CE Monograph

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IOP Management in Today's Practice: The Age of Outflow

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FACULTY

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COPE approved for 2.0 credits for optometrists
COPE Course ID: 65265-GL
COPE Course Category: Glaucoma

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Learning Method and Medium

This educational activity consists of a supplement and twenty (20) 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 2.0 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 eyes with glaucoma, providing strategies to achieve target intraocular pressure levels with newer topical agents that home in on the trabecular meshwork, and interpreting clinically relevant data supporting the efficacy and safety of these new agents.

Target Audience

This activity is intended for optometrists caring for patients with glaucoma.

Learning Objectives

Upon completion of this activity, optometrists 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 agents for lowering intraocular pressure through outflow mechanisms

Accreditation Statement

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IOP Management in Today's Practice: The Age of Outflow

Introduction

Following nearly 2 decades of innovation stagnation, 2 new drugs—latanoprostene bunod (LBN) and netarsudil—with novel mechanisms of action were approved for the reduction of intraocular pressure (IOP) in eyes with primary open-angle glaucoma (POAG) or ocular hypertension (OHTN). These drugs act in the trabecular meshwork (TM)—the site of angle pathology that leads to elevated IOP—to restore aqueous humor outflow and lower IOP. LBN is a nitric oxide (NO)-donating formulation of the prostaglandin analogue (PGA) latanoprost. Upon dosing, the drug dissociates into latanoprost, which increases uveoscleral outflow, and butanediol mononitrate, which liberates NO, which in turn relaxes trabecular smooth muscle and increases trabecular outflow. Netarsudil is a Rho kinase (ROCK) and norepinephrine transporter (NET) inhibitor. Inhibition of ROCK also relaxes trabecular cells to increase trabecular outflow and acts in the ciliary body to reduce aqueous humor production, whereas inhibition of NET lowers episcleral venous pressure, further lowering IOP. The development and commercialization of LBN and netarsudil provide clinicians with new tools to lower IOP in patients with glaucoma. In this educational activity, the mechanisms of action of these drugs, as well as their efficacy and safety profiles, will be reviewed. Through a series of case studies, the use of these drugs in clinical practice will also be illustrated.

Modern Management of Open-Angle Glaucoma and Ocular Hypertension

The selection of primary therapy for open-angle glaucoma (OAG) and high-risk OHTN should be based on several key factors. The ultimate goal of glaucoma therapy is to preserve patients' quality of life,[1,2] so the effect of treatment on quality of life should be considered at the outset. Traditionally, medications have been used as the first line of therapy for IOP reduction, followed, if needed, by laser and then surgery. The recent Laser in Glaucoma and Ocular Hypertension (LiGHT) study demonstrated comparable IOP reduction but far less medication use, lower risk of progression, and fewer surgeries needed in patients with newly treated POAG or OHTN who received primary selective laser trabeculoplasty compared with medications.[3] Likewise, the advent of minimally invasive glaucoma surgery has broadened the indications for surgical glaucoma intervention, positioning surgery as an option earlier in the treatment scheme than traditional procedures such as trabeculectomy and tube shunts, primarily because of the more favorable safety profile of minimally invasive glaucoma surgical procedures over more traditional procedures.[4] If medical therapy is elected as first-line treatment, the choice of a primary agent should be based on considerations of efficacy, safety/tolerability, convenience (once-daily dosing is preferred), and cost. Although newer drugs might offer benefits over

older drugs, there is often a lag between drug approval and widespread market access, and the potential out-of-pocket costs to patients are an important consideration.

Once a drug is selected, it should be applied in both eyes if both need treatment. The drug's efficacy should then be assessed over ≥ 2 on-treatment visits, comparing IOP with (ideally) multiple pretreatment values.[5] The monocular therapeutic drug trial—in which 1 eye is treated and the other serves as a control to gauge spontaneous IOP variations between visits—is no longer recommended[2] because of a spate of research demonstrating that it poorly predicts long-term IOP reduction and fellow-eye response to the same medication.[6–8]

Glaucoma and the Trabecular Meshwork

Intraocular pressure is determined by the balance of aqueous humor inflow and outflow. Aqueous humor is manufactured by the epithelium of the ciliary processes of the ciliary body and exits the eye through the trabecular outflow pathway and, secondarily, the uveoscleral outflow pathway. In eyes with POAG, the TM is altered and aqueous outflow is reduced.

Glaucoma-mediated TM alteration results in stiffening of the TM tissue. Stiffness is a biomechanics term that describes a tissue's tendency to resist deformation when a force is applied to it. In glaucoma, the tissue is the TM and the force is the IOP. Trabecular meshwork stiffness arises in eyes with glaucoma because of 2 factors: the contractile tone of the trabecular endothelial cells and changes within the makeup of the extracellular matrix (ECM) of the TM.[9] These 2 factors interact: increased TM cell contraction leads to ECM changes, and ECM changes can increase TM cell tone. Together, this interaction increases TM stiffness which, in turn, can impede aqueous egress through the trabecular outflow tract, thus raising IOP. The TM in eyes with glaucoma is 20 times stiffer than that in healthy eyes.[9]

Nitric Oxide and the Trabecular Meshwork

It stands to reason, therefore, that relaxing TM contractile tone, altering the makeup of ECM—or both—could increase trabecular outflow and lower IOP. There is a meaningful role for NO in achieving TM relaxation. Nitric oxide in an endogenous signaling molecule[10,11] generated naturally by the enzyme NO synthase,[10] which regulates many functions throughout the body.[11] One key action of NO is relaxation of smooth muscle to regulate blood flow.[11–13] Another action is to relax the smooth muscle in the TM in order to lower IOP.[14]

In healthy eyes, NO is synthesized in the endothelium of uveal vasculature, Schlemm canal, and the ciliary body.[15,16] Nitric oxide is known to increase trabecular outflow facility in the human anterior segment,[17] and NO donors lower IOP in animal models.[11] The mechanism by which NO lowers IOP is via relaxation of cells in the TM and Schlemm canal via activation of the cyclic guanosine monophosphate signaling pathway[18] and subsequent inhibition of actin-myosin interactions **(Figure 1)**,[11] which leads to increased aqueous outflow and IOP reduction.[15,19]

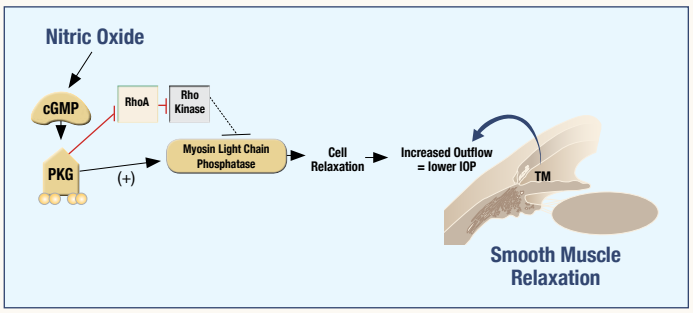


Figure 1. Pathway of nitric oxide leading to smooth muscle relaxation[11]
Abbreviations: cGMP, cyclic guanosine monophosphate; IOP, intraocular pressure; PKG, protein kinase G; TM, trabecular meshwork.

