VYZULTA, n=278; timolol, n=136).[1,2]

†__VOYAGER study design:__ Phase 2, randomized, investigator-masked, parallel-group dose-ranging study comparing VYZULTA with Xalatan (latanoprost) 0.005% in patients with open-angle glaucoma or ocular hypertension (N=413) to determine the optimal drug concentration of VYZULTA in reducing IOP. The primary efficacy endpoint was reduction in mean diurnal IOP at Day 28.[3]

‡IQVIA FIA April 2023; MMIT Portal, June 2023.

GO TO **VYZULTAHCP.com**

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
- 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 full Prescribing Information on adjacent page.

References: 1. Weinreb RN, Scassellati Sforzolini B, Vittitow J, Liebmann J. *Ophthalmology*. 2016;123(5):965-973. **2.** Medeiros FA, Martin KR, Peace J, Scassellati Sforzolini B, Vittitow JL, Weinreb RN. *Am J Ophthalmol*. 2016;168:250-259. **3.** Weinreb RN, Ong T, Scassellati Sforzolini B, Vittitow JL, Singh K, Kaufman PL; VOYAGER Study Group. *Br J Ophthalmol*. 2015;99(6):738-745. **4.** VYZULTA. Prescribing Information. Bausch & Lomb Inc. **5.** Weinreb RN, Liebmann JM, Martin KR, Kaufman PL, Vittitow JL. *J Glaucoma*. 2018;27(1):7-15.

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VYZ.0022.USA.24

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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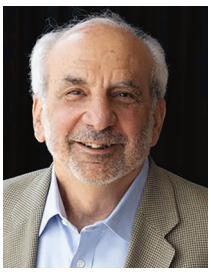

The 21st Annual Scientific Meeting of the Optometric Glaucoma Society, held October 10-11, 2023, in New Orleans, brought together leading experts who shared with us the latest glaucoma findings, ongoing clinical challenges, and progress made over the last 50 years in evaluating this "black beast" of a disease, as one speaker put it.

Our OGS Honoree, Janey Wiggs, MD, PhD, submerged us deeply into the waters of glaucoma genetics, an area of research holding the promise of uncovering the molecular events underlying disease. Truthfully, we treat glaucoma but don't really know what's causing it.

Dr. Wiggs' team, as part of a global consortium, has identified hundreds of DNA risk variants characterizing many features of primary open-angle glaucoma (POAG). In the future, polygenic risk scores will help us identify glaucoma suspects with a high likelihood of disease, who may have more severe presentations or earlier onset, and who could benefit from greater surveillance. I think we can all say a collective "amen" to potentially identifying and managing glaucoma sooner.

In the President's Lecture, Richard K. Parrish III, MD, took us on a 50-year journey through structural and functional evaluation, starting with his early days training at some of the country's top eye institutions. It's hard to believe the breadth of information available with today's OCT when just five decades ago, glaucoma clinicians were drawing concentric circles to document optic nerve cupping. Not to use a trite advertising slogan from the '60s, but we really have "come a long way, baby."

Research Excellence Awardee Brad Fortune, OD, PhD, gave us an intriguing picture of glaucoma-associated changes to the retinal structure uniquely presenting on OCT. From hypodense holes to INL pseudo-cysts, you may be wondering whether you missed several installments of your favorite journal reporting these signs. Investigators have been studying these phenomena for 15 years and learning how to use them to detect and monitor glaucoma.

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

MURRAY FINGERET, OD

Founding Member and Past President, Optometric Glaucoma Society
Editor, New Developments in Glaucoma

OGS HONOREE

Advances in Glaucoma Genetics

Janey Wiggs, MD, PhD

Genetics holds the key to many of our health problems. Numerous disease processes can be better understood and managed with the right genetic approach. For glaucoma, the discovery and characterization of genes that contribute to individual susceptibility offers the field of glaucoma three important opportunities:

First, genetics can help identify the molecular events underlying disease. We treat glaucoma, but we really don't know what's causing it. Secondly, identifying molecular events that are dysregulating physiologic processes can lead to pathways for novel therapeutics that address root issues. Lastly, pinpointing genes that contribute to glaucoma offers an opportunity to assess patient risk before disease develops. Genetic testing can identify people at risk presymptomatically, so screening, testing, and therapy can be targeted to high-risk suspects and patients likely to rapidly progress.

Fortunately, the field of glaucoma genetics has seen dramatic advancements in technology, such as next-generation sequencing, leading to a number of gene discoveries.

A HERITABLE CONDITION

Glaucoma is one of the most heritable of all human conditions, and it spans the lifespan. Some babies are born with congenital glaucoma while other individuals are affected with glaucoma throughout their lives.

Though uncommon, early-onset forms of the disease such as juvenile open-angle glaucoma (JOAG) and anterior segment dysgenesis syndromes are inherited as Mendelian traits caused by rare mutations that tend to occur in families. For many years, we had identified just 10 causative genes for early-onset glaucoma, but last year my group uncovered two more.

In contrast, adult forms of glaucoma such as

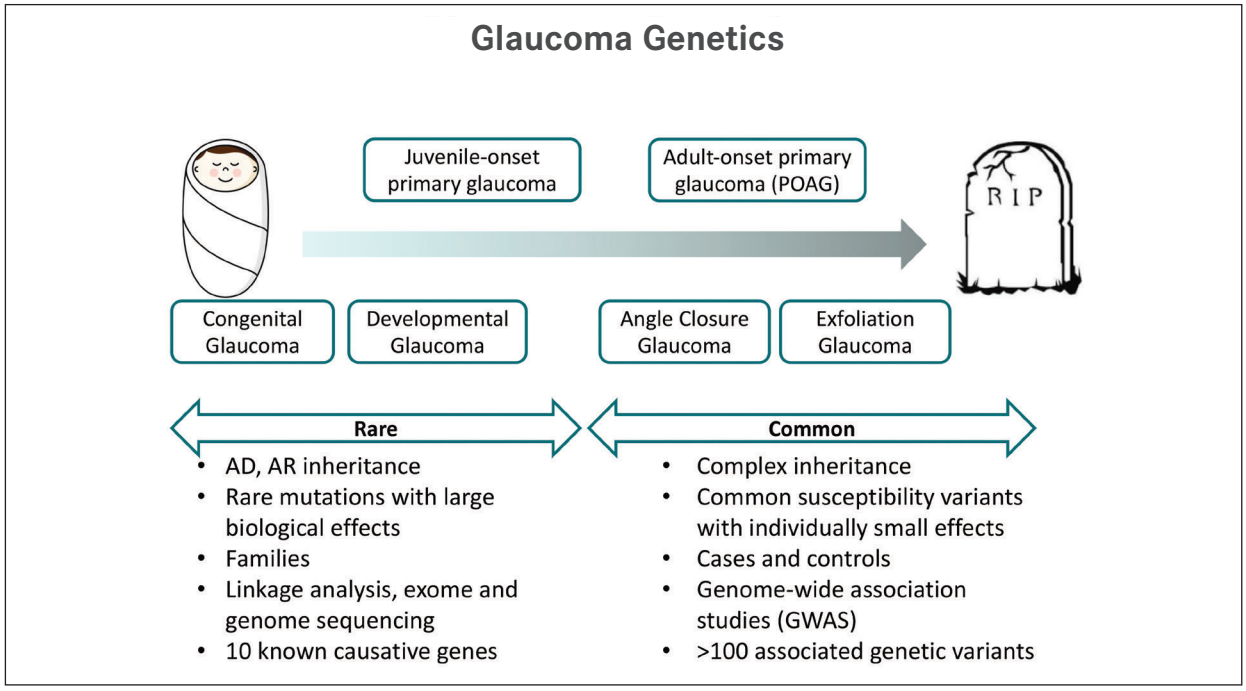

FIGURE 1. Not Just a Disease of Aging.
Genetics research is changing the way we view glaucoma.
Images: Janey Wiggs, MD, PhD

primary open-angle glaucoma (POAG), angle closure, and exfoliation syndrome, are relatively prevalent in populations and have complex inheritance due to joint effects of common susceptibility variants or alleles that individually have a negligible effect on disease risk but in aggregate can reach the disease threshold.

Since adult-onset forms of glaucoma don't always occur in families, researchers conduct genome-wide association studies (GWAS) to compare the distribution of DNA variants between cases and controls. Recently, we published a paper noting more than 300 genes associated with adult-onset glaucoma,[1] and over the last several years we've used the data from our POAG GWAS to develop polygenic risk profiling for different populations.

