Say NO to Glaucoma

Leo Semes, OD ,FAAO

Ashley Cowart, OD, FAAO

Course Outline

I. Lowering intraocular pressure (IOP) has been the mainstay of glaucoma and ocular hypertension management for decades. Beginning with a simple topical strategy, a prostaglandin analog PGA) or beta-blocker (BB) is considered the best initial strategy (1). This recommendation follows setting a target pressure based on a number of clinical findings that are beyond the scope of this course.

II. Latanoprost became commercially available over 20 years ago. An emerging chemical modification of the latanoprost molecule includes the addition of a nitric-oxide (NO) moiety. Vyzulta ™ (latanaprostene bunod 0.024% ophthalmic solution) was approved by the US Food and Drug Administration in November 2017 (2). The mechanism and site of action are both interesting and will be detailed below.

III. Nitric oxide (NO) was named "molecule of the year" in 1992 (3). NO was discovered in the 1770s by Joseph Priestly, in England (4). Although nitroglycerin was synthesized and found to have a vasodilatory effect in the 1840s, and, by the 1870s, had been widely used along with related nitrate compounds to treat patients with angina and hypertension, no one connected these chemicals' effects on vascular tissues with NO for the next century (5). In 1977, Murad found that it was, in fact NO release that accounts for the vasodilatory effect of nitroglycerin and related compounds (6,7).

IV. Several years later, while studying vasodilation in response to acetylcholine, Robert Furchgott observed that, in the absence of the endothelial lining, the smooth muscle cells of vessels were *un*able to relax in response to acetylcholine (8). He postulated that some substance produced by the endothelium was required for the relaxation of vessels, setting off an intense search to identify this substance, known then as endothelium-derived relaxing factor (EDRF). This designation remained for the rest of the decade.

V. In 1987, nearly a decade after the elucidation of NO's role in nitrate-induced vasodilation, Moncada and Ignarro discovered independently that NO is in fact the mystery EDRF that had long been sought after by researchers (9, 10). To honor their pioneering work "concerning nitric oxide as a signaling molecule in the cardiovascular system," the 1998 Nobel Prize in Physiology of Medicine was awarded to Furchgott, Ignarro, and Murad (11). The discovery of marked a major advancement in the history of physiology. Endothelial-cell-derived NO's critical role in vasodilation became the focus for NO-donating compounds in glaucoma management.

VI. A new focus for the management of glaucoma has become the trabecular meshwork. The hypothesis is that impaired aqueous drainage is the initiation of the cascade of glaucomatous damage. It is thought that this then *results* in increased intraocular pressure. While this hypothesis appears contrary to much of the conventional concept of glaucoma, the primary risk factor for glaucoma remains elevated IOP. In fact, the only means to minimize glaucomatous damage is to reduce that primary risk factor. The 2015 version of the American Academy of Ophthalmology's Preferred Practice Pattern does not even include elevated IOP as part of the definition. (12). This leads to newer thinking suggesting that there may be some *non-IOP related insult* that occurs to raise IOP. This is what has pinpointed

the trabecular meshwork as that potential site and has brought about the development of latanoprostene bunod.

VII. Development of the specific molecule included clinical trials that resulted in FDA-approval in the USA. The mechanism of action of latanoprost is enhancing uveoscleral outflow (13). Addition of a NO moiety is thought to bolster IOP reduction by two means. First, enlarging pores of the trabecular meshwork as well as activity at the endothelial-cell level of the trabecular vasculature to enhance blood flow (2, 14). These combined actions are thought to be responsible for enhanced IOP-lowering compared to latanoprost alone (15).

VIII. The side-effect profile of latanoprostene bunod is similar to that of the latanoprost formulation alone. These include predominantly reversible eyelash growth and largely permanent increased iris and periocular pigmentation (2). The adverse events reported from the initial clinical trials are also familiar, conjunctival hyperemia, eye irritation and pain and pain at the instillation site (2, 16, 17). These occurred at rates greater than 2% but all were observed to occur in fewer than 10% of patients enrolled in the clinical trials.

IX. Non-IOP related factors continue to emerge as components of the glaucoma risk spectrum. Looking to the future, we may find ourselves investigating blood flow to the optic nerve, inner retina and perhaps even the trabecular meshwork. These directions may also include the larger sphere of systemic blood flow as well as such extrinsic factors such as cerebrospinal fluid pressure (18). We have known that systemic absorption of topically applied medications has systemic implications. Specifically the Beta-blockers slow heart rate and have the potential for significant adverse pulmonary effects (19-22). So we should exercise caution in those

scenarios and recognize that these effects can be identified and minimized (23,24). Newer compounds such as latanoprostene bunod may offer alternatives.

X. The prevalence of glaucoma continues to be underestimated. In fact, a greater proportion of high-risk patients may be overlooked than previously thought (25). As optometrists on the front line of primary eyecare, we can work together to lessen the vision- and sight-threatening burden of glaucoma. Now we will have new weapons in that fight.