In glaucoma, NO metabolism is altered. Nitric oxide levels in the anterior chamber are reduced in eyes with glaucoma compared with levels in healthy controls[20–22]; in addition, less NO is produced locally by TM and Schlemm canal cells.[22] In the ciliary body, the number of anterior longitudinal muscle fibers—responsible for mechanical opening of the TM through tension on the scleral spur—is also reduced.[22] This can affect the contractile tone of the TM which, as described previously, can contribute to TM stiffness, reduced aqueous outflow, and, consequently, elevated IOP.[9]

New Drugs Target the Trabecular Meshwork

In 2017, 2 new drugs were approved for IOP reduction in the United States—LBN and netarsudil—both of which have their direct IOP-lowering effects in the TM, and one of which—LBN—incorporates the activity of NO into its mechanism of action in the TM. These are the first 2 drugs in more than 2 decades with novel mechanisms of action.

Latanoprostene Bunod: A Nitric Oxide–Donating Formulation of Latanoprost

LBN is a novel molecule consisting of the PGA latanoprost and a NO-donating moiety butanediol mononitrate. Upon instillation, the molecule dissociates into its 2 active components. Latanoprost, a familiar PGA, lowers IOP by enhancing uveoscleral outflow, whereas NO lowers IOP through direct action in the TM.[11,14]

LBN's effect on IOP has been evaluated in several clinical studies. The phase 3 APOLLO and LUNAR studies randomized subjects with POAG or OHTN in a 2:1 ratio to receive 3 months of treatment with either once-daily LBN or twice-daily timolol, 0.5%.[23,24] These 2 studies were designed to evaluate the noninferiority (equal to or better than) of LBN compared with timolol as the primary end point. Intraocular pressure was assessed at 8 AM, 12 PM, and 4 PM at baseline and at 2 weeks, 6 weeks, and 3 months after starting treatment. **Table 1** shows the IOP-lowering and safety results of the APOLLO and LUNAR studies. In the APOLLO study, LBN provided statistically significantly greater IOP reductions than did timolol at all 9 time points, whereas in the LUNAR study, LBN lowered IOP significantly more than did timolol at 8/9 time points. Both drugs were associated with low rates of ocular irritation and conjunctival hyperemia.

Table 1. Summary of the Phase 3 APOLLO and LUNAR Studies of LBN vs Timolol[23,24]

	APOLLO		LUNAR	
	LBN	Timolol	LBN	Timolol
	(n = 284)	(n = 133)	(n = 278)	(n = 136)
Baseline IOP, mm Hg	26.7	26.5	26.6	26.4
Mean IOP reductions at 3 months, mm Hg	8-9	6.7-7.4	7.5-8.8	6.6-7.9
Significance	LBN > timolol at all 9 time points ($P \leq .002$)		LBN > timolol at 8/9 time points ($P \leq .025$)	
Common side effects	**(n = 283)**	**(n = 135)**	**(n = 277)**	**(n = 135)**
Eye irritation, %	3.9	2.2	7.2	4.4
Conjunctival hyperemia	2.8	1.5	9.0	0.7

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

In a pooled analysis of the APOLLO and LUNAR data sets, 3-month mean diurnal IOP reduction was 32% and IOP was statistically lower in the LBN group than in the timolol group at all 9 time points **(Figure 2)**.[25] In an open-label extension study, in which crossover from timolol to LBN was permitted, mean IOP reductions through 12 months of follow-up ranged from 32% to 34%, with additional reductions in mean diurnal IOP of 6.3% to 8.3% in eyes crossing over from timolol to LBN.[26] Adverse events were primarily mild to moderate (> 99.5%) and included conjunctival hyperemia (5.9%), eye irritation (4.6%), and eye pain (3.6%).

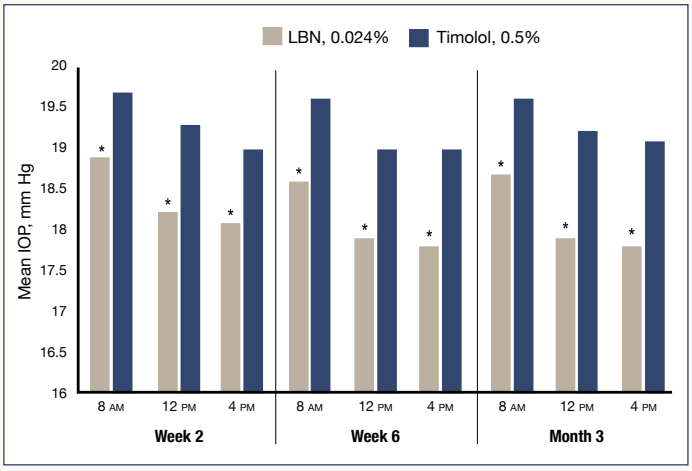


Figure 2. Mean IOP at all time points in the pooled analysis of APOLLO and LUNAR data[25]

*$P < .001$

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

The VOYAGER study was a phase 2 dose-finding comparison of LBN and latanoprost **(Table 2)**.[27] In this study, 4 concentrations of LBN, each dosed once daily at night, were compared with latanoprost, 0.005%, dosed once daily at night. Intraocular pressure was measured at 8 AM, 12 PM, and 4 PM at baseline and at 1, 2, and 4 weeks after starting treatment. Mean diurnal IOP reduction at the week-4 time point (the study's primary end point) was significantly greater in the LBN, 0.024%, group (the approved dose) than in the latanoprost group (9.00 vs 7.77 mm Hg; $P = .005$). Although the concentration of latanoprost in each of the 4 LBN groups was greater than that in the latanoprost group, evidence suggests that increasing latanoprost concentration does not increase efficacy.[28]

Table 2. Efficacy and Safety Outcomes at Week 4 in the VOYAGER Phase 2 Study of LBN vs Latanoprost[27]