Early-Onset Glaucoma Discovery

Initially, we used genetic testing to identify individuals with known gene mutations in early-onset glaucoma. We offered gene carriers genetic counseling according to their inheritance patterns, along with targeted surveillance and timely initiation of therapy. We also began compiling a database of individuals who may benefit from gene-based therapies once developed.

Then, as a way to begin looking for new genes in early-onset glaucoma, a fellow in my lab, Ryan Collantes, identified 12 large families from the Philippines to be tested for gene mutations. As it turns out, the Philippines houses an ethnically diverse population with a number of founder populations—an effect that reduces genomic variability over time, promising to facilitate genetic discovery.

We performed whole exome sequencing, which looks at the coding part of the genome, and found mutations in known glaucoma genes in four of the families. Three had myocilin (MYOC) mutations similar to those found in Caucasian European populations, and one had a PAX6 mutation. For the remaining families, we filtered the data for features that would be expected in disease-causing mutations and found that three of the families had mutations in EFEMP1, a gene that hadn't previously been associated with early-onset glaucoma.[2] All three mutations showed the evolutionary conservation expected for disease-causing mutations.

Seeking to better understand EFEMP1's role in early-onset glaucoma, we considered the gene's role in other diseases. EFEMP1 causes Doyne's honeycomb retinal dystrophy and Malattia Leventinese as a result of a single missense allele causing the Arg345Trp mutation.[3] We also looked at other findings and uncovered one report of a family with adult-onset glaucoma shown to have a rare

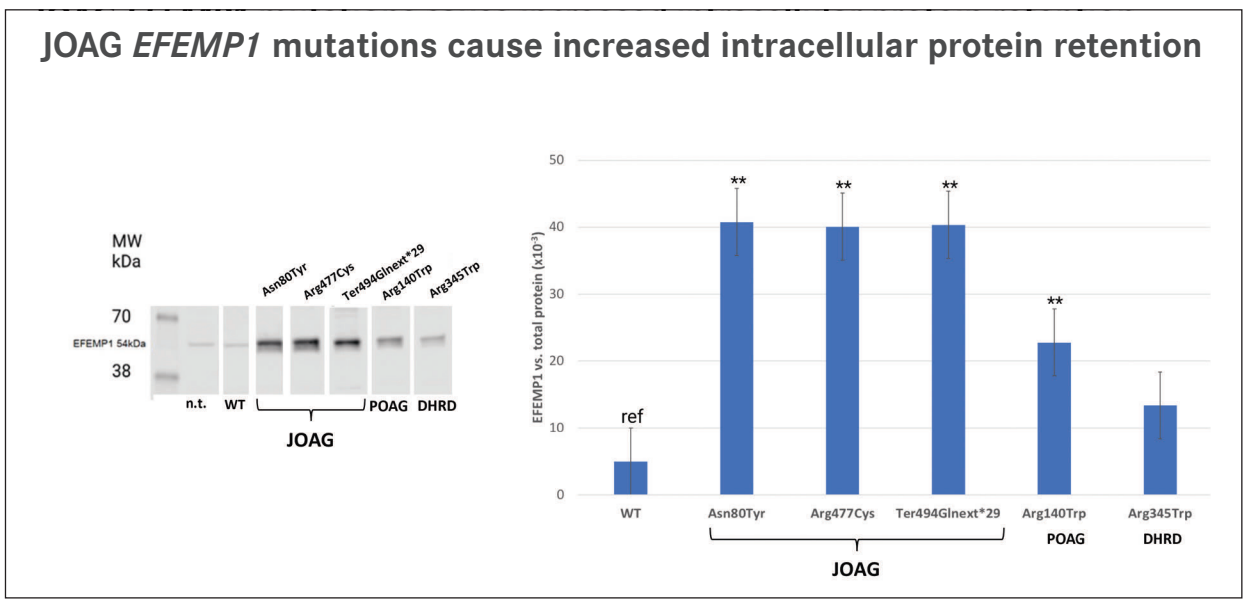

FIGURE 2. Uncovering How Mutations Cause Severe Disease.
We found variants in early-onset glaucoma had much more intracellular retention of aggregated protein.

variant.[4] Some noncoding variants in the genomic region that include EFEMP1 have also been associated with IOP and POAG, according to GWAS findings.[5,6] However, our report was the first of EFEMP1 in early-onset glaucoma.

My group wanted to understand how the gene's mutations cause severe disease so we engineered plasmid constructs with the mutated protein, and transfected cells, or artificially introduced nucleic acids into cells. We found the mutant protein was aggregated in the cell and not secreted as it normally would have been. Compared with adult-onset glaucomas and Doyne's cases, the mutations in early-onset glaucoma had much more intracellular retention—a common disease-causing defect.

We hypothesized that mutations causing severe juvenile glaucoma are retained almost 100% intracellularly, with a few exceptions. The Doyne's mutation is a special case in which the protein is normal but escapes and forms subretinal deposits. And the variant uncovered in the family with adult-onset glaucoma was partially secreted, a kind of an intermediate phenotype.

Our findings pointed to EFEMP1 as a new gene target for JOAG. Interestingly, while this is a relatively common cause of disease in the Filipino population, EFEMP1 mutations have not been observed in juvenile glaucoma families from the US. We are uncertain whether this is due to a founder phenomenon or differences in families' background genetics and want to learn more about the mechanism causing intracellular protein retention.

Another gene discovery last year came from our studies of several small families, more typical of those in the US population. A specific mutation was found in the THBS1 gene in two Australian families, and one US family. Though these families had different ethnicities, they all had mutations in the same amino acid residue of thrombospondin (THBS1).

To help us validate these results, Haojie Fu and colleagues at Boston Children's Hospital made a CRISPR (gene-edited) mouse with the mutation. The team showed that the mouse exhibited features of glaucoma, including elevated pressure, reduced aqueous outflow, and retinal ganglion cell loss, as well as an accumulation of aggregated protein material in the outflow pathways.[7] Importantly, this was not intracellular, but extracellular, aggregated protein material that increased over time and was correlated with elevated intraocular pressure.

We then developed an in vitro assay enabling us to modify plasmids by injecting different amino acids into the altered genes' amino acid residue. This revealed a correlation between the amount of protein destabilization and extracellular matrix accumulation of aggregated protein, confirming a direct relationship between the mutations, protein misfolding, and extracellular protein aggregation.

Our subsequent hypothesis is that THBS1 mutations in early-onset glaucoma lead to secretion of an abnormal protein that aggregates in the trabecular meshwork and reduces outflow. The two genes we found last year in diverse ethnic populations both impact the extracellular matrix—an encouraging finding considering the number of other proteins in the extracellular matrix we can begin to target.

Genetic Factors and POAG

We created the International Glaucoma Genetics Consortium to facilitate large GWAS by producing the sample size needed to study genes for complex inheritance diseases such as POAG.

After studying more than 34,000 POAG cases and more than 300,000 controls across the globe, we identified 44 previously unreported risk loci and confirmed 83 known loci in POAG.[6] The majority of genes discovered had consistent effects across multi-ethnic ancestries.

Importantly, we learned that DNA variants, called "SNPs," affected disease risk similarly across populations. Most of the genes acted through elevating intraocular pressure, partly due to an ascertainment issue because IOP was a defining feature of many of the cohorts recruited, but which nevertheless appeared to be an important genetic component to disease risk. We also found that the genes discovered by the GWAS were associated with different biological processes and pathways, such as response to laminar fluid shear stress, lipid transport and storage, blood vessel morphogenesis, and vascular development.

HARNESSING THE POWER OF GWAS

To leverage the findings from our POAG GWAS and reach some of our clinical goals, we assessed individual subjects' aggregate number of variants and created a score based on the total number of risk alleles. The concept of a polygenic risk score was previously used by cardiology researchers, who showed, for example, that people with a high burden of common risk alleles for heart attack had the same overall risk score as individuals with rare Mendelian inherited variants.[8]

A High Genetic Burden and POAG

We and our Australian colleagues began looking at the overall disease risk of having a high genetic burden in the setting of POAG.[9] Jamie Craig's group found in the Australian ANZREG population that individuals in the 90th percentile of a given polygenic risk score had 15 times greater risk of disease, 5-to-10-year earlier onset, a thinner retinal nerve fiber layer, and increased need for incisional surgery than those at the bottom of the distribution. The team also showed that people in the 90th percentile had a faster rate of visual field progression.[10] We found in a study with Nazlee Zebardast, a young colleague at Mass Eye and Ear,[11] that OHTS participants in the 90th percentile of the risk score were more likely to convert from ocular hypertension to POAG.

