CE MONOGRAPH

Navigating New Approaches for Glaucoma Management

THE ROLE OF NITRIC OXIDE

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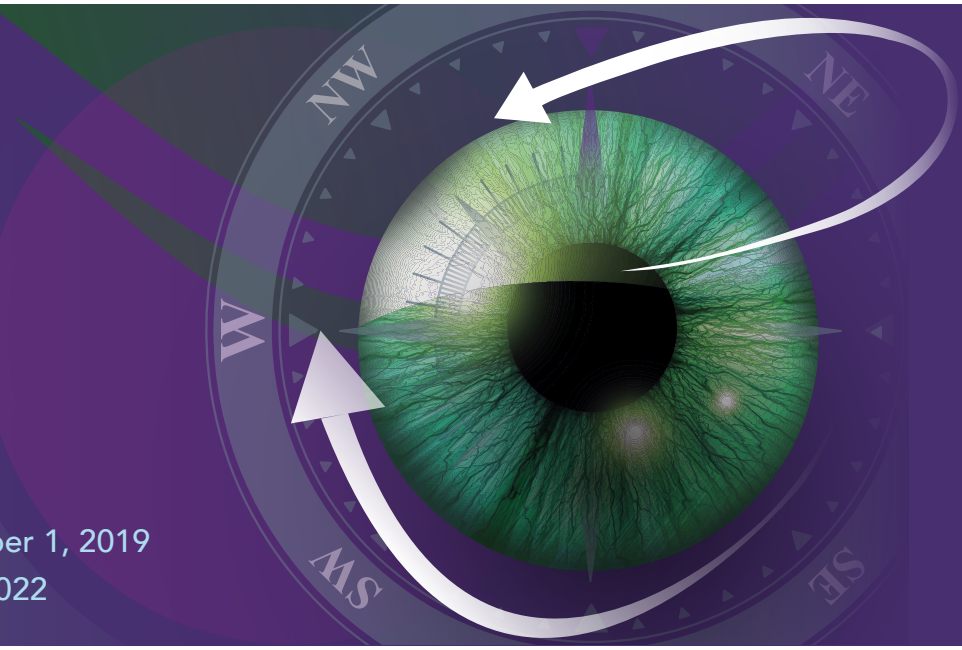

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COPE approved for 1.5 credits for optometrists
COPE Course ID: 65097-GL
COPE Course Category: Glaucoma

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LEARNING METHOD AND MEDIUM

This educational activity consists of a supplement and fifteen (15) study questions. The participant should, in order, read the learning objectives contained at the beginning of this supplement, read the supplement, answer all questions in the post test, and complete the Activity Evaluation/Credit Request form. To receive credit for this activity, please follow the instructions provided on the post test and Activity Evaluation/Credit Request form. This educational activity should take a maximum of 1.5 hours to complete.

CONTENT SOURCE

This continuing education (CE) activity captures content from a regional dinner meeting series.

ACTIVITY DESCRIPTION

To address the educational needs of optometrists, this case-based program will focus on elucidating the role of nitric oxide in glaucomatous eyes, including treatment strategies that use nitric oxide's mechanism of action on the trabecular meshwork to increase aqueous humor outflow and to achieve target intraocular pressure levels via new therapeutic options. Case discussions will interpret clinically relevant data supporting the efficacy and safety of this nitric oxide–donating treatment option. The desired results of this activity are for optometrists to improve their management of patients with glaucoma early in the disease process when outflow treatments can be most effective in helping prevent glaucoma progression.

TARGET AUDIENCE

This educational activity is intended for optometrists.

LEARNING OBJECTIVES

Upon completion of this activity, participants will be better able to:

- Describe the downstream signaling effects of nitric oxide in relation to glaucoma
- Discuss the effects of nitric oxide on the trabecular meshwork
- Apply data from clinical trials on nitric oxide–donating agent(s) for lowering intraocular pressure

ACCREDITATION STATEMENT

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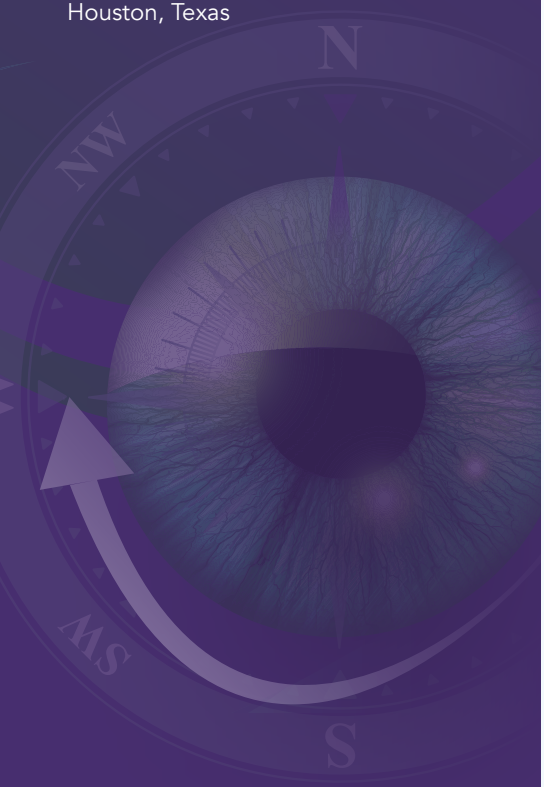

Navigating New Approaches for Glaucoma Management
THE ROLE OF NITRIC OXIDE

INTRODUCTION

Glaucoma is a progressive optic neuropathy that is estimated to affect more than 3 million Americans and to account for up to 12% of all cases of blindness.[1] Intraocular pressure (IOP) is the only modifiable risk factor for glaucoma,[2] and results from multiple large prospective randomized controlled clinical trials have proven the benefit of IOP lowering for both normal-tension and hypertensive disease.[3-6]

Treatment for ocular hypertension and glaucoma is usually initiated with medical therapy, and newer drugs with novel mechanisms of action are now available. This educational activity focuses on the role of nitric oxide (NO) in glaucoma and of latanoprostene bunod (LBN), a novel NO-donating prostaglandin F2α analogue, for IOP lowering. The activity will review the science pertaining to NO as a therapeutic target for glaucoma; summarize results from clinical trials establishing the efficacy, safety, and tolerability of LBN; and present case-based discussions illustrating application of the data to implement evidence-based approaches for patient care with this new agent.

GLAUCOMA AND THE TRABECULAR MESHWORK

Intraocular pressure is the balance between aqueous humor production and its outflow. Aqueous humor is produced by the nonpigmented ciliary epithelial cells in the posterior chamber and then travels in the channel between the iris and the lens into the anterior chamber. Aqueous humor outflow from the anterior chamber occurs through 2 pathways: the trabecular outflow and the uveoscleral outflow **(Figure 1)**.[7] In the trabecular outflow pathway—also known as the "conventional" outflow pathway—aqueous humor percolates through the trabecular meshwork (TM) into Schlemm canal, where it enters collector channels, flows into aqueous veins, and then moves into episcleral veins.