	LBN, 0.006% (n = 82)	LBN, 0.012% (n = 85)	LBN, 0.024% (n = 83)	LBN, 0.040% (n = 81)	Latanoprost (n = 82)
Baseline IOP, mm Hg	26.1	26.25	**26.0**	26.0	26.15
Mean IOP reduction, mm Hg	7.8	8.3	**9.0**	8.9	7.8
Significance vs latanoprost	.913	.258	**.005**	.009	–
Common side effects	**(n = 82)**	**(n = 84)**	**(n = 83)**	**(n = 81)**	**(n = 82)**
Eye irritation, %	1.2	2.4	**3.6**	6.2	0
Conjunctival hyperemia	1.2	3.6	**4.8**	3.7	0

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

The single-arm, open-label JUPITER study evaluated LBN in 130 Japanese patients with OHTN, POAG, and normal-tension glaucoma (NTG).[29] In Japan, most OAG is of the NTG variety. The mean baseline IOP of this cohort was 19.6 mm Hg, well within the normal range. Following 12 months of treatment, mean IOP was reduced by 22% ($P < .001$): the most common adverse events were conjunctival hyperemia (17.7%), eyelash growth (16.2%), and ocular irritation/pain (11.5%/10%).

Although not available in the United States, nipradilol is an NO-donating beta blocker approved in Japan for the reduction of IOP. Long-term IOP-lowering efficacy has been demonstrated in eyes with NTG,[30] and short-term improvement in ocular blood flow has also been described.[31] Other NO-donating drugs in development include formulations of bimatoprost and carbonic anhydrase inhibitors.[32,33]

Netarsudil: A Rho-Kinase Inhibitor

Netarsudil is a novel ROCK inhibitor. Rho kinase is an enzyme that regulates the shape and movement of cells through action on the cytoskeleton. Inhibition of ocular ROCK leads to smooth muscle relaxation of both the TM and the episcleral veins. Thus, netarsudil acts to increase trabecular outflow both by increasing aqueous outflow through the TM[34,35] and by decreasing pressure within the episcleral venous system, thus reducing downstream resistance to outflow.[34] Netarsudil also inhibits the action of NET, which has the effect of increasing adrenergic activity within the eye, which in turn suppresses aqueous humor production.[34,35]

Netarsudil has been studied in a series of glaucoma clinical trials. The ROCKET-1 and ROCKET-2 studies were 3-month phase 3 comparisons of netarsudil, 0.02%, dosed once or twice daily and timolol, 0.5%, dosed twice daily,[36] whereas ROCKET-4 was a similarly designed study in which primary efficacy was assessed after 3 months and safety assessed through 6 months.[37] All 3 of these studies were designed to establish noninferiority of netarsudil to timolol as the primary end point.[36,37] Intraocular pressure was measured at 8 AM,

Table 3. Efficacy and Safety Outcomes of ROCKET-1, ROCKET-2, and ROCKET-4 Phase 3 Studies of Netarsudil vs Timolol[36,37]

	ROCKET-1 (All Eyes)		ROCKET-1 (Eyes With IOP < 25 mm Hg)		ROCKET-2		ROCKET-4	
	Netarsudil (n = 202)	Timolol (n = 209)	Netarsudil (n = 113)	Timolol (n = 124)	Once-Daily Netarsudil (n = 251)	Timolol (n = 251)	Netarsudil (n = 186)	Timolol (n = 186)
Baseline IOP, mm Hg	21.8-23.4	21.5-23.4	20.6-22.4	20.5-22.5	20.4-22.5	20.7-22.5	20.7-22.4	20.7-22.4
Mean IOP reduction, mm Hg	3.3-5.0	3.7-5.1	3.7-5.1	3.2-4.7	3.3-4.6	3.7-5.1	3.9-4.5	3.9-5.2
Significance	Netarsudil inferior to timolol		Netarsudil noninferior to timolol		Netarsudil noninferior to timolol		Netarsudil noninferior to timolol	
Common side effects	**(n = 203)**	**(n = 208)**	–	–	**(n = 251)**	**(n = 251)**	**(n = 351)**	**(n = 357)**
Conjunctival hyperemia, %	53.2	8.2	–	–	50.2	10.8	47.9	9.2
Conjunctival hemorrhage, %	13.3	0.5	–	–	14.7	0	16.0	3.1
Corneal verticillata, %	5.4	0	–	–	8.8	0.4	24.5	0

Abbreviation: IOP, intraocular pressure.

10 AM, and 4 PM at baseline and at 2 weeks, 6 weeks, and 3 months while on treatment. **Table 3** shows the efficacy and safety outcomes of these studies. In ROCKET-1, mean IOP reductions in the timolol group were greater than those in the once-daily netarsudil group, and the criteria for noninferiority were not met.[36] However, a post hoc analysis of eyes with baseline IOP < 25 mm Hg revealed that once-daily netarsudil was statistically noninferior to timolol. In ROCKET-2, only eyes with baseline IOP < 25 mm Hg were included in the primary analysis; in these eyes, once-daily netarsudil was also statistically noninferior to timolol. In ROCKET-4, netarsudil met the criteria for noninferiority to timolol in the per-protocol analysis that included eyes with IOP < 25 mm Hg at baseline.[37] Across these 3 studies, netarsudil had a substantially higher rate of hyperemia than did timolol and was also associated with the development of both conjunctival hemorrhages and corneal verticillata.[36,37] The incidence of both verticillata (24.5%) and conjunctival hemorrhages (16.0%) was higher in the 351 patients receiving netarsudil in the longer ROCKET-4 safety analysis than in patients in the 3-month ROCKET-1 and ROCKET-2 studies, whereas the rate of hyperemia (47.9%) in ROCKET-4 was consistent with that of the 3-month observations.

In addition to these phase 3 studies, netarsudil, 0.02%, was compared with latanoprost in a 4-week phase 2 study.[38] In this monotherapy study, subjects were randomly assigned to treatment with netarsudil or latanoprost, each dosed once daily. The primary end point was diurnal IOP reduction at week 4. At week 4, mean IOP reduction was 5.7 mm Hg for netarsudil and 6.8 mm Hg for latanoprost; in the statistical analysis, netarsudil was found to be inferior to latanoprost. Hyperemia occurred in 24% of the 68 patients receiving netarsudil and in 11% of the 74 patients receiving latanoprost.

Netarsudil was also studied in eyes with low baseline IOP.[34] A total of 11 healthy volunteers received 7 days of once-daily netarsudil. From a mean baseline IOP of 17.4 mm Hg, mean IOP was 3.5 mm Hg lower in netarsudil-treated eyes than in vehicle-treated fellow control eyes, and episcleral venous pressure was also significantly reduced in netarsudil-treated eyes. Mild or moderate hyperemia was reported in all netarsudil-treated eyes.