To test the polygenic risk score's ability to detect disease in a given population, we turned to the UK biobank, which includes primarily Caucasian British individuals.[12] We found that people in the 90th percentile were 7 times more likely to have POAG than those in the 10th percentile. In addition, cases in the 90th percentile were more likely to have features of glaucoma such as higher intraocular pressure, thinner nerve fiber layer and ganglion cell complex, and differences in corneal hysteresis and resistance factor. The polygenic risk score did a reasonably good job of identifying POAG cases in a large, admittedly somewhat ethnically homogeneous, population.

Environmental and Biological Risk Factors

We've used the polygenic risk score in a few other ways. A 2021 study we did with Lou Pasquale investigated the effect of caffeine on glaucoma risk.[13] Overall, caffeine didn't have a strong effect on intraocular pressure unless

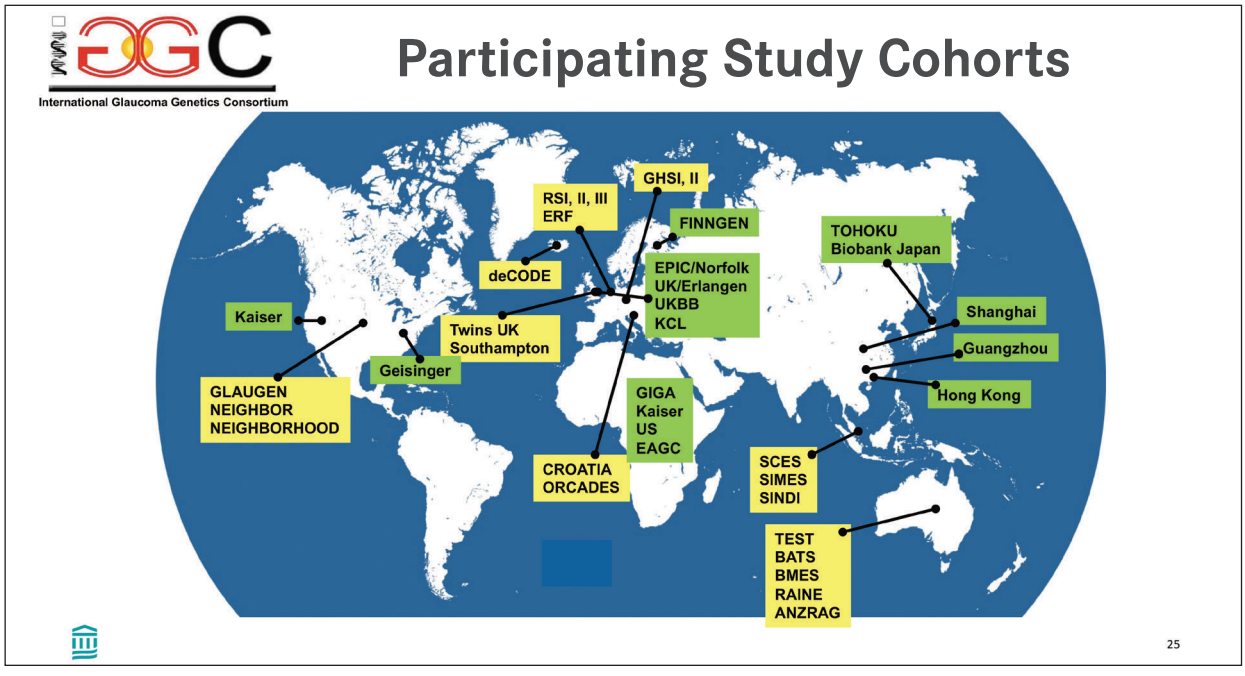

FIGURE 3. International Glaucoma Genetics Consortium.
This map illustrates the global study teams in our consortium that contributed to our final analysis.

individuals were in the high polygenic risk percentile. Then, the higher score combined with greater caffeine intake was associated with increased intraocular pressure and risk of glaucoma. We found similar results when looking at polygenic risk and a MYOC mutation, which causes a Mendelian type of glaucoma. People with the mutation and high polygenic risk were more likely to have disease than those with the mutation alone.[14]

We've also started teasing apart the biological pathways identified in our GWAS to create polygenic risk scores for each pathway. So far, Inas Aboobakar, a fellow in the lab studying the mitochondrial proteins TXNRD2 and ME3, has found that those with a high genetic burden in this pathway are more likely to have paracentral central vision loss. Interestingly, this same pathway impacts NADPH production and is related to the NAD+ pathway that Simon John, PhD, and others have suggested is involved in glaucoma pathogenesis.

THE FUTURE

Looking ahead, many genes still need to be discovered for early-onset glaucoma, and we're working to better understand the genes we have. The dark matter of the genome, the non-coding area, is another area of focus to look for additional causality. We have much to learn about polygenic risk, including how it is inherited in families, so that we can best counsel gene carriers.

GWAS have identified hundreds of POAG risk variants that characterize many features of glaucoma; now we're trying to better understand the underlying mechanisms impacted by these genes. Polygenic risk scores can help us identify individuals with a high likelihood of disease, who may have more severe presentations or earlier onset, and who could benefit from increased surveillance. We've shown that risk scores can affect genetic and environmental risk factors, and may be associated with clinical features such as paracentral scotoma and mitochondrial disorders. And while polygenic risk can impact other factors, we want to learn if the reverse is also true. These are just a few of the many questions we have left to answer. ■

Janey Wiggs, MD, PhD, is the Paul Austin Chandler Professor of Ophthalmology, Co-Director of the Glaucoma Center of Excellence, and Associate Director of the Ocular Genomics Institute, at Harvard Ophthalmology; and Associate Director of the Howe Laboratory at Mass Eye and Ear.

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PRESIDENT'S LECTURE

Fifty Years of Evaluating Structural and Functional Change in Glaucoma

Richard K. Parrish III, MD

After the last 50-plus years of advancing technology to evaluate structural and functional changes in glaucoma, we know significantly more than we did when I completed medical school in the mid-1970s, but we still have much to learn. Though the tools we rely on to manage this "black beast" of a disease are imperfect, they are vital in our ability to identify, monitor, and manage glaucoma in our patients.

EARLY HISTORY WITH STRUCTURE AND FUNCTION (1972-1982)

As a medical student in the early 1970s, we were using direct ophthalmoscopes to evaluate structure at the Indiana University School of Medicine. The instruments, offering a monocular, non-stereoscopic, 5-degree field of view, reflected light from a bulb at right angles through a mirror or prism, and projected a spot through the iris to illuminate the retina. We never dilated the pupil, and frankly, I'm not sure I saw an optic nerve before I graduated. To assess function, I learned enough to pass anatomy and physiology, but I'm not sure if I ever did a confrontation visual field on anyone in my four years at school.

As an intern at the University of Alabama at Birmingham (UAB) in the mid-'70s we still rarely dilated patients, in large measure because the university relied on its world-class optometric and ophthalmic facilities to manage most of the patient workload. If a question came up about a patient's visual function, we likely waved our fingers to the side of the individual's face and said something to the effect of, "Do you see something over here?" The only concept of visual field loss we had was tied to clearly defined hemianopic defects associated with strokes. I can't remember recording a single visual acuity, probably because any patient with a visual complaint was sent straight to the Department of Ophthalmology.

During my residency in the late '70s at Wills Eye Hospital, we were still using mainly undilated direct ophthalmoscopy to evaluate structure. Occasionally, we turned to a Hruby lens, a -58.6 D plano-concave lens placed in front of the cornea to produce a magnified image of the retina. Also available was the Goldmann Contact lens, with its three mirrors angled at 59, 67, and 73 degrees to indirectly view the fundus and anterior chamber, with the central lens to view the posterior pole. The Goldmann lens aided in identification of angle structures and had a large flange that vaulted over the cornea and required coupling fluid, which made the procedure messy.

When it came to describing and documenting the appearance and size of optic nerve cupping, most residents were limited to drawing circles within circles. Dr. Spaeth had 35 mm Kodachrome film to produce non-stereoscopic color disc photographs for his private patients, but the equipment rarely was used for patients in the resident glaucoma clinic.