In the uveoscleral, or "nonconventional", outflow pathway, aqueous moves through and between the tissues of the ciliary body, into the supraciliary and suprachoroidal spaces, and eventually into the vortex veins and orbital vessels. Aqueous outflow through the uveoscleral pathway is independent of IOP and decreases with age.[8]

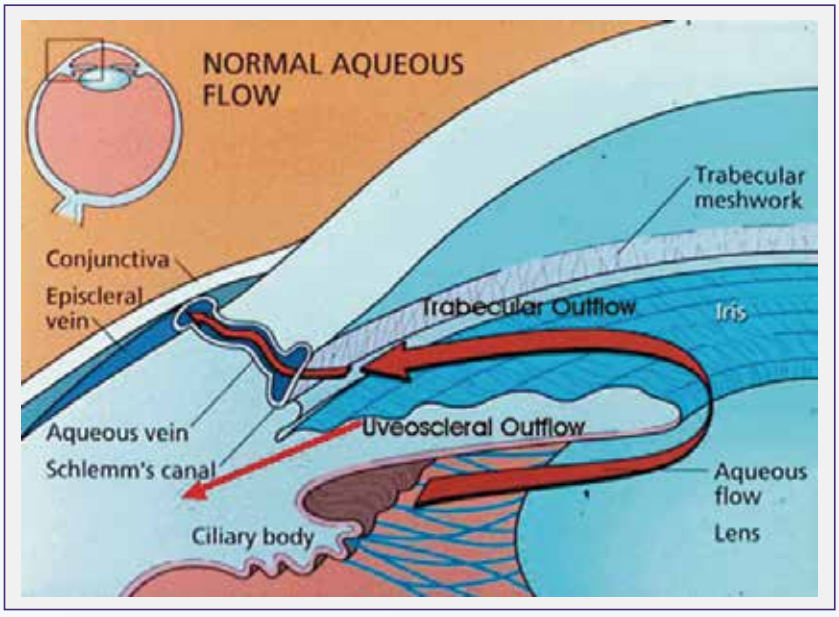

Figure 1. Aqueous humor outflow from the anterior chamber through the trabecular and uveoscleral outflow pathways[7]
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The trabecular outflow pathway is the primary route of aqueous outflow, and resistance to aqueous outflow through the TM is thought to be the main cause of increased IOP in primary open-angle glaucoma (POAG).[9] The TM is divided into 3 regions: the inner uveal meshwork, the middle corneoscleral meshwork, and the juxtacanalicular tissue that is the site of greatest resistance to outflow.[10] The juxtacanalicular tissue is made up of a loosely arranged extracellular matrix and endothelial cells, elastic fibers, and an inner wall with vacuoles and finger-like projections into Schlemm canal.

Aqueous outflow through the trabecular pathway is dependent on IOP. In a healthy eye, the TM responds to an increase in IOP by decreasing resistance to outflow in order to maintain homeostasis.[8] In eyes with ocular hypertension or glaucoma, increased cell contractility and extracellular matrix deposition in the juxtacanalicular tissue increase outflow resistance and the ability of the tissue to respond to elevated IOP, leading to increased IOP.

NITRIC OXIDE: ROLE IN INTRAOCULAR PRESSURE REGULATION AND GLAUCOMA

Nitric oxide is a ubiquitous endogenous signaling molecule that has a critical role in many physiologic processes, including IOP regulation. Nitric oxide initiates a pathway leading to inhibition of actin-myosin interaction that results in TM cell relaxation, widening of the intercellular spaces in the juxtacanalicular tissue and Schlemm canal, and increased aqueous outflow **(Figure 2)**.[11]

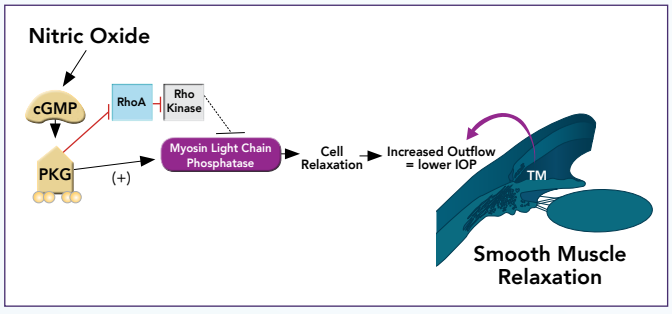

Figure 2. Pathway of nitric oxide leading to smooth muscle relaxation[11]
Abbreviations: cGMP, cyclic guanosine monophosphate; IOP, intraocular pressure; PKG, protein kinase G; TM, trabecular meshwork.

Knowledge of the role of NO on the TM and trabecular aqueous outflow suggests NO augmentation as a therapeutic approach for glaucoma. Further evidence to support this idea derives from studies showing that IOP in animal models is affected by interventions that increase or decrease NO levels in the eye.[12,13] In humans, data show that compared with controls, eyes with open-angle glaucoma have lower levels of NO metabolites in the aqueous humor and of NO in TM and Schlemm canal tissue **(Figure 3)**.[14-16] In addition, analyses of data from the Nurses' Health Study and Health Professionals Follow-Up Study show an association between higher dietary nitrate intake and decreased risk for POAG.[17]

Historically, medications used to lower IOP in eyes with ocular hypertension or glaucoma have acted primarily by reducing aqueous humor production or facilitating aqueous outflow through the uveoscleral pathway. Nitric oxide–donating compounds represent a new class of IOP-lowering drugs that can address the underlying disease pathophysiology in the TM.

This new class of IOP-lowering drugs includes nipradilol, an NO-donating beta blocker that is commercially available in

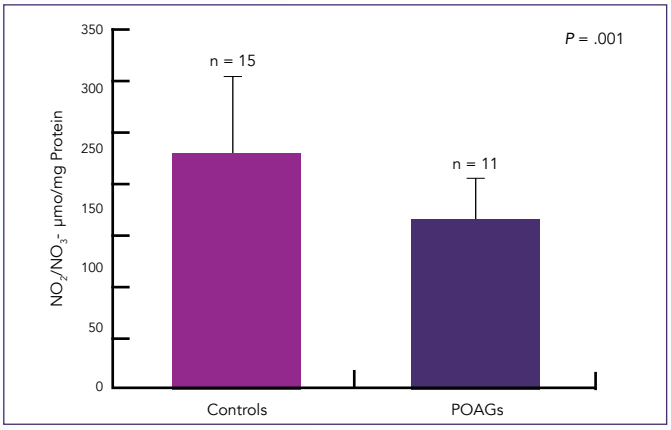

Figure 3. Nitric oxide levels in the aqueous humor of controls and of patients with glaucoma[15]
Abbreviation: NO, nitric oxide; POAG, primary open-angle glaucoma.
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Japan and approved in that country for the reduction of IOP in patients with glaucoma.[18] Studies evaluating nipradilol reported that it reduces IOP in patients with normal-tension glaucoma (NTG) and that it increases ocular blood flow in eyes with NTG as well as in normal eyes.[19,20] In addition, compounds that link bimatoprost, brinzolamide, and other carbonic anhydrase inhibitors with an NO-donating moiety are being developed as IOP-lowering medications.[21,22]

LBN is an NO-donating drug that is commercially available in the United States, with a US Food and Drug Administration–approved indication for the reduction of IOP in patients with open-angle glaucoma or ocular hypertension.[23] LBN is composed of the prostaglandin analogue latanoprost acid linked to the NO-donating moiety bunod. It received US Food and Drug Administration approval for marketing in November 2017,[24] and is recommended to be instilled as 1 drop in the affected eye(s) once daily in the evening.[23]

LATANOPROSTENE BUNOD: EFFICACY AND SAFETY DATA REVIEW

LBN, 0.024%, was compared with timolol maleate, 0.5%, in 2 phase 3 trials, APOLLO and LUNAR.[25,26] Each study included approximately 400 patients who were randomized 2:1 to use LBN once daily in the evening or timolol twice daily for 3 months. Mean untreated IOP at baseline in all study groups was approximately 26.5 mm Hg.