Netarsudil is also available in a fixed combination with latanoprost. This fixed combination, dosed once daily, has been studied in phase 2 and 3 clinical trials.[39,40] In phase 2 testing, the fixed combination lowered IOP significantly more at day 28 by a mean of 1.9 mm Hg more than did latanoprost monotherapy and by a mean of 2.6 mm Hg more than did netarsudil monotherapy. Hyperemia occurred in 40% of the 78 patients receiving netarsudil, in 40% of the 73 patients receiving the fixed combination, and in 14% of the 73 patients receiving latanoprost.[39] In the phase 3 MERCURY 1 trial, the fixed combination was statistically superior to either of its components; mean diurnal IOP with the fixed combination was 1.5 mm Hg lower than with latanoprost alone and 2.5 mm Hg lower than with netarsudil alone at month 3.[40] The nature and frequency of adverse events was similar to those seen in the phase 2 study.

Case Illustrations

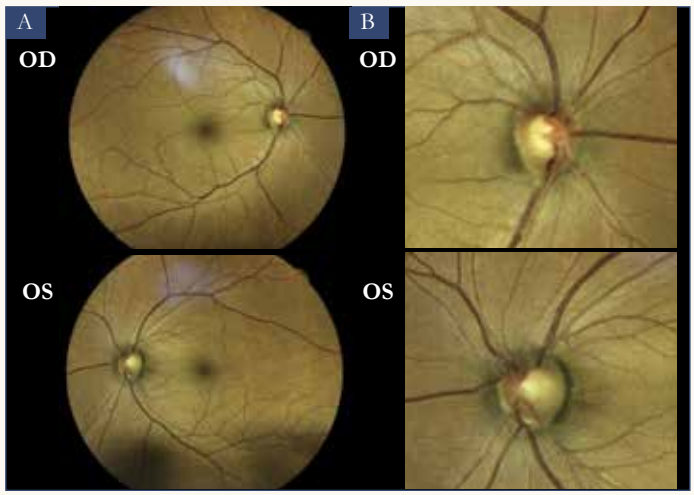
At the time of case development, LBN and netarsudil were the 2 new agents available with which the authors had experience.

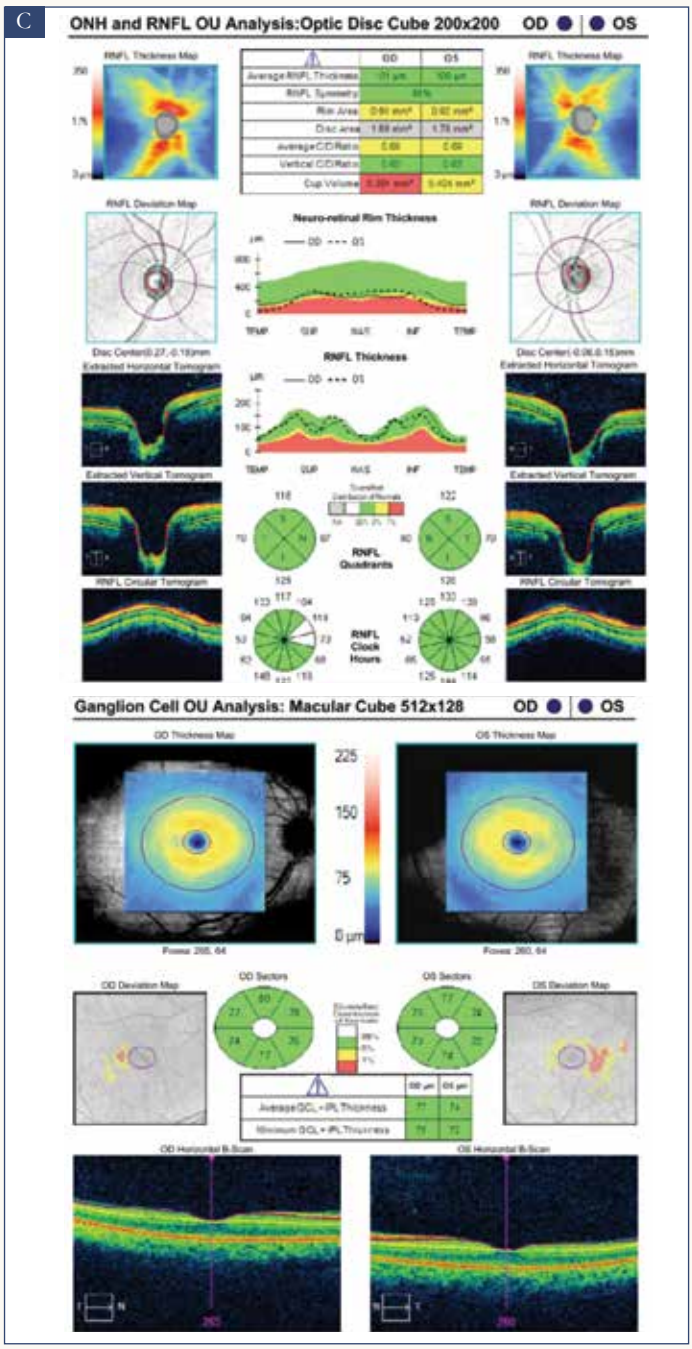
Case 1: Ocular Hypertension

From the files of Michael Chaglasian, OD

A 57-year-old male had a history of elevated IOP (24-32 mm Hg) in both eyes over the past 3 years. His visual acuity (VA) was 20/20 OU, with a small myopic correction. Central corneal thickness (CCT) was 551 µm OD and 565 µm OS. ***Figure 3*** *shows his optic nerves, optic nerve and macular optical coherence tomography (OCT) images, and visual fields (VFs). He had no family history of glaucoma, and his medical history was significant only for type 2 diabetes, high blood pressure, and high cholesterol.*

The optic nerves feature generous cups—approximately 0.65 to 0.7 OU—but the rims are intact and there are no obvious retinal nerve fiber layer (RNFL) defects, no significant peripapillary atrophy, and no disc hemorrhages. The OCT images reveal