To assess function, confrontation visual fields were mainly relegated to the neurology clinic, and technicians normally handled Goldmann visual fields; the results were highly suspect if residents performed them. In 1979, the first standard automated perimetry device, the Octopus, was available for Dr. Spaeth's private clinic patients.

Thinning Rims, Disc Changes, and Improving Perimetry

As a fellow at Bascom Palmer Eye Institute in the early '80s, we were still drawing circles to document the cup, but now with more attention to neuroretinal rim thickness. A decade earlier, Doug Anderson and Ralph Kirsch had published a landmark paper[1] describing the association between cupping and glaucomatous optic neuropathy, with the help of stereoscopic images. Finally, the field of glaucoma was gaining an appreciation of focal neuroretinal rim thinning.

Awareness also was increasing about optic disc changes characterized by the so-called "Drance" or

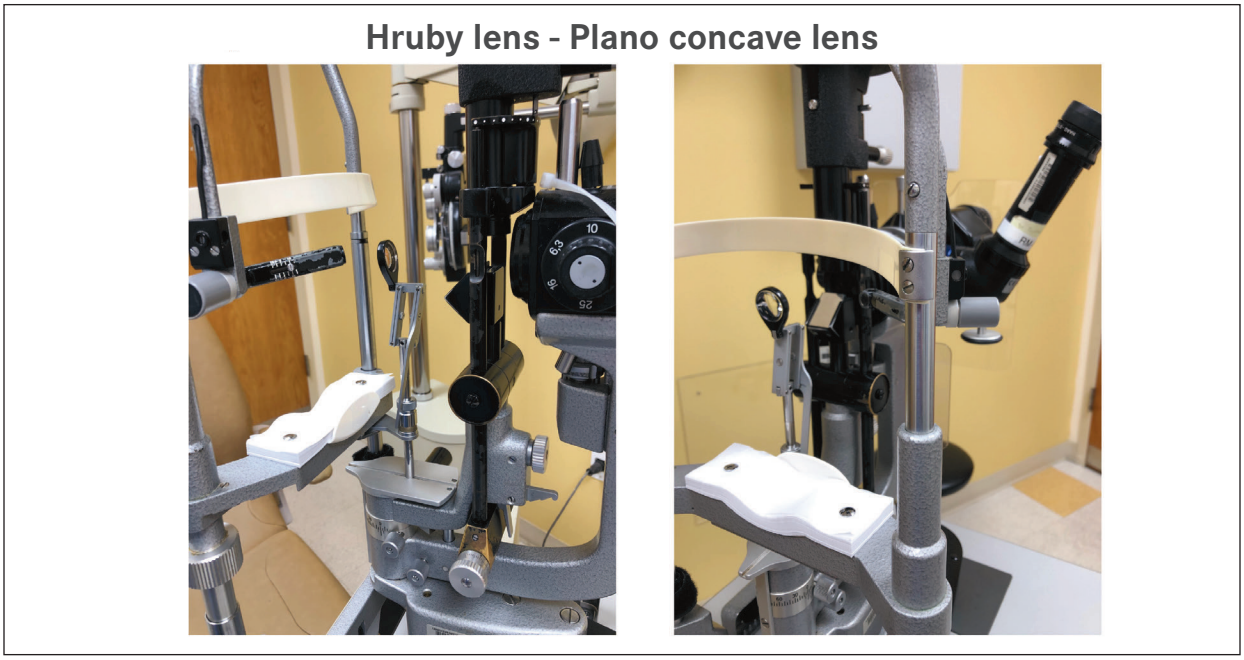

FIGURE 1. Hruby Lens.
As a fellow at Bascom Palmer Eye Institute, I began routinely using the Hruby lens, which is still my favorite way to look at the optic nerve.
Images: Richard K. Parrish III, MD

"splinter hemorrhage," described in 1977.[2] In their single report, Drance, et al., had documented a flame-shaped disc hemorrhage at the 1:00 position as a sign of acute ischemic optic neuropathy. Subsequently, the team wrote that such a presentation was associated with "chronic simple glaucoma" and "ocular hypertensives who developed field defects."[3]

Our structural evaluations were improving with the ability to sequentially review stereo disc photographs as 35 mm slides in a viewer. And I routinely used the Hruby lens, which is still my favorite way to look at the optic nerve. Though the Goldmann Contact lens was considered the gold standard to view the angle, the need for a coupling agent and the potential to impact the ocular surface made it less than ideal.

Evaluating functional change often involved kinetic (non-static) perimetry using a Goldmann bowl-type perimeter with I4e, II4e, III4e, IV4e, and V4e targets. Offering us a kind of topographic map of the visual field, the perimeter produced strikingly accurate findings when performed by trained technicians. However, the introduction of standard automated perimetry with the Octopus really marked the transition to a much more quantitative visual field.

For my fellowship project, I began testing the reproducibility of the so-called "Squid" automated kinetic perimeter, which developers believed held the promise of exceeding the Octopus and defining targets. Unfortunately, technical flaws negated the instrument's usefulness, as noted in our peer-reviewed paper,[4] and I joke the device may now serve as one of the sunken reefs off the coast of Key Biscayne.

MODERN DAY STRUCTURAL AND FUNCTIONAL EVALUATION (1982-2024)

By the late 1980s, we had furthered our structural understanding when a German research team showed us a normal range for the optic disc, cup, and neuroretinal rim size with a paper on the ISNT rule.[5] The group reported that normal neuroretinal rim area ranged from 0.80 to 4.66 mm^2 (mean, 1.97 ± 0.50 mm^2) and was significantly correlated ($p<0.00001$) to the optic disc area, with the thickest area in the inferior region, followed by the superior, nasal, and temporal regions. In the researchers'

findings, only two of 457 discs (0.4%) exhibited the thinnest neuroretinal rims in a region outside of temporal. In fact, 15 years earlier, Anderson and Kirsch had reported that focal rim thinning along the vertical axis of the visual field was most the characteristic feature of glaucomatous damage.

In addition, the Goldmann Contact lens was rarely used to evaluate structure, and we began to see the rise of bioconvex lenses for slit lamp biomicroscopy. Like indirect ophthalmoscopes, the lenses used the eye's refractive power as a convex lens component. Today, the classic +90D seems to be the most popular lens although I prefer the +78D, which has greater magnification. Many of our younger, technologically minded residents also favor the Super 66® and Digital Series 1.0x (both from Volk), which offer virtually no magnification.

While all the bioconvex lenses are useful tools to evaluate structure, it's worth remembering the images are inverted and need to be manipulated for an upright view. That's one reason why I and a few of my faculty colleagues continue to use the Hruby lens. We appreciate not having to go through a series of slit lamp gyrations to confirm what we are seeing. Some of my residents marvel at the direct view offered by my Hruby lens when giving it a try.

Ongoing Hurdles in Evaluating Structure

Despite advancing technology, evaluating structure remains one of our great challenges. We have seen the rise and fall of various imaging devices to help us evaluate the retinal nerve fiber layer (RNFL). Many of us recall in 1991 the introduction of the Heidelberg Retina Tomograph (HRT) and in 1999 the HRT II confocal retinal scanning laser tomography devices using reflectivity to deliver 3D photos of the optic nerve and retina. As effective as the HRT II was, it later would be eclipsed by optical coherence tomography (OCT). For a time, scanning laser polarimetry emerged with a confocal scanning laser ophthalmoscope and integrated polarimeter (Zeiss GDx VCC) to quantitatively look at the RNFL.

In the late 2000s, we lost our 35 mm sequential Kodachrome photographs when Kodachrome phased out its last products in 2009. Then we moved to simultaneous digital disc images from Nidek, which eventually became obsolete. Now, at my institution, sequential digital paired images are rapidly shot in a way to generate a stereoscopic pair—which should indicate the challenge today of using

What you see and why

	Field of view	Magnification	Working distance
Slit Lamp Lenses			
90D	**89**	**0.76**	**7mm**
Digital Wide Field	124	0.72	5mm
Super Field NC [1]	116	0.76	7mm
78D	**97**	**0.93**	**8mm**
Super 66	**96**	**1.0**	**11mm**
Digital 1.0x	**72**	**1.0**	**12mm**
Digital High Mag	70	1.3	13mm
Indirect Lenses			
20D	**60**	**3.13**	**50mm**
28D	**69**	**2.27**	**33mm**
Pan Retinal 2.2	73	2.68	40mm
Digital Clear Field	72	2.79	37mm

[1]The Super Field lens was not included in this review. It is comparable to the digital wide field lens, but with less glare.