Follow-up visits in APOLLO and LUNAR were scheduled at week 2, week 6, and month 3, and IOP was measured at 8 AM, 12 PM, and 4 PM at each visit.[25,26] Both APOLLO and LUNAR met their primary efficacy end point, demonstrating noninferiority of LBN to timolol in its IOP-lowering efficacy at each of the specified time points at each follow-up visit.

In APOLLO, mean reductions from baseline IOP across all time points at all visits ranged from 7.7 to 9.1 mm Hg for the LBN group and from 6.6 to 8.0 mm Hg for the timolol group ($P \leq .002$), and mean IOP was significantly lower in the LBN group than in the timolol group at every time point at all visits ($P < .001$) **(Figure 4)**.[25] Adverse events occurred at similar rates in the 283 patients receiving LBN and the 135 patients receiving timolol. The most common adverse events were eye irritation (3.9% for LBN, 2.2% for timolol) and conjunctival hyperemia (2.8% for LBN, 1.5% for timolol).

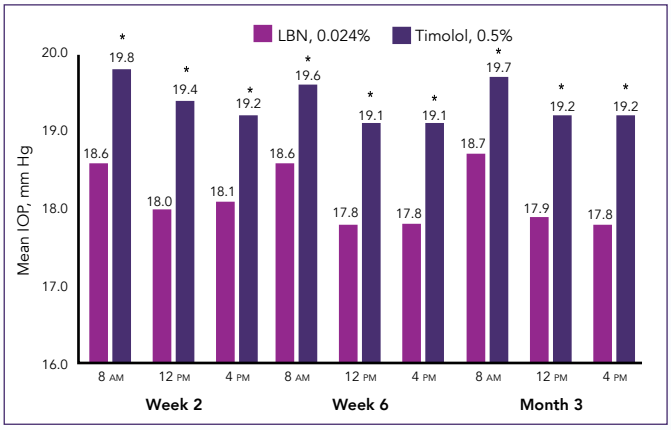

Figure 4. Mean intraocular pressure across all 9 time points in the APOLLO study[25]

Abbreviations: IOP, intraocular pressure; LBN, latanoprostene bunod.

* $P \leq .002$ vs timolol

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In LUNAR, mean IOP reductions across all assessments ranged from 7.5 to 8.8 mm Hg for LBN and from 6.6 to 7.9 mm Hg for timolol.[26] At all time points at all visits, except at 8 AM at the week 2 visit, mean IOP was significantly lower in eyes treated with LBN than in eyes treated with timolol ($P \leq .025$) **(Figure 5)**.[26] As in APOLLO, the most common adverse events in the 277 patients receiving LBN and the 135 patients receiving timolol in LUNAR were eye irritation (7.2% for LBN, 4.4% for timolol) and conjunctival hyperemia (9.0% for LBN, 0.7% for timolol).

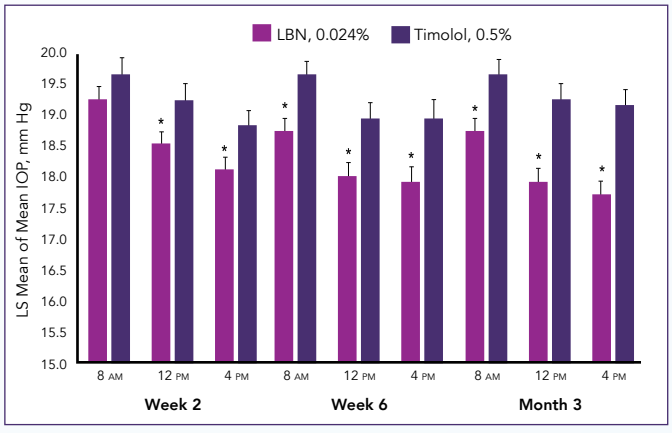

Figure 5. Mean intraocular pressure across all 9 time points in the LUNAR study[26]

Abbreviations: IOP, intraocular pressure; LBN, latanoprostene bunod; LS, least squares.

* $P \leq .025$ vs timolol

Reprinted from *American Journal of Ophthalmology,* 168, Medeiros FA, Martin KR, Peace J, Scassellati Sforzolini B, Vittitow JL, Weinreb RN, Comparison of latanoprostene bunod 0.024% and timolol maleate 0.5% in open-angle glaucoma or ocular hypertension: the LUNAR study, 250-259, Copyright 2016, with permission from Elsevier.

Data on long-term efficacy and safety of LBN were gathered in an open-label extension study that included 737 patients from APOLLO and LUNAR who continued on LBN or were crossed over from timolol beginning at month 3.[27] Open-label treatment with LBN continued for 9 months in APOLLO and for 3 months in LUNAR. In this extension study, patients who crossed over from timolol had an additional 6.3% to 8.3% reduction in mean diurnal IOP, which provides further evidence that LBN has a more potent IOP-lowering effect than does timolol. Adverse events in patients using LBN over a longer term were primarily mild to moderate in severity, with the most common being conjunctival hyperemia (5.9%), eye irritation (4.6%), and eye pain on instillation (3.5%).

Of interest, considering that a prostaglandin analogue is currently considered first-line treatment for IOP lowering, LBN was compared with latanoprost, 0.005%, in the phase 2, randomized, double-masked VOYAGER study.[28] VOYAGER randomized 413 patients to once-daily treatment with latanoprost or 1 of 4 different concentrations of LBN. Mean diurnal IOP decreased by an average of 1.23 mm Hg more in patients treated with LBN, 0.024%, than in those treated with latanoprost ($P = .005$). Although LBN, 0.024%, contains a higher concentration of latanoprost than does latanoprost, 0.005%, the higher amount is not likely to explain the greater IOP-lowering effect of LBN, considering evidence that increasing the dosage of latanoprost 2.5-fold does not increase its treatment benefit.[29] Because of this, it might stand to reason that the NO-moiety in LBN contributes to this greater efficacy, but this has yet to be fully supported. The adverse event profile of LBN in VOYAGER was consistent with the experience in the phase 3 trials, with pain upon instillation and conjunctival and ocular hyperemia being the most common adverse events associated with LBN.[28]

LBN, 0.024%, was also investigated in the JUPITER study conducted in Japan, which enrolled 130 patients with ocular hypertension or open-angle glaucoma, including NTG, pigmentary, or pseudoexfoliative disease.[30] At baseline, untreated IOP in study eyes averaged 19.6 mm Hg and was between 15 and 21 mm Hg in 75% of eyes. The results of JUPITER indicate that LBN is effective in eyes with a lower starting IOP. After 52 weeks of treatment, mean IOP in study eyes decreased by an average of 5.2 mm Hg (-26.3%). Mean IOP in LBN-treated fellow eyes (n = 126) decreased from 18.7 mm Hg at baseline to 14.4 mm Hg (-23%) after 52 weeks. The most common ocular adverse events associated with LBN in the study eyes were conjunctival hyperemia (17.7%), growth of eyelashes (16.2%), eye irritation (11.5%), and eye pain (10.0%); all ocular adverse events were mild to moderate in severity.