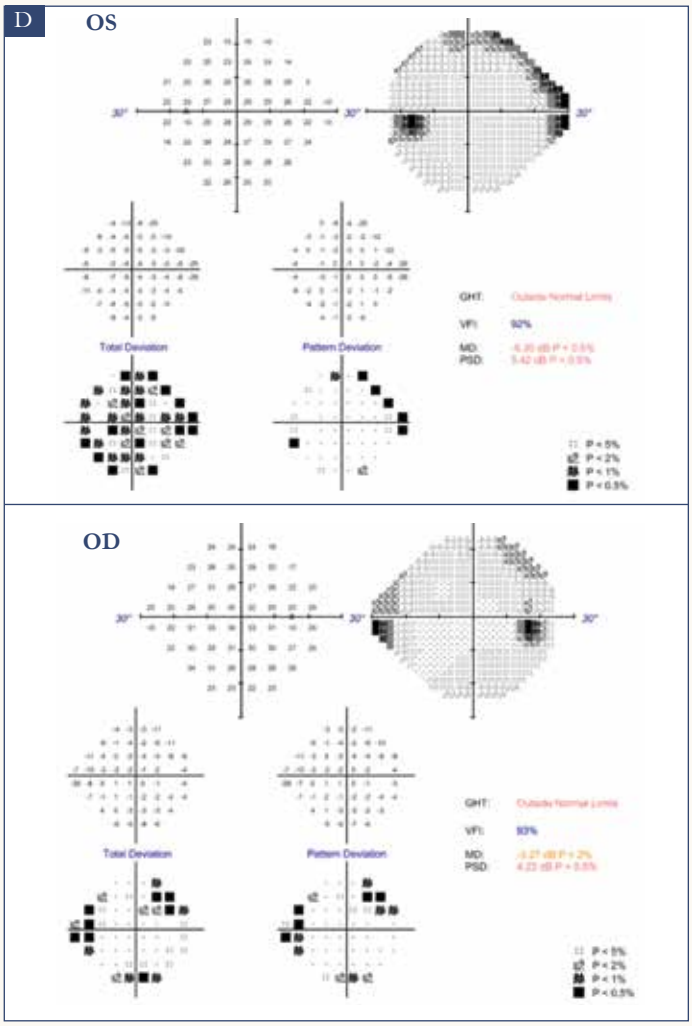


Figure 3. Optic nerves (A and B), optic nerve and macular optical coherence tomography images (C), and visual fields (D) of the patient presented in Case 1

intact RNFL OU as well as normal macular thickness. The VFs, however, show a possible nasal step and a superotemporal defect OD, and some focal rim artifact OS. Given the high rate of false-positive VF defects observed in the Ocular Hypertension Treatment Study (OHTS),[41] the VF tests were repeated and VFs were normalized in both eyes.

Given normal structural (OCT) and functional (VF) testing, this patient was diagnosed with OHTN. The OHTS demonstrated that IOP reduction in eyes with OHTN can delay or prevent the development of POAG, but also suggested against routine treatment for all eyes with OHTN because the overall risk of developing glaucoma is low (approximately 10% every 5 years).[42] Using the OHTS and European Glaucoma Prevention Study risk calculator,[43] the patient's 5-year risk for developing POAG was 22%, so treatment was recommended. LBN, 0.024%, was selected because it is the most effective single agent available. After a 4-week treatment period, IOP was 19 mm Hg OD and 20 mm Hg OS, which more than met the OHTS goal of 20% IOP reduction. Stinging upon instillation was reported, which the patient said was mild and tolerable. The patient will be seen 3 to 4 times/year, and VF and OCT testing will be repeated at least annually.

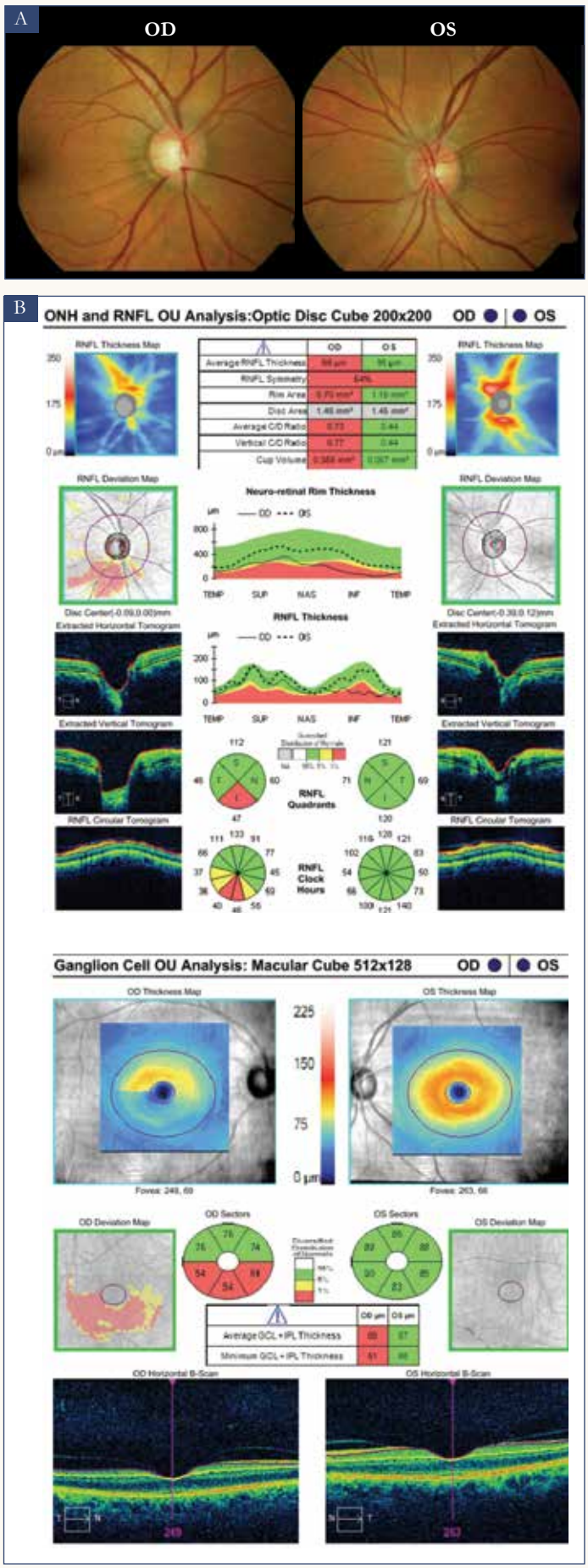


Figure 4. Optic nerves (A), optic nerve and macular optical coherence tomography images (B), and visual fields (C) of the patient presented in Case 2

Case 2: Early Primary Open-Angle Glaucoma

Form the files of Michael Chaglasian, OD

A 56-year-old male presented for his first examination in several years. He had a family history of glaucoma, and his own medical history was significant for asthma, for which he used an inhaler. His VA was 20/20 OU uncorrected, and he used readers for near distances. His slit-lamp examination was unremarkable, and his angles were open on gonioscopy. His IOP was 28 mm Hg OD and 21 mm Hg OS; CCT was 571 µm OD and 585 µm OS. ***Figure 4*** *shows his optic nerves, optic nerve and macular OCT images, and VFs.*