FIGURE 2. Biconvex Lenses for Slitlamp Biomicroscopy
The rise of biconvex lenses for slit lamp biomicroscopy gave us many choices with which to view the optic nerve and retina.
Table courtesy of eyeguru.org: https://eyeguru.org/blog/volk-lens-review/

VYZULTA®
(latanoprostene bunod ophthalmic solution), 0.024%

GO FOR IOP CONTROL FROM THE START

Go for monotherapy with VYZULTA
for your open-angle glaucoma or ocular hypertension patients.

POWERFUL IOP REDUCTION

Up to 9.1 mmHg IOP reduction from baseline in 2 pivotal Phase 3 studies[1]*

EXCELLENT TOLERABILITY

<1% Low incidence of hyperemia and <1% discontinuation due to any ocular AE[1,3]

UNIQUE DELIVERY OF NITRIC OXIDE

Dual MOA: Unique delivery of nitric oxide and latanoprost acid improve outflow[3-5]

*VYZULTA demonstrated a mean IOP reduction of 7.5-9.1 mmHg from baseline across 9 evaluated time points over 3 months vs 6.6 mmHg-8.0 mmHg for timolol 0.5%.[1,2] **APOLLO and LUNAR study designs:** Two Phase 3, randomized, multicenter, double-masked, parallel-group 3-month studies were conducted comparing the IOP-lowering effect of once-daily VYZULTA with that of twice-daily timolol 0.5% in patients with open-angle glaucoma or ocular hypertension: APOLLO (VYZULTA, n=284; timolol, n=133) and LUNAR (VYZULTA, n=278; timolol, n=136).[1,2]

GO TO **VYZULTAHCP.com**

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
- 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 full Prescribing Information on adjacent page.

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VYZ.0022.USA.24

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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photographs to evaluate structural progressive change. Despite the obstacles, I still find it beneficial to have at least one baseline photo to make comparisons over time.

OCT Changes Glaucoma Evaluation

Perhaps no technology has so altered the landscape of glaucoma evaluation as OCT. In 1996, Zeiss introduced the first OCT device, which produced images based on reflected near-infrared light. Six years later, the company followed up with the Stratus time domain (TD) OCT using interferometry to generate images with an axial resolution of 10 µm. Spectral-domain (SD) OCT showed up next, with its spectrophotometer and Fourier transformation to generate images with an axial resolution of approximately 5 µm. The Heidelberg Spectralis, Zeiss Cirrus, and Optovue RTVue-100 all offered SD-OCT and evolved over time with new iterations, sometimes under new names. In 2015, we saw the first swept-source (SS) system from Topcon, offering a light source wavelength centered at ~1 µm that swept across a narrow band of wavelengths. In my mind, it remains to be seen whether SS-OCT offers additional benefits over its spectral-domain predecessor.

Visual Field Testing Improvements

Our ability to evaluate functional changes in glaucoma patients has come a long way over the years, starting with the entrance of the Humphrey Field Analyzer (HFA) static threshold perimetry device in 1984. The technology has been a dominant player in the functional testing space, and subsequent versions have included the HFA II-I and HFA3. In the late 1990s, we saw the appearance of Frequency Doubling Technology (FDT) Perimetry, although I can't recall seeing many patients with findings from this technology.

Testing strategies also have dramatically improved since the mid-'80s—with the entrance of HFA Full Threshold 30-2 in 1984, utilizing a grid of 76 points spanning the central 30 degrees of the visual field; 24-2 came three years later. Humphrey STATPAC was introduced in 1987, with a reported sensitivity of 93% and specificity of 84%.[6] The Swedish interactive thresholding algorithms (SITA) entered the field, eventually replacing Full Threshold Humphrey FASTPAC in 1997.[7] Twenty years later, SITA Faster arrived in 2018 for the HFA3. In between, Short Wave Automated Perimetry (SWAP) emerged using a blue stimulus on a yellow background to stimulate cone and rod photoreceptors in the retina but overall has failed to meet many of our expectations.

EVALUATING THE OPTIC DISC

Over time, our evaluation of the optic disc has improved with a greater understanding of structural anatomy and advancing technology. By the late '80s, assessing the optic disc usually involved first determining the disc diameter or circumference (i.e., linear rim) and then examining the optic nerve and nerve fiber layer using direct or indirect ophthalmoscopes.

In 1990, Quigley, et al., offered us parameters for a normal range of disc sizes using the cup-disc (C/D) ratio.[8] And in 2002, Dr. Spaeth outlined a Disc Damage Likelihood Scale[9] describing eight stages of damage based on the circumferential extent of neuroretinal rim loss, or more simply, width of the neuroretinal rim. Though complex, the DDLS essentially conveyed that a small optic cup in a small disc may indicate glaucomatous damage, which others have reported,[10] yet, a large cup in a large disc might be normal for that patient and present

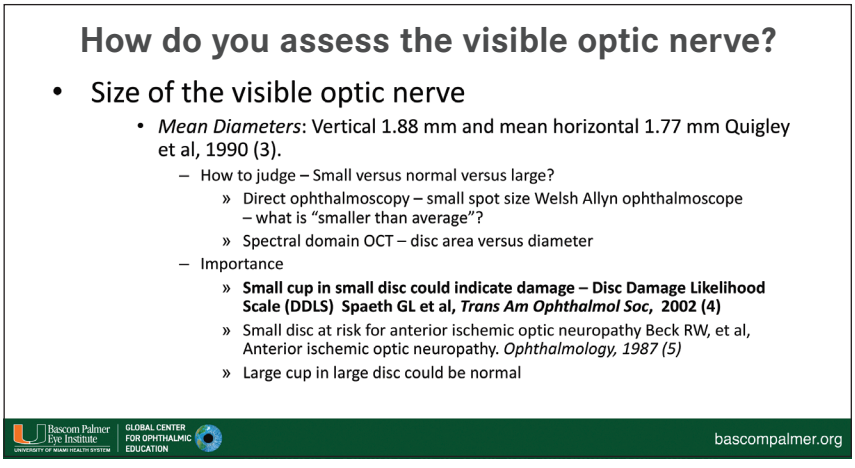

FIGURE 3. Disc Damage Likelihood Scale
Dr. Spaeth published a paper outlining a method to estimate the amount of optic nerve damage caused by glaucoma.[9] Though the DDLS was found to be as reproducible as the C/D ratio system of estimating the amount of disc damage in glaucoma patients, clinicians found it difficult to understand.

since birth.

In addition, we were given general guidelines for observing the disc using direct and indirect ophthalmoscopes. We were instructed, for example, that normal disc size should be roughly the size of the small aperture (5 degrees) when using a Welch Allyn direct ophthalmoscope.[11] Indirect slit lamp biomicroscopy had its own set of specifications.

Thankfully, OCT technology has saved us when it comes to determining disc size. It's important to note that SD-OCT defines disc size in terms of the disc area unlike methods calculating the diameter. The Cirrus HD-OCT from Zeiss, the device with which I'm most familiar, offers normative databases to quantitatively compare optic nerve head (ONH) measurements and the thicknesses of the RNFL, macula, and ganglion cell plus inner plexiform layer (GCIPL) to a database of normal subjects.

Thankfully, OCT technology has saved us when it comes to determining disc size. It's important to note that SD-OCT defines disc size in terms of the disc area unlike methods calculating the diameter.

– Richard K. Parrish III, MD

Looking at disc size, for example, the device's normative database areas fall into three main buckets: a lower third (<1.58 mm^2), a middle tertile (1.58-1.88 mm^2), and the largest findings (>1.88 mm^2). Since an average disc area falls between 1.58 and 1.88 mm^2, a disc area that is larger than 2.5 mm^2 or smaller than 1.33 mm^2 wouldn't be applicable for this normative database and other technology would be needed.

USING TODAY'S STRUCTURAL AND FUNCTIONAL DATA TO MAKE DECISIONS

In 2024, thanks to a wealth of information available from today's SD-OCT devices, I can look for evidence of structural and functional change on the OCT reports to help make decisions for patients, in addition to using traditional methods. I search for structural changes, particularly RNFL loss, to aid in my diagnoses of glaucoma suspects, and continue to weigh findings of structural loss more heavily when looking for signs of progression in mild to moderate glaucoma. Once disease reaches moderate to advanced stages, I rely on both structural and functional data to aid in management decisions for patients. Individuals thought to be rapidly progressing on visual fields likely already have a tremendous amount of RNFL loss.