CASE DISCUSSIONS

Case 1

From the Files of Danica Marrelli, OD

A 58-year-old white male presented in February 2017 for a glaucoma evaluation. He was referred because of his optic disc appearance and family history of glaucoma. The patient's mother had glaucoma. He did not know the stage, but reported that she had vision loss and her only treatment had been topical medications.

The patient was a high myope (-8.0 D OU) who wore glasses for correction. His only medical issue was dyslipidemia, for which he used no medication, and he was allergic to penicillin.

The patient's examination findings just prior to his referral were best-corrected visual acuity (BCVA) of 20/20 OU; normal pupils and slit-lamp examination results; IOP of 18 mm Hg OU; cup-to-disc ratio of 0.55v OU in a relatively small optic nerve; and pavingstone degeneration OU. On presentation for glaucoma evaluation in February 2017, BCVA was 20/20 OU; IOP was 19 mm Hg OD and 21 mm Hg OS; and central corneal thickness was 607 µm OD and 615 µm OS. On gonioscopy, the angles were open to the ciliary body. There were no secondary signs of glaucoma.

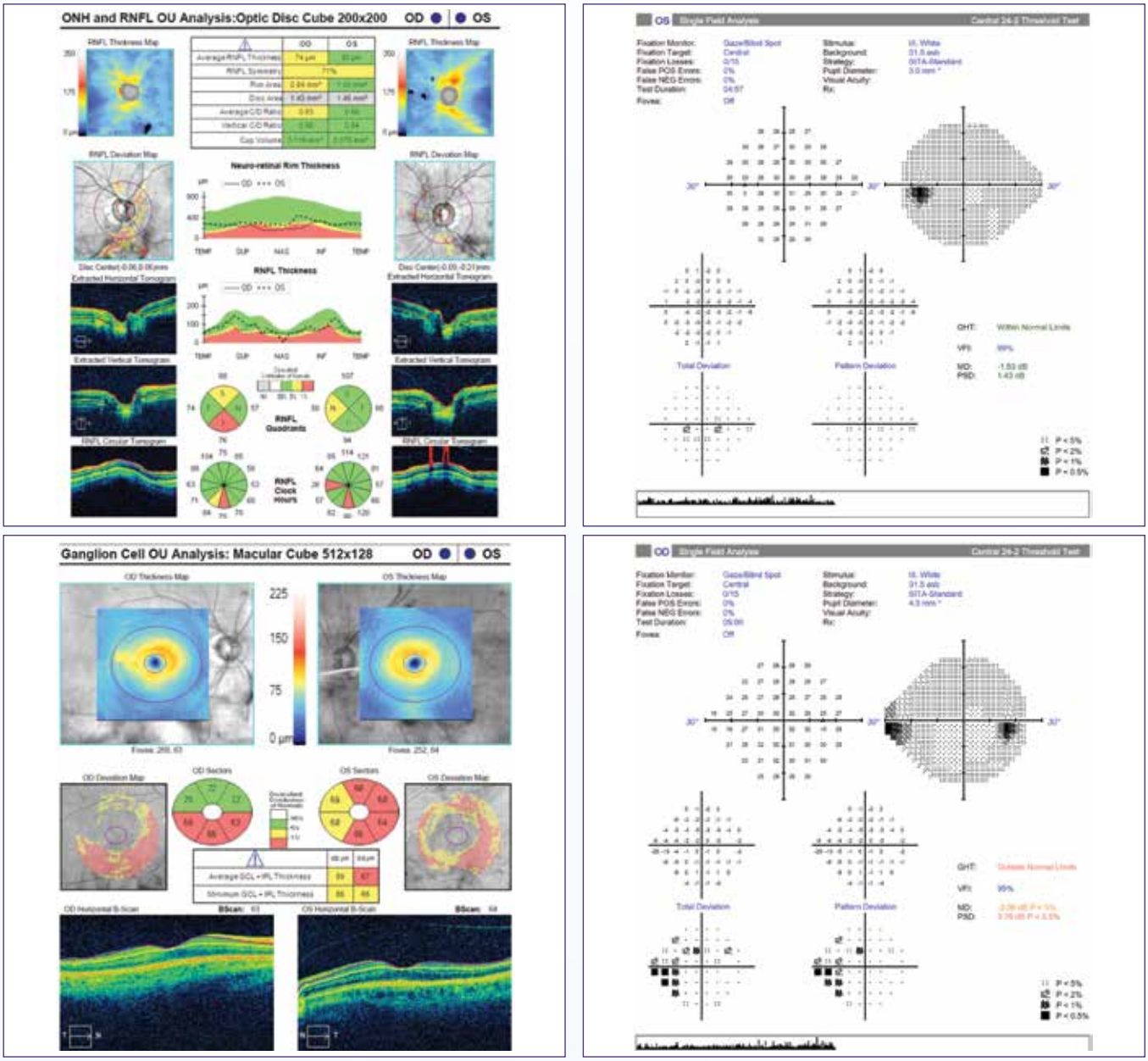

Figure 6. Imaging and visual fields of the patient in Case 1. Note that there is an artifact causing an artificially reduced retinal nerve fiber layer thickness in the nasal portion of the retinal nerve fiber layer circular tomogram and on the temporal, superior, nasal, inferior, temporal (TSNIT) curve.

Figure 6 *shows findings from imaging and visual fields. The retinal nerve fiber layer (RNFL) shows thinning OU, but with more thinning OD than OS.*

Dr Marrelli: Would you diagnose glaucoma in this patient?

Dr Madonna: I think that more information is needed. His family history, small discs with a larger cup, and RNFL thickness asymmetry are concerning. Although he appears to have some RNFL thinning, RNFL might be approximately 20 µm thinner on average in high myopes than in emmetropes.[31]

Dr Marrelli: Do you routinely perform macular ganglion cell analysis in high myopes?

Dr Madonna: I get a macular scan and optic nerve scan in all patients. I do not use the information for diagnosis, but it is something I like to follow as part of my evaluation for glaucoma because high myopes have a thinner RNFL, owing to the myopia and not to glaucoma. One needs to be very careful about using optical coherence tomography (OCT) RNFL measurements in diagnosing glaucoma in high myopes.

Dr Marrelli: I agree. Although we might expect to see that the ganglion cell layer and RNFL are thinner in high myopes, change over time in these layers should not be any greater than that in other patients.

Dr Chaglasian: I also get macular OCT in patients with glaucoma because these images can be helpful in both diagnosis and in following patients over time. For patients with other conditions, eg, diabetes, these images can help identify pathology not related to glaucoma. I agree that the findings need to be interpreted cautiously in high myopes because of the potential for artifactual and false-positive readings of the ganglion cell layer in the macular region.