This patient has asymmetric IOP (higher OD), asymmetric optic nerve cupping (worse OD), OCT evidence of RNFL and macular thinning inferiorly OD (and normal OS), and a superior paracentral VF defect OD (and essentially normal OS). This is either unilateral OAG (in which case secondary glaucoma, such as pseudoexfoliation, pigmentary, steroid related, and inflammatory, should be considered) or very asymmetric POAG. There is really no evidence of glaucoma in the left eye, but it could manifest later, so close observation is reasonable in this eye. The right eye, however, has POAG and warrants IOP reduction. In this case, the patient preferred bilateral treatment

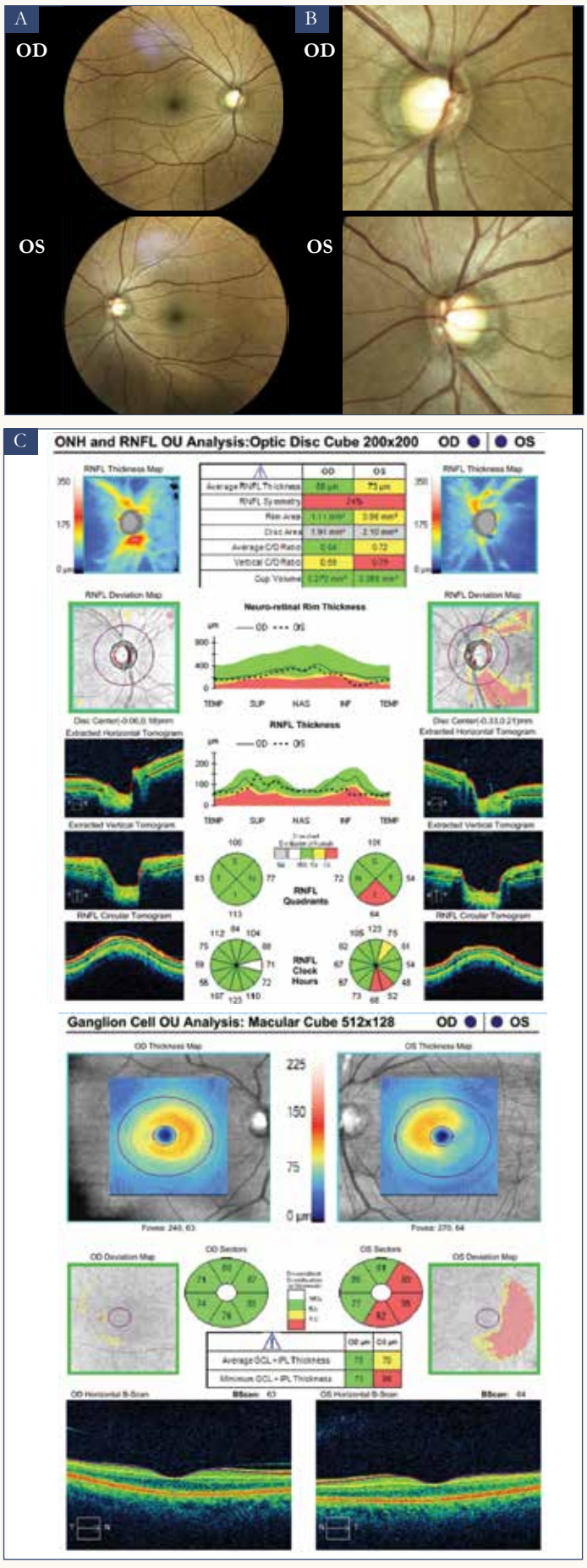


Figure 5. Optic nerves (A and B), optic nerve and macular optical coherence tomography images (C), and visual fields (D) of the patient presented in Case 3

out of an abundance of caution for the left eye. On the basis of major clinical studies, the recommended therapeutic goal for early-to-moderate POAG is 25% to 30% IOP reduction.[2] A trial of generic latanoprost failed to lower IOP significantly (IOP after 4 weeks of therapy was 25 mm Hg OD and 20 mm Hg OS), so LBN was prescribed. After 4 more weeks, IOP was 18 mm Hg OD and 15 mm Hg OS. No adverse events were noted. The patient will be seen 3 to 4 times/year, and VF and OCT testing will be repeated at least annually.

Case 3: Normal-Tension Glaucoma

From the files of Michael Chaglasian, OD

A 64-year-old female was referred for evaluation of suspicious-appearing optic nerves. She had no significant medical history and is on no systemic medications. Her VA was 20/20 OU, with a small myopic correction. Intraocular pressure ranged from 16 to 19 mm Hg OU over several visits, and CCT was 537 µm OD and 541 µm OS. ***Figure 5*** *shows her optic nerves, optic nerve and macular OCT images, and VFs.*

This patient has normal IOP, with average to slightly thin CCT OU. Her optic nerves have large cups, but the nerves themselves are also very large (and asymmetrically so, with the

