

THE LITERATURE



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A RANDOMISED, CONTROLLED COMPARISON OF LATANOPROSTENE BUNOD AND LATANOPROST 0.005% IN THE TREATMENT OF OCULAR HYPERTENSION AND OPEN ANGLE GLAUCOMA: THE VOYAGER STUDY

Weinreb RN, Ong T, Sforzolini BS, et al¹



ABSTRACT SUMMARY

The VOYAGER study is an industry-sponsored investigation organized as a prospective, randomized, investigator-blinded, parallel-group, dose-ranging study of latanoprostene bunod (LBN). Five groups that were similar at baseline ($n =$ approximately 80 each) included LBN at different doses (0.0006%-0.04%) and latanoprost (0.005%) with good study retention ($> 95\%$). The primary endpoint was IOP reduction at study's end. Secondary endpoints included IOP reduction at midpoint visits and the proportion of subjects with a mean diurnal IOP of 18 mm Hg or less. Adverse events such as diminished vision, discomfort, and hyperemia were monitored.

IOP decreased in all groups. Compared with latanoprost, the reduction was statistically significantly greater when using LBN 0.024% and 0.04% (1.23 mm Hg difference [$P = .005$] and 1.16 mm Hg difference [$P = .009$], respectively, at the 28-day point, for example). The absolute additional IOP reduction of LBN over latanoprost at most time points was about 1 mm Hg. The 0.024% and 0.04% LBN groups also had a greater proportion of patients with a mean diurnal IOP of 18 mm Hg or less (approximately 60%-70%) compared to the latanoprost group (approximately 45%; $P < .05$). Although the LBN groups showed a higher incidence of dry eye or ocular surface discomfort with instillation of higher drug doses, conjunctival hyperemia was similar among all groups.

DISCUSSION

What makes LBN different from other IOP-lowering agents?

LBN is a molecule specifically developed to decrease IOP that is unique in that the agent affects both aqueous humor outflow pathways, trabecular and uveoscleral. Acted upon by ubiquitous esterases found in the eye, LBN breaks apart into latanoprost acid (well known to promote uveoscleral outflow) and butanediol mononitrate (a nitric oxide-donating molecule purported to improve trabecular outflow based on direct effects on trabecular meshwork [TM] cells and in animal models).^{2,3}

How effective is LBN at decreasing IOP?

The VOYAGER study adequately demonstrated that LBN lowered IOP and was statistically superior to latanoprost. Although the absolute reduction was modest, the bar set for noninferiority to a prostaglandin analogue is actually quite high, given that prostaglandins are so effective at lowering IOP. Unanswered points remain such as the persistence of IOP-lowering effects long term, the effects of ocular surface discomfort on real-world adherence, and the ability of LBN to act in addition to or synergistically with other IOP-lowering agents such as aqueous suppressants. Moreover, aqueous humor parameters in humans have not been parsed out with LBN. Nitric oxide-donating drugs such as nitroglycerin and sodium nitroprusside cause vasodilation, so IOP effects could have been accomplished through lowering episcleral venous pressure as well in this study.⁴

Although great success has been seen with topical agents promoting uveoscleral outflow, a dearth of drugs that augment TM/conventional outflow has persisted. This situation may be changing, thanks to nitric oxide-donating molecules described herein, continued investigation into Rho-kinase inhibitors,⁵ and the creation of methods by which to image aqueous humor outflow such as aqueous angiography that may spur the development of drugs that act upon the TM/conventional outflow pathway.⁶

IMPORTANCE OF NORMAL AGING IN ESTIMATING THE RATE OF GLAUCOMATOUS NEURORETINAL RIM AND RETINAL NERVE FIBER LAYER LOSS

Vianna JR, Danthurebandara VM, Sharpe GP, et al⁷

ABSTRACT SUMMARY

Using the Spectralis (Heidelberg Engineering), Vianna et al carefully evaluated the effects of aging on glaucoma-relevant optical coherence tomography (OCT) parameters such as Bruch membrane opening-minimum rim width (BMO-MRW), peripapillary retinal nerve fiber layer (RNFL) thickness, and other parameters. Patients were observed in a longitudinal fashion (median follow-up of 4 years and imaged at 6-month intervals; $n = 192$ patients treated for glaucoma and $n = 37$ healthy controls). Statistical analyses with least-square regression and linear mixed effects modeling were used to estimate the average rates of change and differences in those rates between the groups, respectively.

Over the course of the study, a similar proportion of patients in the control and glaucoma groups experienced a decline in BMO-MRW and RNFL thickness, and that decline was not

statistically different (controls, 35% and 31% vs glaucoma, 42% and 31%, respectively). Controls experienced a significant reduction in BMO-MRW ($-1.92 \mu\text{m}/\text{y}$) and RNFL thickness ($0.45 \mu\text{m}/\text{y}$). Treated glaucoma subjects showed *additional* but not statistically significant reductions in the rate of BMO-MRW ($-1.26 \mu\text{m}/\text{y}$) and RNFL thickness ($-0.40 \mu\text{m}/\text{y}$) loss compared to controls. The investigators also noted that baseline age and IOP exerted different influences on the rate of change in OCT parameters. The BMO-MRW was the only neuroretinal parameter whose rate of change was significantly influenced by baseline age; this parameter's loss was ameliorated with age.