Once we get to the patient's "floor," when structural loss no longer is detectable on retinal imaging, obviously functional findings supersede structure. We're still doing research to find out what constitutes the floor. One team tried to estimate it and found that more GCIPL tissue remained above the floor in advanced glaucoma compared to other measurements, suggesting GCIPL thickness was a better candidate for detecting progression.[12] The bottom line is we're seeking more definitive answers. Despite tremendous strides made over the last 50 years in evaluating structural and functional change in glaucoma, we still have a great deal to learn. ■

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RESEARCH EXCELLENCE AWARDEE

Unusual Structural Signs of Glaucoma and Progression

Brad Fortune, OD, PhD

Over the last 15 years, investigators have been studying unusual changes in retinal structure associated with the development of glaucoma. These phenomena are difficult to detect by clinical examination alone, but readily revealed using optical coherence tomography (OCT). Importantly, they can interfere with commonly used measurements to detect disease and track progression and can lead to incorrect conclusions about the status of disease.

Gaining an awareness about the unique appearance and patterns of these sometimes-subtle OCT manifestations is a useful step toward recognizing them, and may offer clinicians additional information with which to make more informed patient management decisions for their glaucoma patients.

HYPODENSE HOLES OF THE RNFL

The first suspicious sign was uncovered by Don Hood's laboratory at Columbia University. At ARVO in 2010, members of Don's group introduced what they called "hypodense holes."[1] These apparent holes were identified on OCT circumpapillary B-scans within the retinal nerve fiber layer (RNFL) of glaucoma suspects and patients. As the circle scan moved around the disc, researchers noticed a lack of reflectance in areas that appeared optically like holes. The report from Xin, et al.[1] noted the holes tended to be at the poles adjacent to major vessel trunks within the superior and inferior quadrants, and proximate to or within NFL defects. They were detected in 25% of glaucoma suspects and patients, although none were found in age-matched healthy controls.

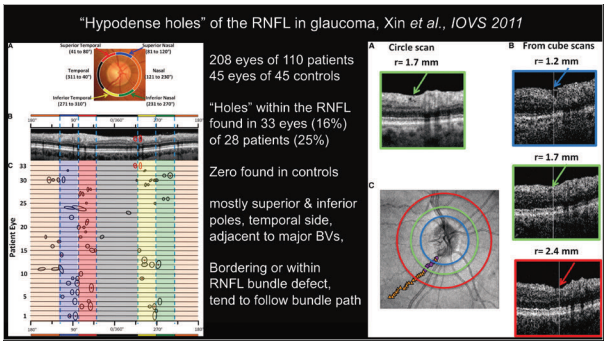


FIGURE 1. Hypodense Holes on OCT.
As part of their research on hypodense holes, Xin, et al.,[1] used a grid scan of the macula to map the holes' position. In Figure 1, Panel C reveals the holes are actually tube-like in shape.
Images adapted by Brad Fortune, OD, PhD, from Xin, et al.

PIRDS & PARAVASCULAR DEFECTS

The story regarding the discovery of these holes continued to unfold in 2015 with a group of investigators not specifically looking at glaucoma, publishing a paper on a structural sign they had uncovered and named "perivascular inner retinal defects," or "PIRDs."[2] Muraoka, et al., wrote that PIRDs appeared on fundus photography as spindle- or caterpillar-shaped dark areas along the major retinal vessels, disconnected from the optic disc. On OCT cross-sections, PIRDs looked like cystoid- or fissure-like spaces, while longitudinal OCT sections revealed most PIRDs were wide defects located in the inner retina or beneath major retinal vessels, frequently deviating into the vitreous cavity.

The researchers reported, of 41 eyes with PIRDs, 90% were myopic and 51% had high myopia. Fifty-one percent showed epiretinal membrane (ERM) in the macular area as PIRDs were forming along the temporal arcade vessels that increasingly deviated toward the fovea by ERM traction. Thirty-five had visual field defects commonly associated with Bjerrum scotoma (75%) and nasal steps (59%), corresponding to PIRD locations.

The researchers concluded that PIRDs primarily occurred in eyes with high myopia or ERM, and their pathogenesis may be the result of deviated retinal vessels from axial elongation or ERM traction. In addition, PIRDs tended to cause retinal dysfunction in the areas they were located and sometimes overlapped with retinal lesions previously reported as RNFL/inner retinal cleavage, paravascular retinal cysts, or lamellar holes.

This finding was intriguing to many of us in glaucoma

FIGURES 2A and B. Paravascular Defects.[3]
In Figure 2A, the top left and right images reveal paravascular defects can appear like the hypodense holes from Xin, et al. In Figure 2B, the circumpapillary B-scan in the red inset box is associated with the yellow line on the main en face image. The appearance of the hypodense hole changes along the infratemporal vein where the retinal parenchyma has been separated from the vessel.
Images: Brad Fortune, OD, PhD

research. A year later, we collaborated with Don Hood's group on a study[3] that was a follow-up to the Xin, et al., paper on hypodense holes. Using many of the glaucoma patients and suspects from the 2011 research, this study utilized widefield grid scans to evaluate the holes' topography.

Of 19 eyes, 13 were characteristic of the PIRDs noted by Muraoka, et al., and extended beyond the circumpapillary region, and of the 13, 9 had previously associated ERM and/or high myopia. The remaining 6 revealed paravascular defects in a small region that didn't fit the previously described appearance of PIRDs and were related to an RNFL arcuate defect. However, the holes seen on the circumpapillary OCT scans of glaucoma patients and suspects were associated with local glaucomatous damage, high myopia, and ERMs, effectively outlining a class of retinal tissue defects that heretofore weren't as widely appreciated.

PERIPAPILLARY RETINOSCHISIS

Several teams of investigators have documented an association of peripapillary retinoschisis (PPRS) with glaucoma, but our paper was the first to show the condition is not only more prevalent in glaucoma, but also related to the rate of glaucomatous progression.[4] Our group compared functional, structural, clinical, and demographic characteristics between glaucomatous peripapillary retinoschisis (PPRS) cases and controls in 166 glaucoma suspects and patients.

We found no significant differences ($p>0.05$) in age, sex, visual acuity, central corneal thickness, IOP, or presence of vitreous adhesion between PPRS cases and controls. However, PPRS eyes tended to have a higher cup-to-disc ratio ($p=0.06$), thinner RNFL ($p=0.02$), and worse visual field mean deviation ($p=0.06$) than controls (age-matched glaucomatous eyes without PPRS).

On OCT scans, we noted hyperreflective structures spanning the PPRS eyes and observed morphology and spacing consistent with Müller glia, suggesting that during PPRS, Müller cells inner processes exhibit increased signal attenuation and cast "shadows" onto distal retina. We concluded glaucomatous PPRS was associated with faster overall rates of RNFL thinning and visual field deterioration, and showed Müller cell involvement on OCT. We also showed that PPRS can occur bilaterally and recur within the same eye. Importantly, we found, as several other previous reports had also demonstrated, PPRS can interfere dramatically with the OCT image segmentation and measurement of peripapillary RNFL thickness, among the most common OCT parameters used for detection of glaucoma and progression monitoring. Our paper showed clearly that the presence of PPRS can mask dramatic progression of RNFL thinning revealed only upon resolution of the schisis, without closer inspection of the OCT B-scans and/or advanced image segmentation analysis.

INL PSEUDO-CYSTS, "MICROCYSTIC MACULAR DEGENERATION," AND OUTER RETINAL THICKNESS

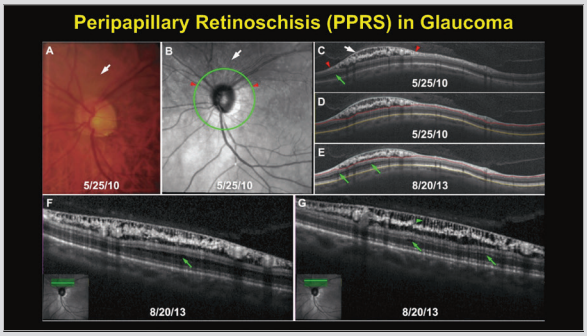
To demonstrate the next retinal phenomenon, it's useful to turn to experimental studies we've conducted on

Features of Peripapillary Retinoschisis and Müller Cell Morphology

Images adapted by Brad Fortune, OD, PhD, from Fortune, et al.[4]

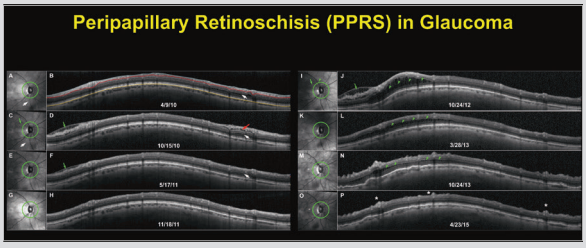
In **Figure 3A** the infrared SLO reflectance image illuminating an area of peripapillary retinoschisis in **Panel B**, looks slightly darker. However, **Panels C through E** reveal on circumpapillary B-scans a massive schisis separating the internal limiting membrane (ILM) from the ganglion cell inner plexiform layer (GCIPL). The RNFL bundle can be seen in the schisis cavity although the ganglion cell layer (GCL) is likely located along the base of the schisis cavity. **Panels F and G** were made without, and then with, segmentation, as RNFL thickness is roughly twice what it would be normally. To measure NFL and demonstrate progression, we went to great pains to re-segment just the bundles.