I believe the macular OCT is also helpful to look for structure-function correlation between the OCT and visual field. Although changes on OCT and visual field do not always

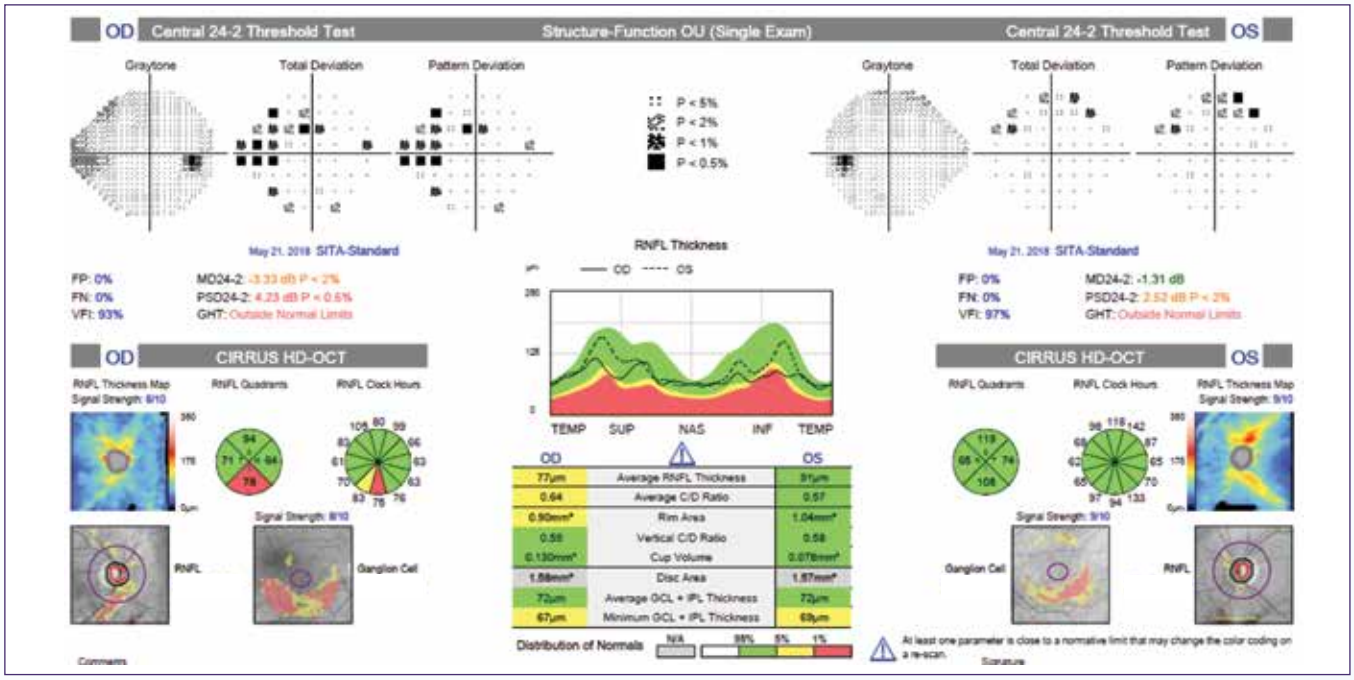

Figure 7. Repeated visual fields and retinal nerve fiber layer images of the patient in Case 1

correlate, we can be more confident about our diagnosis when they do. If the findings do not match up and a diagnosis of glaucoma is uncertain, then I start looking at what risk factors for glaucoma progression are present to help me decide if I can monitor the patient or should initiate therapy.

Dr Marrelli: In looking at the structure and function in this patient, there is some correlation between RNFL thinning and a visual field defect, but it is not a perfect correlation. I was not convinced that this patient had glaucoma. When I am uncertain, I am never afraid to wait and watch for changes.

Although the patient's family history, optic disc appearance, and visual field raised suspicion, it was the first time he had done visual field testing, so I wanted to see if the findings were repeatable. In the Ocular Hypertension Treatment Study, 86% of initial abnormal reliable visual fields were not confirmed on retest.[32]

Dr Madonna: We should not forget that patients can have preperimetric glaucoma, in which there is structural change without function loss. Conversely, this patient has visual field loss without obvious structural loss in the OS. Without obvious structural change, I would likely follow him rather than start treatment.

Dr Marelli: Even when I am certain that a patient has glaucoma, I always get at least 3 IOP readings before I start therapy. In this patient, I wanted to be sure that I was not missing a higher IOP. On return visits, his IOP ranged from 16 to 20 mm Hg OD and from 16 to 21 mm Hg OS.

He also had a second visual field test done fairly soon after the first and a third after 6 months. On repeat testing, the visual field defect in his right eye became a little bit inferior but was primarily superior, which correlated better with the structural evaluations of the ganglion cell layer and RNFL, and he began to show a consistent but mild superior defect in the left eye that correlated with some inferior thinning **(Figure 7)**.

Dr Madonna: The serial OCT testing also shows evidence of more structural damage and of a greater intereye difference. The asymmetry in RNFL thickness has increased from 6 to 14 µm, and the superior and inferior peaks in the RNFL TSNIT (temporal, superior, nasal, inferior, temporal) curve are blunted in the right eye.

Dr Marrelli: Would you diagnose NTG in this patient?

Dr Chaglasian: I would just call it open-angle glaucoma. Identifying glaucoma as normal tension has a potential implication for setting an IOP reduction target of 30%, similar to reduction targets in patients with OAG, and for evaluating the patient for other conditions that have been associated with NTG, such as migraine or Raynaud phenomenon.[33] NTG might also be more difficult to treat, but it also tends to be less progressive than high-tension glaucoma.[34,35]

Dr Marrelli: The classic patient with NTG is an older woman who has migraines and disc hemorrhages, someone I would want to avoid treating with a beta blocker, but there is no other real implication for management. Many feel that beta blockers should be avoided in patients with NTG because they might adversely affect optic nerve perfusion.[36]

On the basis of the repeat testing, I was more confident diagnosing glaucoma in this patient and initiating treatment. What would be your target IOP considering he has mild glaucoma, his peak IOP is 20 or 21 mm Hg, and he is also relatively young?

Dr Madonna: I think there is a tendency to aim for a 30% lowering because that is within the range attainable with a prostaglandin analogue.[37] Achieving a 30% lowering, however, is more likely when the untreated IOP is at least in the mid-20s, so it might be more difficult in this patient.[38] Nevertheless, I would still set my target at 13 to 15 mm Hg, which corresponds to approximately a 30% lowering.

Dr Marrelli: I tell students that I do not set the target IOP according to what I think I can achieve, but rather according to what I think is appropriate for controlling the patient's glaucoma. I think the IOP in this patient should be 14 to 15 mm Hg, so the next question is, How can I reach that?

Dr Madonna: The results of the JUPITER study come to mind. In this study, treatment with LBN, 0.024%, reduced mean IOP from 19.6 mm Hg at baseline to 14.4 mm Hg.[30]

Dr Marrelli: LBN was not available when I was initiating treatment for this patient. I wanted to start him on a prostaglandin analogue, but his wife was concerned that the medication might change the color of his blue eyes. A colleague of mine started the patient on a beta blocker. At return visits after 1 and 2 months, his IOP was 17 to 18 mm Hg OD and 16 to 18 mm Hg OS.