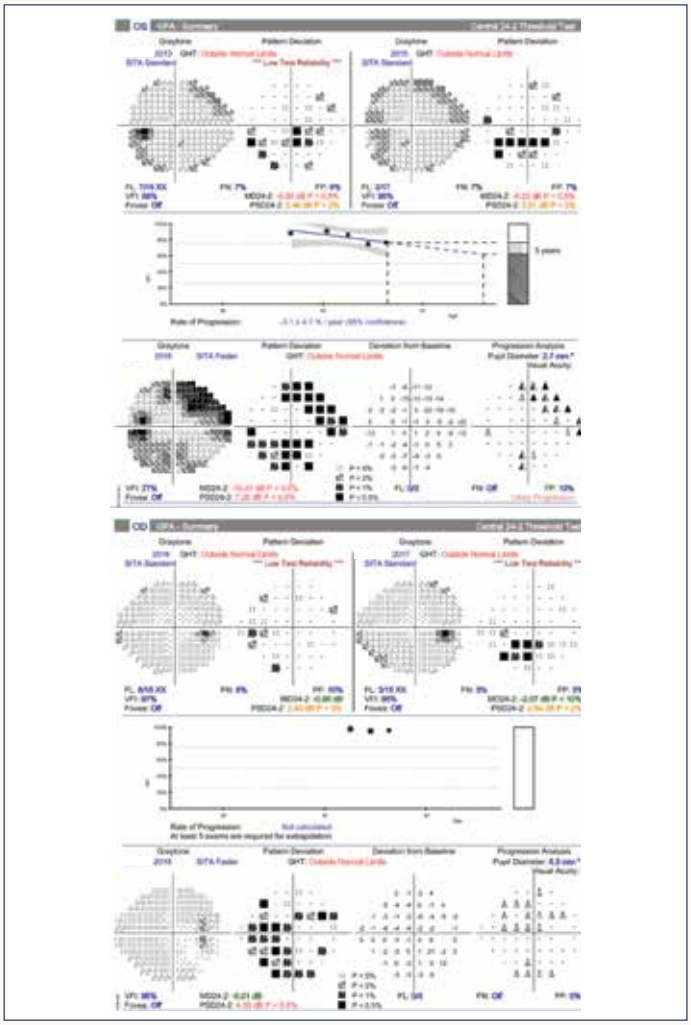


Figure 6. Serial visual fields of each eye of the patient presented in Case 4

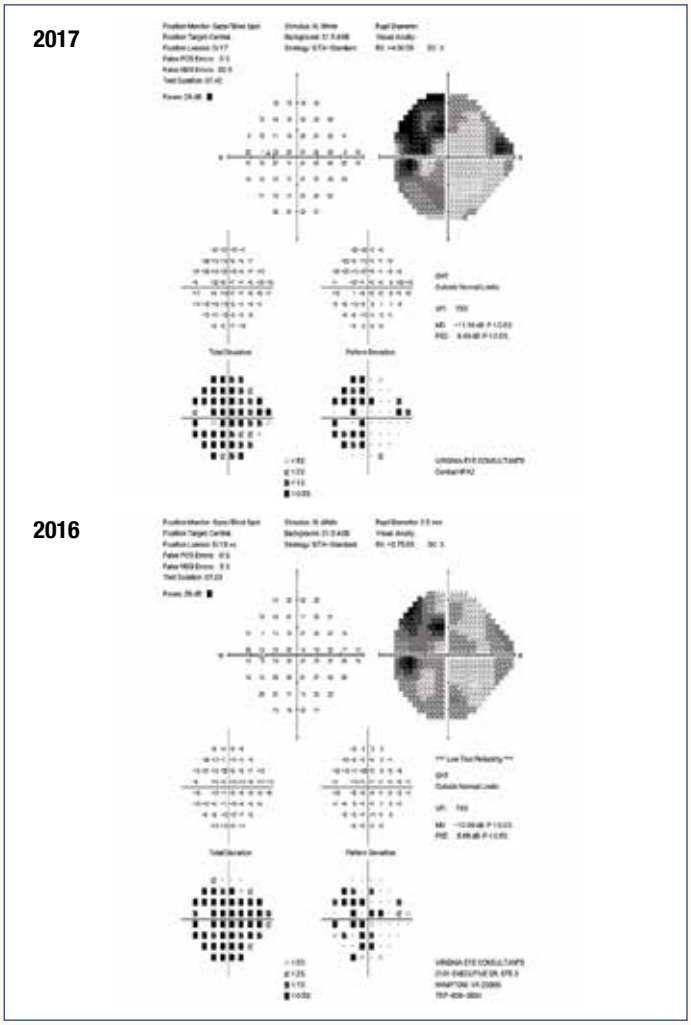


Figure 7. Visual fields from the left eye of the patient presented in Case 5

right being larger than the left), so large physiologic cups would be expected. Structural and functional testing can assist in differentiating between physiologic and glaucomatous cupping. The RNFL and macular OCTs are normal OD and abnormal OS, and the VFs are consistent: normal OD and abnormal OS. There is structure-function correlation, with inferior structural damage and superior field loss OS. This is asymmetric NTG. The goal of therapy in NTG is a 30% IOP reduction, consistent with the Collaborative Normal-Tension Glaucoma Study findings.[2] Because it has been shown to effectively lower IOP in eyes with low baseline IOP,[29] LBN was started in both eyes. After 4 weeks of treatment, IOP was 13 mm Hg OD and 14 mm Hg OS. Therapy was continued, and the patient will be seen 3 to 4 times/year, with annual repeat VF and OCT testing.

Case 4: Progression on Medications

From the files of Michael Chaglasian, OD

An 88-year-old female with a 6-year history of POAG and untreated IOP of 24 to 25 mm Hg OU had been previously well controlled on a PGA. Recently, however, her IOP had been creeping up to the low 20s, and at her most recent visit, IOP was 21 mm Hg OD and 22 mm Hg OS. Serial VFs demonstrate a progressive 3.1 dB/year decline in mean deviation ***(Figure 6)****.*

This patient's IOP is inadequately controlled on PGA monotherapy, and she is progressing. A reasonable target IOP for this patient would be approximately 17 mm Hg, which represents ~30% reduction from her untreated baseline. To maintain her once-daily dosing regimen, netarsudil was added to her left eye. Three weeks later, IOP was 16 mm Hg; the patient reported mild hyperemia that she felt was tolerable. Therapy was continued, and the patient will be seen 3 to 4 times/year, with annual repeat VF and OCT testing.

Case 5: Very Low Target Intraocular Pressure

From the files of Walter O. Whitley, OD, MBA

An 81-year-old male with a 10-year history of advanced POAG presented complaining of foreign body sensation in both eyes. He was pseudophakic OU and had undergone trabeculectomy OD and iStent trabecular microbypass implantation OS. His current ocular medications included the dorzolamide/timolol fixed combination 3 times daily OS and artificial tears 4 times daily OU. His current IOP was 10 mm Hg OD and 14 mm Hg OS. He had recently confirmed VF progression OS ***(Figure 7)****.* The VF of the left eye shows progression of both the superior and inferior defects over a 1-year period. The defect is close to fixation. The progression occurred at IOP levels in the low- to mid-teens. This patient needs a lower IOP OS to prevent

further progression, which could threaten his central VA. The Canadian Glaucoma Study demonstrated that an additional 20% IOP reduction in progressing patients can prevent further progression.[44] Also, a recent study established that in eyes progressing at low IOP, achieving single-digit IOP can stop further progression, although this often requires surgical intervention.[45] Because it is the most effective single agent available and because it has demonstrated efficacy in eyes with low baseline IOP, LBN was added to the left eye. Four weeks later, IOP was 8 mm Hg, and no adverse events were noted. Therapy was continued, and the patient will be evaluated at least every 3 months, with VF and OCT testing at least annually. Future VF assessment will include 10-2 testing to carefully monitor the central VF.