FIGURE 3A



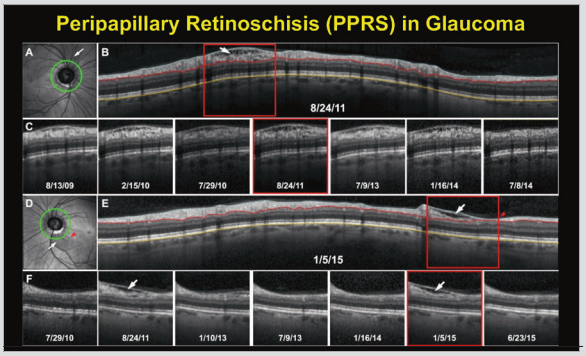
In **Figure 3B** it's evident the peripapillary retinoschisis is evolving over time. Several years later in this series, a schisis is visible in the outer retina even though the inner retinal schisis has collapsed a bit.

FIGURE 3B



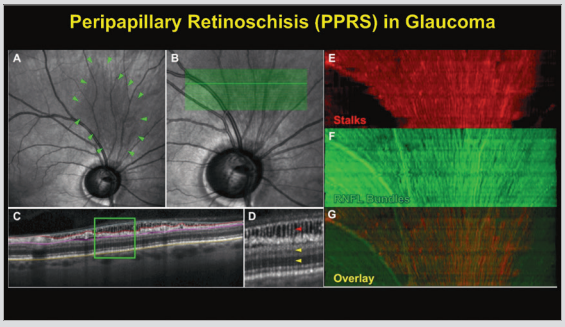
In **Figure 3C** a schisis collapsing and reforming can be seen over various time points as the NFL continues to thin. This finding is pathological because the vessels, which are normally embedded in the NFL, are protruding into the vitreous cavity. Once NFL starts to disappear, the vessels either remodel into the outer retina or protrude into the vitreous, or both. It's important to note peripapillary retinoschisis happens in the position of an NFL defect. The infrared reflectance image in **Panel D** points to evidence between the red and white arrows the schisis is reforming and collapsing again. The NFL at the final time point is dramatically thinned from its initial appearance.

FIGURE 3C



In **Figure 3D**, bridging structures or "stalks" that cross the schisis cavity can be seen in **Panel D**. On magnification, it's apparent the stalks flare out laterally and cast shadows similar to Müller cell morphology. **Panel E** shows segmented stalks colored in red, **Panel F** shows segmented NFL bundles colored in green, and the **Panel G** overlay of **Panels E** and **F** reveals no overlap; the stalks are located between the axon bundles.

FIGURE 3D



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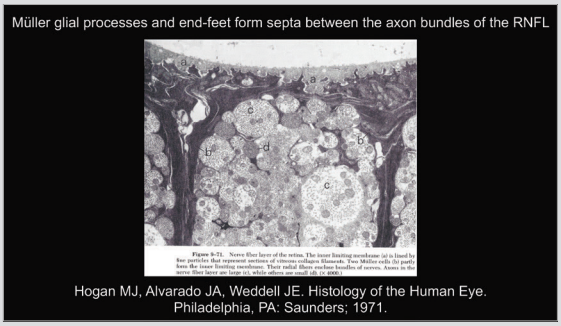
non-human primates revealing these animals can develop severe bow-tie atrophy and loss of their inner retinas.[5] This phenotype, which we had initially termed idiopathic bilateral optic atrophy,[6,7] has since been associated by Sara Thomasy and colleagues at UC-Davis with a mutation in the OPA1 gene, which causes dominant optic atrophy in humans. These apparent microcystic spaces, or "pseudo-cysts," as histological findings indicate,[5] can form in the inner nuclear layer (INL) any time there is significant loss of the inner retina (i.e., in any optic neuropathy), particularly if rapid progression occurs[5,6] and lead to inner retina loss such that the inner plexiform layer (IPL) ends

In **Figure 3E** depicting a 1971 histologic image from Hogan, et al.,[1] the inner retinal processes of the Müller cells separating the NFL bundles can be seen. The cells flare out where their footplates join the ILM. Some researchers have argued Müller cells act like optical fibers[2] that transmit light between the inner and outer retina through their cell bodies. However, if the cells are stretched out and no longer capable of conducting light, they may cast a shadow similar to the stalk characteristics of peripapillary retinoschisis. We think peripapillary retinoschisis can serve as a kind of proxy to observe Müller cells in the living eye.

FIGURE 3E



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up against the internal limiting membrane (ILM).

Clear examples of these findings in clinical glaucoma have been shown by Brazerol, et al., who demonstrated that glaucomatous damage leads to a gradual thickening of the INL and potential development of microcystic macular edema in more severe glaucoma cases.[8] The group defined these changes, along with nerve fiber layer (NFL) and ganglion cell layer (GCL) loss, as "glaucoma-associated retrograde maculopathy." As part of their investigation, researchers created a GCL map of one of the studied glaucoma eyes and showed the INL in the diseased eye appeared thicker than a healthy control. NFL thickness was plotted as a stage of glaucoma severity against ganglion cell inner plexiform layer (GCIPL) thickness and revealed a tight correlation; as NFL thinned, the sum of the INL and IPL thickened. However, glaucoma eyes without microcystic macular edema had a significant inverse association of INL thickness with disease severity. I speculate that this is the result of a mechanical effect, whereby the remaining retina expands axially as the inner retina degenerates, likely due to involvement of Müller cells preventing total "collapse" of the retina to the degree that would otherwise match loss of the inner retina.

Supporting this idea, Kristian Franze and colleagues uncovered that epiplakin (EPPK1), which is thought to play a role in intermediate filament organization, was highly expressed in macular Müller cells.[9] EPPK1 knockout in a human Müller cell-derived cell line led to a decrease in traction forces and changes in cell size, shape, and filopodia characteristics. The take-home is, as the inner retina disappears in glaucoma, there's only so much Müller cells will shorten before the outer retina starts to thicken.

This is consistent with the ideas Brandon Lujan and Jon Horton posited in a 2013 paper[10] in which they argued that the INL doesn't collapse in severe optic atrophy due to inward and lateral vitreous traction exerted by intact or partially detached posterior hyaloid membrane. The posterior hyaloid inserts into the retinal internal limiting membrane (ILM), itself bound to the footplates of Müller cells that serve in part as a retinal scaffold. Some of the volume formerly occupied by degenerated cells is replaced by fluid-filled microcysts in the INL. Furthermore, the authors added, patients with relatively mild volume loss, weak vitreous traction, strong intercellular adhesion, or macula-sparing optic neuropathies don't develop microcysts.

In 2015, Hasegawa, et al., found that microcystic INL lesions in glaucomatous eyes were closely associated with NFL/GCL thinning and worse visual field rates of progression, and may indicate progressive damage in glaucoma.[11] They determined the pseudo-cysts occurred in rapidly declining eyes based on visual fields, mean deviation, and rate of change over time. In other words, having an advanced stage of glaucoma and/or rapid progression significantly increased the odds of having pseudo-cysts.