I counseled the patient that I did not expect a prostaglandin analogue would change his eye color because that effect typically occurs in patients with hazel eyes.[39] He consented to switch treatment and was started on latanoprost, but after 1 month, his IOP was still 18 mm Hg OD and 17 mm Hg OS.

I considered if poor adherence or poor instillation technique explained the lack of benefit. The patient claimed he was using the medication as prescribed, and I believed him because his eyelashes were growing. I evaluate appropriate instillation technique by asking patients during a visit to show me how they put in a drop of artificial tears; this patient had no problem with administration. Then, I considered if I had missed the true peak IOP.

Although I had measured IOP several times before initiating treatment, I told the patient to stop using his medication and had him return after 1 month for diurnal IOP measurements. None of the values were above 21 mm Hg. Samples of LBN arrived that day, and I started the patient on LBN. At multiple follow-up visits, his IOP ranged from 13 to 16 mm Hg OD and 12 to 15 mm Hg OS. The patient reported mild stinging with drop instillation, but he tolerated the LBN well, and he is continuing to do well after 18 months of treatment.

Dr Madonna: I think the medication washout was a good idea and that it is something we do not do often enough. I believe that there are hyper-responders to some medications, and the only way we will identify them is to reestablish a baseline before starting a new medication.

Dr Marrelli: My favorite phrase in the glaucoma clinic is to say, "Step down from the ledge." And what I mean by that is that there is no need to make a rash decision when choosing therapy, which in this case would have been to add a second medication. I aim to keep treatment as simple as possible.

Case 2
From the Files of Michael Chaglasian, OD

A 67-year-old female presented wanting new reading glasses and reporting that she noticed an occasional shadow in her right eye. She was last seen for an examination 7 years ago, and her last medical examination occurred 18 months ago.

The patient was in good health and had no remarkable personal ocular history, but her mother and uncle had glaucoma. She believed that her relatives were using multiple medications for their glaucoma and had other treatments, but she did not know if they had significant vision loss.

The patient's BCVA was 20/20 OU. Slit-lamp examination results were unremarkable. Intraocular pressure was 36 mm Hg OD and 24 mm Hg OS. Pachymetry test results were 540 µm OD and 550 µm OS. Gonioscopy showed the angle was open to the ciliary body band and light pigmentation. Dilated examination revealed an old small posterior vitreous detachment, which accounted for the shadow the patient described.

Figure 8 *shows her optic nerve photographs, visual fields, and OCT images. The visual field shows a superior defect OD. The OCT of her right eye shows inferior RNFL and ganglion cell layer thinning. The left eye also shows inferior RNFL and ganglion cell layer loss, but it is less than that in the right eye.*

Dr Chaglasian: Given all the clinical findings, it is clear that this patient has glaucoma and needs treatment. The question is when to start treatment, and would you be comfortable having her come back on another day to measure IOP again before starting therapy?

Dr Madonna: Considering her IOP, I expect that some practitioners would want to start treatment immediately. I like to measure IOP at 3 visits before starting treatment, so I would want her to return for additional measurements.

Dr Marrelli: As a general rule, I do not start treatment to lower IOP the first time I see a patient, but I make exceptions according to the extent of structural damage and the level of IOP. In this particular case, I would be comfortable having the patient come back a few times to measure IOP.

If the IOP was unchanged, and considering the patient's relatively young age along with the significant visual field defect in the right eye, I would try to achieve 45% to 50% IOP lowering in the right eye. If, however, the IOP in the right eye was only 24 mm Hg when remeasured on the next day and 26 mm Hg a week later, I might be comfortable targeting an IOP of 20 mm Hg, but would also choose a medication that would reduce IOP fluctuation because this is also a risk factor for glaucoma progression.[40] Prostaglandin analogues have been shown to reduce IOP fluctuation.[41]

Dr Chaglasian: I agree that it would be helpful to have the patient return for repeat IOP measurements before starting treatment. The information will provide a better understanding of IOP peak, range, and diurnal fluctuation, which is important information for choosing treatment and assessing the response. The patient needs to be informed, however, that she has glaucoma. It is important that she returns for follow-up because the glaucoma needs to be treated, and further evaluation will determine the best approach for treatment.

Do new medications for glaucoma have a role in treating patients like this who present with moderate-stage disease at a young age?

Dr Madonna: A goal when treating any patient is to achieve the desired benefit with the lowest treatment burden. Considering the results of the phase 2 and 3 clinical trials comparing LBN with latanoprost and timolol, respectively, LBN could be considered a good choice for this patient because of its potential to provide maximum IOP lowering with the convenience of a single drop.[25,26] Although it remains to be proven, I also think about the potential for treatment with an NO-donating compound to structurally modify the TM in a way that could reduce the risk of progression long term.

Dr Marrelli: If it turns out that I am aiming for a 45% to 50% reduction in IOP in this patient, I expect she might need to be treated with > 1 medication. Still, I prefer to start with monotherapy, and I would recommend starting this patient on LBN. Then, if further IOP lowering is needed, I would add another agent.

Treatment options and goals were discussed with the patient, and she was started on LBN once every evening OU. After 2 weeks, IOP was 20 mm Hg OD and 18 mm Hg OS. The patient denied any significant side effects and continued on