Summary and Take-Home Points

- POAG is a progressive optic neuropathy, characterized by optic nerve damage, RNFL defects, and VF loss that will affect an estimated 3.3 million American adults by 2020
- Approximately ≥ 50% of people with POAG are undiagnosed and untreated; opportunistic screening at the time of routine vision examinations is an ideal way to identify undiagnosed cases
- POAG leads to increased stiffness in the TM, which reduces aqueous outflow via the trabecular pathway and raises IOP
- The approach to treatment for POAG is reduction of IOP, with the goal of preserving long-term quality of life
- Two new drugs—LBN and netarsudil—lower IOP by reducing TM stiffness and increasing trabecular outflow
- LBN lowers IOP through the actions of latanoprost, which increases uveoscleral outflow, and NO, which relaxes trabecular cells and increases trabecular outflow via activation of the cyclic guanosine monophosphate signaling pathway
- In clinical trials, LBN lowered IOP more than did latanoprost or timolol
- Netarsudil lowers IOP through up to 3 mechanisms: increased trabecular outflow, reduced aqueous production, and reduced episcleral venous pressure
- In clinical trials, netarsudil lowered IOP comparably to timolol in eyes with low baseline IOP (< 25 mm Hg)
- Side effects of both drugs are generally mild to moderate and not generally sight threatening; LBN causes hyperemia and instillation discomfort, whereas netarsudil causes hyperemia, conjunctival hemorrhages, and corneal verticillata

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1. Which was a finding of the LiGHT study comparing laser with medications for primary glaucoma therapy?
   a. Medication use was more common in the laser group
   b. IOP reduction was better in the medication group
   c. Surgery was required more often in the medication group
   d. Progression was more common in the laser group

2. When selecting primary therapy for glaucoma, which factors should be considered?
   a. Efficacy, safety, and color of the bottle cap
   b. Safety, tolerability, and family history of glaucoma
   c. Efficacy, cost, and CCT
   d. Efficacy, safety, and cost

3. How effective is a monocular therapeutic drug trial as a treatment strategy?
   a. It is highly predictive of both treatment eye and fellow eye response to different drugs
   b. It is highly predictive of long-term IOP reduction
   c. It is highly predictive of fellow eye response to the same medication
   d. It is no longer recommended; instead, IOP should be assessed over multiple visits

4. How does glaucoma affect aqueous humor outflow?
   a. There is no effect on outflow
   b. Trabecular outflow is increased
   c. Uveoscleral outflow is increased
   d. Trabecular outflow is decreased

5. Which of the following effects of TM stiffening/cell contraction is accurate in glaucomatous eyes?
   a. TM cell contraction is typically decreased
   b. The ECM of TM remains unchanged
   c. Changes to the ECM can increase TM cell tone
   d. Decreased TM cell contraction can lead to ECM changes

6. Alterations of NO metabolism in glaucoma include:
   a. Elevated NO levels in the anterior chamber
   b. Decreased NO production by cells in the TM and Schlemm canal
   c. Increased number of anterior longitudinal fibers in the ciliary muscle
   d. All the above

7. Nitric oxide lowers IOP by activation of the _____ signaling pathway.
   a. Adrenal-pituitary-hypothalamic
   b. Cyclic guanosine monophosphate
   c. ROCK-NET
   d. Uveoscleral

8. How does NO affect the TM?
   a. Increases stiffness, which forces aqueous humor through the TM
   b. Increases efficacy of PGAs to lower uveoscleral outflow
   c. Increases TM cell contractility to pump aqueous into Schlemm canal
   d. Relaxes smooth muscle to facilitate aqueous humor egress through the trabecular outflow pathway

9. Netarsudil lowers IOP by:
   a. Increasing uveoscleral outflow
   b. Increasing episcleral venous pressure
   c. Increasing aqueous humor production
   d. Relaxing trabecular cells and increasing trabecular outflow

10. In phase 2 and pooled phase 3 study analyses, LBN was shown to lower IOP more than did _____.
    a. Latanoprost and netarsudil
    b. Carbonic anhydrase inhibitors and timolol
    c. Latanoprost and timolol
    d. Brimonidine and timolol

11. In the JUPITER study of Japanese eyes with low baseline OP, LBN lowered IOP by approximately _____.
    a. 10%
    b. 14%
    c. 22%
    d. 30%

12. In eyes with IOP < 25 mm Hg at baseline, netarsudil lowered IOP:
    a. More than did latanoprost
    b. More than did LBN
    c. Less than did dorzolamide
    d. Comparably to timolol

13. In a study of healthy volunteers with normal IOP, which of the following is true regarding netarsudil?
    a. Hyperemia did not occur in healthy volunteers
    b. IOP was reduced by 3.5 mm Hg more in treated eyes than in control eyes
    c. Episcleral venous pressure was increased
    d. All the above

14. Which of the following is true regarding the netarsudil/latanoprost fixed combination?
    a. It does not lower IOP better than netarsudil alone
    b. It lowers IOP better than netarsudil alone
    c. It lowers IOP comparably to latanoprost
    d. It produces less hyperemia than latanoprost

15. Which of the following side effect scenario is accurate?
    a. Netarsudil is associated with a high rate of eye irritation
    b. LBN can cause conjunctival hemorrhages
    c. Netarsudil can cause corneal verticillata
    d. LBN can cause hyperemia

16. In a pooled analysis of 2 phase 3 studies, LBN lowered mean diurnal IOP by ____ at 3 months.
    a. 15%
    b. 24%
    c. 32%
    d. 44%

17. The TM in eyes with glaucoma is ____ times stiffer than that in healthy eyes.
    a. 7
    b. 13
    c. 20
    d. 35

18. A patient with OHT has had normal VFs for 3 years. The most recent VF shows a new defect. How should this patient be managed?
    a. Patient has developed glaucoma and should be treated
    b. Because the patient has been stable, this is not likely glaucoma, and neuroimaging should be performed to rule out central nervous system lesions
    c. VFs are poorly reliable and this finding should be ignored. The diagnosis of glaucoma should be based on RNFL OCT images instead
    d. Patient should be retested because the VF has a high likelihood of being normal on repeat testing according to the Ocular Hypertension Treatment Study

19. LBN lowers IOP by:
    a. Decreasing uveoscleral outflow and increasing trabecular outflow
    b. Increasing both uveoscleral and trabecular outflow
    c. Decreasing aqueous humor formation
    d. Increasing episcleral venous pressure

20. What is the approximate percent of patients with POAG who remain undiagnosed and untreated?
    a. 20%
    b. 30%
    c. 40%
    d. 50%