DISCUSSION

All optic nerve pathologies, including the glaucomas, affect the appearance of the optic nerve head (ONH). With the advent of modern imaging modalities such as OCT, new diagnostic avenues have opened up by which to refine the examination. As these devices become a major adjunct to the diagnosis and the long-term management of glaucoma, the importance of understanding parameters such as BMO-MRW and adjusting for factors that can significantly affect results with these technologies cannot be overemphasized.

What is BMO-MRW?

The anatomic basis for the human optic disc margin is complex and can vary greatly among individual eyes. Because the clinical estimation of disc margin lacks solid and consistent anatomical and geometric foundations across all patients, inaccuracies can produce erroneous assessments of the neuroretinal rim. This is especially true with a tilted optic nerve configuration. In contrast, OCT imaging of the ONH consistently identifies BMO as a stable landmark and more reliably establishes the outer neuroretinal rim border. This allows for a more accurate assessment of the neuroretinal rim itself.

BMO-MRW is a newly proposed OCT parameter for assessing the ONH in glaucomatous and nonglaucomatous optic neuropathies, and the method uses BMO as a reference point.⁸ BMO-MRW measures the shortest distance from the BMO to the inner limiting membrane. The BMO-MRW parameter assesses the health of the neuroretinal rim while taking into account its varying trajectory relative to the point of the measurement. By offering a measurement of rim width perpendicular to the path of the axons as they exit the eye, BMO-MRW minimizes overestimation of rim tissue and may enhance diagnostic sensitivity.

How important is age?

Almost all biological functions, including ophthalmic, demonstrate senescence.⁹ Age-related ganglion cell loss has been reported but is poorly appreciated by clinicians, because a true count of the number of ganglion cells in a live human as a function of age¹⁰ can never be longitudinal, given the necessity for histological evaluation. Noninvasive imaging such as OCT overcomes longitudinal challenges but does not specifically assess

only ganglion cells, because OCT measurements can comprise cellular and noncellular as well as neuronal and nonneuronal elements.¹¹ Nevertheless, a decline in OCT parameters with age in this article and others¹¹ provides reassurance that decreasing ganglion cell estimates as a function of age in human subjects are real. Recognizing this important variable of age-related loss highlights that not all changes observed on OCT in patients with glaucoma are necessarily due to the disease. This idea has been suspected from a functional standpoint, because visual field changes on standard automated perimetry can be divided into slow and fast components, with the former possibly reflecting age-related losses and the latter true glaucomatous disease.¹² Phrased in this way, successful glaucoma treatment might be best restated as the normalization of the diseased ganglion cell loss rate back to the standard age-related rate. Finally, because age-related ganglion cell loss is likely unavoidable, the onus then shifts to the eye care practitioner to diagnose glaucoma early and to treat patients aggressively before the disease reaches advanced stages, when age-related changes become relatively more significant. ■

- Weinreb RN, Ong T, Scassellati Sforzolini B, et al. A randomised, controlled comparison of latanoprostene bunod and latanoprost 0.005% in the treatment of ocular hypertension and open angle glaucoma: the VOYAGER study. *Br J Ophthalmol*. 2015;99(6):738-745.
- Krauss AH, Impagnatiello F, Toris CB, et al. Ocular hypotensive activity of BOL-303259-X, a nitric oxide donating prostaglandin F₂α agonist, in preclinical models. *Exp Eye Res*. 2011;93(3):250-255.
- Gabelt BT, Kaufman PL, Rasmussen CA. Effect of nitric oxide compounds on monkey ciliary muscle in vitro. *Exp Eye Res*. 2011;93(3):321-327.
- Nathanson JA. Nitrovasodilators as a new class of ocular hypotensive agents. *J Pharmacol Exp Ther*. 1992;260(3):956-965.
- Honjo M, Tanihara H, Inatani M, et al. Effects of Rho-associated protein kinase inhibitor Y-27632 on intraocular pressure and outflow facility. *Invest Ophthalmol Vis Sci*. 2001;42(1):137-144.
- Saraswathy S, Tan JC, Yu F, et al. Aqueous angiography: real-time and physiologic aqueous humor outflow imaging. *PLoS One*. 2016;11(1):e0147176.
- Vianina JR, Danthurebandara VM, Sharpe GP, et al. Importance of normal aging in estimating the rate of glaucomatous neuroretinal rim and retinal nerve fiber layer loss. *Ophthalmology*. 2015;122(12):2392-2398.
- Chauhan BC, Danthurebandara VM, Sharpe GP, et al. Bruch's membrane opening minimum rim width and retinal nerve fiber layer thickness in a normal white population: a multicenter study. *Ophthalmology*. 2015;122(9):1786-1794.
- Caprioli J. Glaucoma: a disease of early cellular senescence. *Invest Ophthalmol Vis Sci*. 2013;54(14):ORSF60-67.
- Harman A, Abrahams B, Moore S, Hoskins R. Neuronal density in the human retinal ganglion cell layer from 16-77 years. *Anat Rec*. 2000;260(2):124-131.
- Harwerth RS, Wheat JL. Modeling the effects of aging on retinal ganglion cell density and nerve fiber layer thickness. *Graefes Arch Clin Exp Ophthalmol*. 2008;246(2):305-314.
- Azarbod P, Mock D, Bitrian E, et al. Validation of point-wise exponential regression to measure the decay rates of glaucomatous visual fields. *Invest Ophthalmol Vis Sci*. 2012;53(9):5403-5409.

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- financial disclosure: receives research materials from Heidelberg Engineering