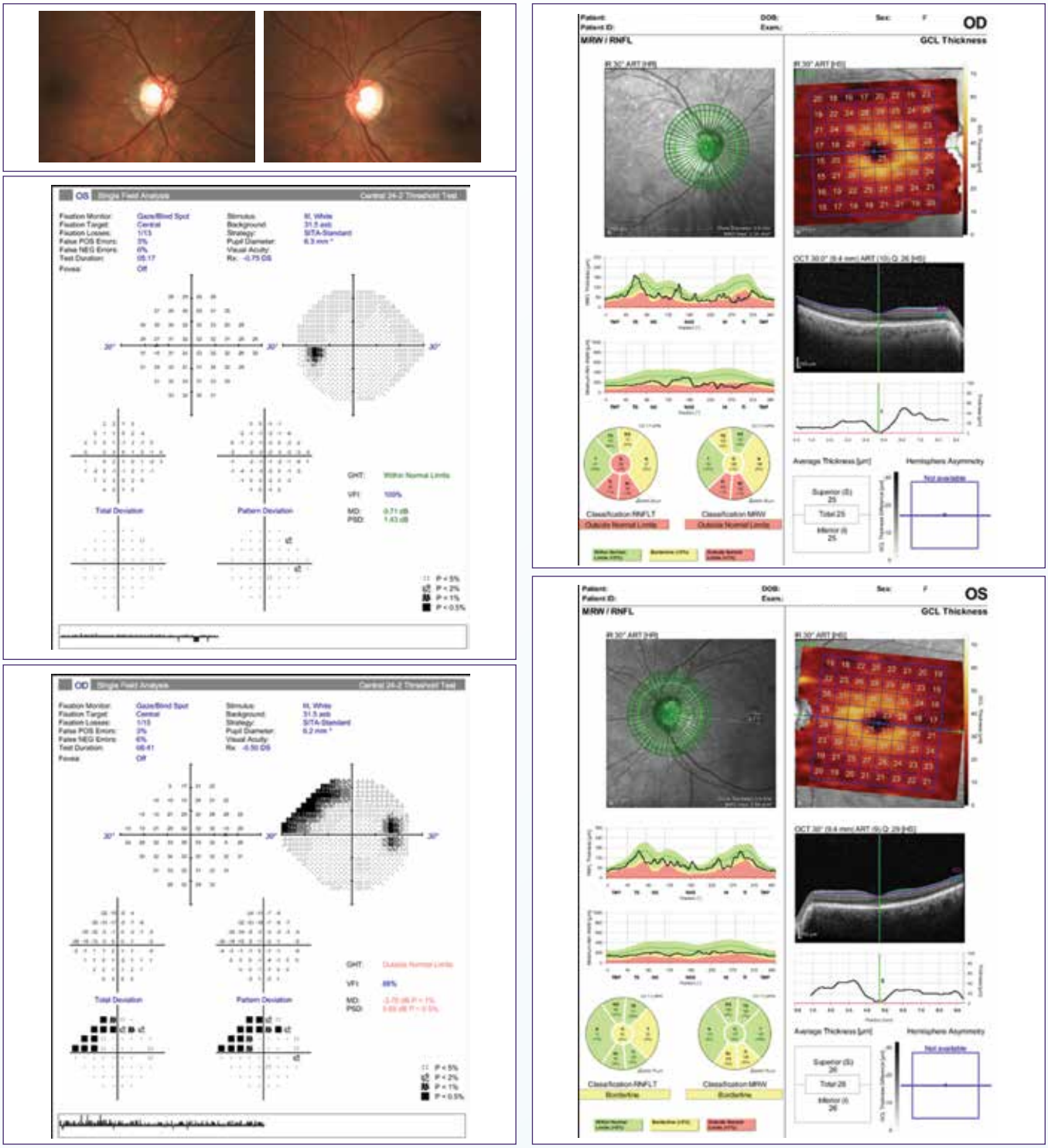

Figure 8. Optic nerve photographs, visual fields, and optical coherence tomography images of the patient in Case 2

LBN. She was instructed to return in 4 to 6 weeks and told that if she was continuing to tolerate LBN and if her IOP was controlled, the next follow-up visit would be after 2 or 3 months. Visit frequency thereafter would be every 3 to 4 months.

Case 3

From the Files of Richard J. Madonna, MA, OD

A 75-year-old black female presented with a history of severe, ischemic branch retinal vein occlusion (BRVO) OD that occurred 8 years earlier. The patient had refused treatment for 2 years after the BRVO and then had multiple laser treatments and anti–vascular endothelial growth factor injections, but she continued to have recurrent macular edema. BCVA was now 20/400 OD and 20/20 OS.

The patient was on amlodipine for hypertension and mesalamine for ulcerative colitis. She was a thin, very active woman, and enjoyed reading.

The patient was diagnosed with POAG at the time she had the BRVO. Her IOP was 23 mm Hg OU at that time. She has been using latanoprost OU and dorzolamide/timolol OU, and had selective laser trabeculoplasty (SLT) performed OS

4 years ago. At visits over the last 12 months, IOP in the left eye was 13, 16, 14, and 13 mm Hg (~39% reduction).

The patient's most recent visual field showed a dense superior arcuate scotoma. The 7-year progression analysis showed a loss of 1.1% per year.

The 7-year progression trend analysis of her OCT showed the inferior RNFL thickness OS was decreasing fairly rapidly at a rate of 3.64 µm/year. She also had macular thinning superior and inferior OS ***(Figure 9)****. The 10-2 visual field showed progressive loss in the inferior hemifield, and the macular OCT showed progressive loss in both hemifields.*

Dr Madonna: This is a monocular woman who is active and an avid reader. She is losing vision in her left eye that will affect her vision-related quality of life by interfering with her ability to read and navigate independently.

I think we would agree that IOP control has not been adequate in this patient. One option would be to switch her latanoprost to LBN because LBN might lower IOP by an additional 1 to 2 mm Hg and might have an additional structural benefit on the TM.[28,42] Before LBN was available, I might have considered adding another medication from another class. Now that we have new medications, however, there are very few patients whom I treat with more than 3 medications.

I would be hesitant to recommend tube surgery in this patient because she is monocular, but I would consider a minimally invasive glaucoma surgical procedure if she needed cataract surgery. Because I have confidence that she will return for follow-up, I might even consider carefully washing out all her medications and starting LBN as monotherapy with the expectation that she will probably need monotherapy.

Dr Chaglasian: I would also want to know the untreated IOP in this patient, and I think that she likely would not experience any real harm from undergoing a washout and having a higher IOP for 1 to 2 weeks. With the availability of new IOP-lowering medications, I find myself doing a washout more often, with the idea that I might ultimately be able to simplify and optimize the treatment regimen.

I recognize, however, that asking patients to return for additional visits can have financial consequences for them and carry other burdens. Therefore, I explain that I truly believe there is benefit from doing a washout or repeat IOP measurements because the information I get could improve the treatment plan.

Dr Marrelli: I am not sure I would be comfortable washing out all medications in this patient who has significant vision loss. I think that switching latanoprost to LBN or to the netarsudil/latanoprost fixed combination are reasonable choices. Netarsudil is a Rho kinase and norepinephrine transporter inhibitor that reduces IOP by increasing aqueous outflow through the TM, decreasing pressure within the episcleral venous system, and suppressing aqueous humor production.[43,44] The phase 3 MERCURY-1 trial investigating netarsudil/latanoprost met its primary efficacy end point, showing statistical superiority of the fixed combination to each of its active components for providing a lower mean IOP at 8:00 AM, 10:00 AM, and 4:00 PM at week 2, week 6, and month 3.[45] Netarsudil/latanoprost lowered IOP by an additional 1.8 to 3.0 mm Hg vs netarsudil and by an additional 1.3 to 2.5 mm Hg vs latanoprost. Conjunctival hyperemia was the most frequent ocular adverse event