UNIFYING EXPLANATION FOR MÜLLER MECHANICS & ONH TISSUE SCHISIS

Offering a mechanistic explanation for these retinal phenomena are several studies published over the last

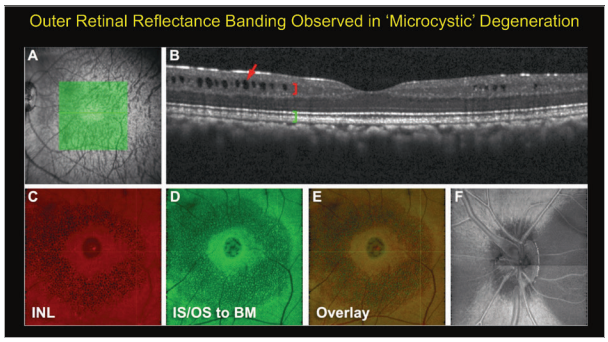

FIGURE 4. Microcystic Macular Degeneration in Primates. Imaging from this non-human primate experimental model exhibits what we formerly called "bilateral optic atrophy." Pseudo-cysts in the INL are indicated by the red arrows in Panel B corresponding to the green line in Panel A on a B-scan through the fovea. Panel D is an en face slab projection image of the IS/OS junction revealing a shadow in the position of the cysts. The Panel F en face reflectance image shows bow-tie atrophy with a characteristic "butterfly" pattern of axon loss affecting the temporal and nasal quadrants. Müller cells are activated in this location, casting shadows between the cysts and creating a darker view of the reflectivity from the deeper retina. Notably, pseudo-cysts occur where the inner retina is normally thickest in health. In this advanced case of microcystic macular degeneration, the pseudo-cysts adopted a C-shaped distribution where the inner retina would have been most robust.

almost 40 years, starting with a landmark paper that came out in 1987.[12] The team, which tracked optic disc photographs and blood vessel analyses over time to assess the optic disc vasculature, reported positional centrifugal shifts in 16 optic discs of 19 glaucoma patients over 10 years. Researchers pointed out the position of the vasculature's major trunks tends to be nasalized in the glaucomatous optic nerve head.

Strongly compelling evidence of longitudinal changes in the position of retinal vessels came in 2014 from Nate Radcliffe et al.,[13] who evaluated the position of the retinal vasculature in progressive glaucoma patients using masked analysis of stereo photos and alternation flicker software. One segment of the team studied positional changes in vessels using a flickering image paradigm while another used traditional measures to evaluate signs of structural progression. Researchers found optic nerve head rim loss and disc hemorrhage, and a trend of increased rate of functional loss, were significantly associated with retinal vessel shifts. Eyes exhibiting positional shifts of the retinal vascular over time were associated with a faster rate of visual field and rim loss, although, the strongest predictor of vessel shifts was the presence of a disc hemorrhage. Similarly, a 2017 paper in non-human primate experimental glaucoma[14] measuring the position of the first bifurcation of the major retinal artery and vein locations found the vessels were displaced toward the optic nerve head as optic nerve head cupping increased.

Somewhat earlier, in 2006, Oyama, et al., underscored the notion of a unified extracellular matrix when writing that collagen fibrils in the optic nerve head form a continuous network serving as a skeletal framework to protect nerve fibers from mechanical stress and sustain blood vessels.[15] They noted the lamina cribrosa contains elastic fibers exhibiting plasticity against mechanical forces affected by elevation of intraocular pressure, while glial cells, with an astrocytic character, are integral in constructing the connective tissue framework characteristic of the optic nerve head.

So, it is important to recognize that the lamina cribrosa is contiguous with the glial-lined extracellular matrix (ECM) of the pre-laminar and retrolaminar optic nerve septa, as well as with the ECM of retinal vessel walls; they are essentially one continuous entity. The lamina cribrosa is a more elaborate collagenous structure than the septa between axon bundles, but ultimately, they are all connected. This understanding provides a substrate for associating the well-known deformations of

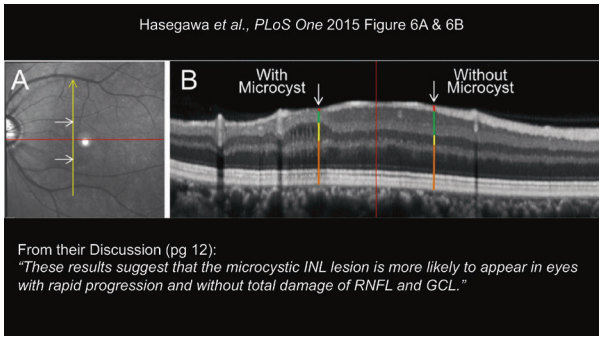

FIGURE 5. Microcystic INL Changes and NFL Defects in Glaucoma. Images from Hasegawa et al.,[11] reveal the widespread nature of NFL loss in progressing eyes and visibly thicker INL containing pseudo-cysts. Such findings likely will interfere with automated segmentation algorithms and OCT's ability to measure thickness.

the lamina cribrosa caused by pathognomonic activity of glaucoma, with retinal vessel displacements documented in the aforementioned studies. That is, mechanical strain resulting from lamina cribrosa deformation may be directly transmitted through the ECM to the retina via blood vessel walls and ILM, straining Müller cells in the process, as they form the septa between axon bundles within the RNFL.

WHAT WE KNOW

It's clear glaucoma exerts a mechanical impact on the retina. Manifestations include perivascular inner retinal defects (PIRDs), peripapillary retinoschisis, and INL pseudo-cysts likely overlapping or exacerbated by high myopia and/or ERM. Peripapillary retinoschisis is associated with RNFL defects and faster glaucomatous progression. And pseudo-cysts, which occur where the inner retina was thickest during health, are related to rapid progression in glaucoma and other optic neuropathies. I outlined in a perspective article a theory to connect glaucomatous optic nerve head deformation with the development of these retinal lesions.[5]

Moreover, we have evidence that Müller glia, which are responsible for much of the retina's mechanobiology and fluid balance, are involved in the retinal presentations discussed. It is likely that future studies about these structural signs and glaucoma in general will reveal additional OCT evidence of reactive gliosis in the living human eye. ■

Brad Fortune, OD, PhD, is the Van Buskirk Chair of Ophthalmic Research, Senior Scientist, Director of Electrodiagnostic Services, and one of the Principal Investigators at the Discoveries in Sight Research Laboratories at Devers Eye Institute.

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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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VYZULTA®
(latanoprostene bunod ophthalmic solution), 0.024%

GO FOR IOP CONTROL FROM THE START

Go for monotherapy with VYZULTA
to give your open-angle glaucoma or ocular hypertension patients:

SIGNIFICANTLY GREATER IOP REDUCTION
vs Xalatan (latanoprost) 0.005% and timolol 0.5%[1-3]*†

<1% EXCELLENT TOLERABILITY
Low incidence of hyperemia and <1% discontinuation due to any ocular AE[4,5]

BETTER MEDICARE PART D COVERAGE THAN EVER BEFORE
~75% coverage in Medicare Part D without a latanoprost failure necessary‡

*__APOLLO/LUNAR study design:__ Two Phase 3, randomized, multicenter, double-masked, parallel-group 3-month studies were conducted comparing the IOP-lowering effect of once-daily VYZULTA with that of twice-daily timolol 0.5% in patients with open-angle glaucoma or ocular hypertension: APOLLO (VYZULTA, n=284; timolol, n=133) and LUNAR (VYZULTA, n=278; timolol, n=136).[1,2]

† __VOYAGER study design:__ Phase 2, randomized, investigator-masked, parallel-group dose-ranging study comparing VYZULTA with Xalatan (latanoprost) 0.005% in patients with open-angle glaucoma or ocular hypertension (N=413) to determine the optimal drug concentration of VYZULTA in reducing IOP. The primary efficacy endpoint was reduction in mean diurnal IOP at Day 28.[3]

‡ IQVIA FIA April 2023; MMIT Portal, June 2023.

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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
- 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 full Prescribing Information on adjacent page.

References: 1. Weinreb RN, Scassellati Sforzolini B, Vittitow J, Liebmann J. *Ophthalmology*. 2016;123(5):965-973. **2.** Medeiros FA, Martin KR, Peace J, Scassellati Sforzolini B, Vittitow JL, Weinreb RN. *Am J Ophthalmol*. 2016;168:250-259. **3.** Weinreb RN, Ong T, Scassellati Sforzolini B, Vittitow JL, Singh K, Kaufman PL; VOYAGER Study Group. *Br J Ophthalmol*. 2015;99(6):738-745. **4.** VYZULTA. Prescribing Information. Bausch & Lomb Inc. **5.** Weinreb RN, Liebmann JM, Martin KR, Kaufman PL, Vittitow JL. *J Glaucoma*. 2018;27(1):7-15.

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