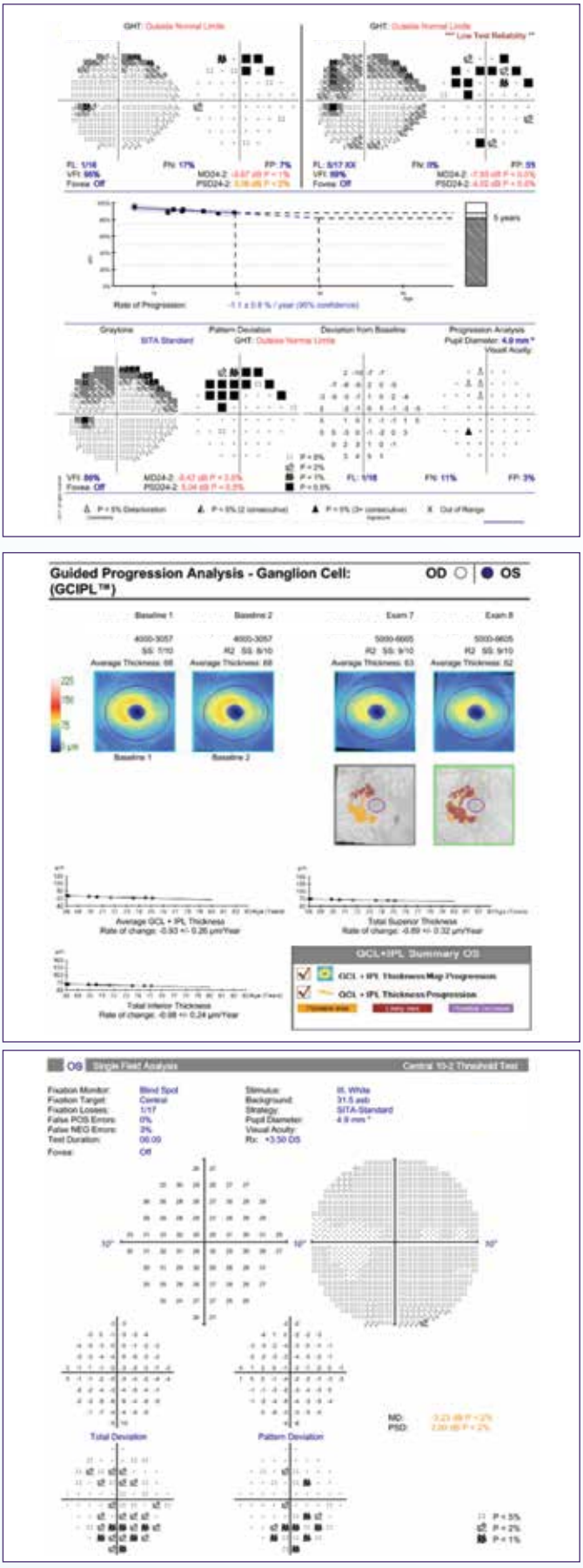

Figure 9. Seven-year progression trend analysis of the left eye of the patient in Case 3

41.0% of 244 patients in the netarsudil group, and in 14.0% of 236 patients treated with latanoprost. In the netarsudil/latanoprost group, 7.1% of patients discontinued treatment because of conjunctival hyperemia.

Performing SLT also could be reasonable. The potential for benefit with SLT might be low in this patient, considering that her IOP is fairly low and that the response to IOP is greater in eyes with a higher baseline IOP.[46] It is likely that SLT will do no harm. Realistically, it might be necessary to initiate > 1 single intervention for this patient.

TAKE-HOME POINTS

Intraocular pressure is a balance between aqueous humor production and outflow.

Aqueous outflow occurs through the TM and uveoscleral pathways.

- Most outflow occurs through the TM pathway

Elevated IOP in POAG is primarily caused by increased aqueous outflow resistance at the TM.

Nitric oxide is a signaling molecule that increases trabecular outflow facility.

LBN links the prostaglandin analogue latanoprost acid with the NO-donating moiety bunod.

- Latanoprost increases uveoscleral aqueous outflow
- Nitric oxide increases trabecular meshwork aqueous outflow

LBN effectively lowers IOP in eyes with low/normal IOP (NTG) to high IOP (POAG).

- In comparative clinical trials, LBN had a greater IOP-lowering effect than did timolol maleate, 0.5%, and latanoprost, 0.005%
- LBN was safe and well tolerated; the most common adverse events associated with its use in the pivotal clinical trials were conjunctival hyperemia (< 10%) and eye irritation (< 8%)

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1. Elevated IOP in eyes with POAG is primarily related to:
   a. Overproduction of aqueous humor
   b. Decreased aqueous humor outflow through the uveoscleral pathway
   c. Increased episcleral venous pressure
   d. Aqueous humor outflow resistance at the TM

2. Nitric oxide lowers IOP by:
   a. Exerting its effect in episcleral endothelial cell smooth muscle
   b. Activating the cyclic adenosine triphosphate signaling pathway
   c. Relaxing cells in the TM
   d. Decreasing aqueous humor production

3. Analyses of data from the Nurses' Health Study and Health Professionals Follow-Up Study showed an association between:
   a. Higher dietary nitrate intake and decreased risk for POAG
   b. Higher dietary nitrite intake and decreased risk for POAG
   c. Use of nitroglycerin and higher IOP
   d. Use of nitroglycerin and increased risk for POAG

4. Which of the following is NOT an NO-donating compound?
   a. Bunod
   b. Netarsudil
   c. Nipradilol
   d. LBN

5. LBN is thought to lower IOP by increasing uveoscleral outflow and _____.
   a. Reducing aqueous humor production
   b. Increasing trabecular outflow
   c. Decreasing episcleral venous pressure
   d. All the above

6. In a phase 2 clinical trial, LBN, 0.024%, lowered IOP from baseline by ___ mm Hg more than did latanoprost, 0.005%.
   a. 0.78
   b. 1.00
   c. 1.23
   d. 1.78

7. Phase 3 clinical trials compared LBN with _____.
   a. Netarsudil
   b. Timolol maleate
   c. Latanoprost
   d. Vehicle

8. In the phase 3 clinical trials, LBN lowered IOP from baseline by _____ mm Hg.
   a. 3.3 to 5.1
   b. 4.7 to 6.8
   c. 6.5 to 8.0
   d. 7.5 to 9.1

9. Which were the most common (< 10%) ocular treatment-emergent adverse events associated with LBN in phase 3 clinical trials?
   a. Conjunctival hyperemia and dry eye
   b. Conjunctival hyperemia and eye irritation
   c. Ocular hyperemia and increased iris pigmentation
   d. Eye pain and foreign body sensation

10. The phase 3 MERCURY-1 trial demonstrated significantly greater IOP-lowering with fixed combination netarsudil/latanoprost than with _____.
    a. LBN
    b. Netarsudil alone and latanoprost alone
    c. Timolol
    d. Vehicle

11. Through which 2 pathways does aqueous humor outflow from the anterior chamber occur?
    a. Trabecular and uveoscleral
    b. Trabecular and nonconventional
    c. Uveoscleral and conventional
    d. None of the above

12. What is the level of NO and its metabolites within the aqueous, TM, and Schlemm canal tissue in eyes with open-angle glaucoma compared with that in healthy eyes?
    a. Greater
    b. Lower
    c. Equal
    d. Unknown

13. LBN is composed of the prostaglandin analogue latanoprost acid linked to _____.
    a. Rho kinase inhibitor
    b. Beta blocker
    c. NO-donating moiety
    d. Additional prostaglandin analogue

14. In the JUPITER study, treatment with LBN, 0.024%, reduced mean IOP by an average of ____ mm Hg from the average baseline measure.
    a. 1.2
    b. 3.6
    c. 4.1
    d. 5.2

15. A patient with OHT has had normal visual fields for 3 years. The most recent visual field shows a new defect. How should this patient be managed?
    a. Patient should be treated immediately or have current treatment reassessed
    b. Neuroimaging should be performed to rule out central nervous system lesions
    c. The visual field finding should be ignored and the patient should be diagnosed on the basis of nerve images instead
    d. Visual fields should first be retested to determine if the defects reappear