XI. Case examples for the use of a NO-donating topical medication to lower IOP

A. As an initial treatment strategy

B. The role when advancing therapy

C. Positioning the molecule for the future – advantages and disadvantages

References.

1. https://www.aao.org/preferred-practice-pattern/primary-open-angle-glaucoma-ppp-2015. Accessed February 10, 2018

2. http://www.vyzulta.com/hcp/ (accessed December 9, 2017)

3. Culotta E, Koshland DE Jr. NO news is good news. Science. 1992;258(5090):1862-5.

4. Steinhorn BS, Loscalzo J, Michel T. Nitroglycerin and Nitric Oxide--A Rondo of Themes in Cardiovascular Therapeutics. N Engl J Med. 2015;373(3):277-80.

5. Murrell W. Nitro-glycerine as a remedy for angina pectoris. Lancet. 1879;80-81:113-5; 151-2; 225-7. http://www.thelancet.com/journals/lancet/issue/vol113no2890/PIIS0140-6736(00)X8912-X]

6. Arnold WP, Mittal CK, Katsuki S, Murad F. Nitric oxide activates guanylate cyclase and increases guanosine 3':5'-cyclic monophosphate levels in various tissue preparations. Proc Natl Acad Sci USA. 1977;74(8):3203-7.

7. Katsuki S, Arnold W, Mittal C, Murad F. Stimulation of guanylate cyclase by sodium nitroprusside, nitroglycerin and nitric oxide in various tissue preparations and comparison to the effects of sodium azide and hydroxylamine. J Cyclic Nucleotide Res. 1977;3(1):23-35.

8. Furchgott RF, Zarwadski JV. The obligatory role of endothelial cells in the relaxation of arterial smooth muscle to acetylcholine. Nature. 1980;288:373-6.

9. Palmer RM, Ferrige AG, Moncada S. Nitric oxide release accounts for the biological activity of endothelium-derived relaxing factor. Nature. 1987;327(6122):524-6.

10. Ignarro LJ, Byrns RE, Buga GM, Wood KS. Endothelium-derived relaxing factor from pulmonary artery and vein possesses pharmacologic and chemical properties identical to those of nitric oxide radical. Circ Res. 1987;61(6):866-79.

11 The Nobel Prize in Physiology or Medicine 1998. https://www.nobelprize.org/nobel_prizes/medicine/laureates/1998/ Accessed December 15, 2017.

12. https://www.aao.org/preferred-practice-pattern/primary-open-angle-glaucoma-ppp-2015

13. Digiuni M, Fogagnolo P, Rossetti L. A review of the use of latanoprost for glaucoma since its launch. Expert Opin Pharmacother. 2012 Apr;13(5):723-45. doi: 10.1517/14656566.2012.662219.

14. Semes, L. Nitric oxide: Historic perspective and recent developments. In, Tsai JC, Gray MJ, Cavallerano AC, Nitric Oxide in glaucoma: What clinicians need to know. Candeo Clinical/Science Communications. White Plains, NY. 2017.

15. Weinreb RN, Ong T, Scassellati SB, 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.

16. Weinreb RN, Sforzolini BS, Vittitow J, Liebmann J. Latanoprostene bunod 0.024% versus timolol maleate 0.5% in subjects with open-angle glaucoma or ocular hypertension: the APOLLO study. Ophthalmology. 2016;123(5):965-973.

17. Medeiros FA, Martin KR, Peace J, Sforzolini BS, 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. Am J Ophthalmol. 2016;168:250-259.

18. http://ophthalmologytimes.modernmedicine.com/ophthalmologytimes/news/ocular-perfusion-pressure-cerebrospinal-fluid-pressure-new-players-glaucoma. Accessed December 10, 2017.

19. Nieminen T, Lehtimäki T, Mäenpää J, Ropo A, Uusitalo H, Kähönen M. Ophthalmic timolol: plasma concentration and systemic cardiopulmonary effects. Scand J Clin Lab Invest. 2007;67(2):237-45.

20. Uusitalo H, Niño J, Tahvanainen K, et. al. Efficacy and systemic side-effects of topical 0.5% timolol aqueous solution and 0.1% timolol hydrogel. Acta Ophthalmol Scand. 2005 Dec;83(6):723-

21. Gandolfi SA, Chetta A, Cimino L, Mora P, Sangermani C, Tardini MG. Bronchial reactivity in healthy individuals undergoing long-term topical treatment with beta-blockers.
Arch Ophthalmol. 2005 Jan;123(1):35-8.

22. Inan UU, Ermis SS, Orman A, et. al. The comparative cardiovascular, pulmonary, ocular blood flow, and ocular hypotensive effects of topical travoprost, bimatoprost, brimonidine, and betaxolol. J Ocul Pharmacol Ther. 2004 Aug;20(4):293-310.

23. Snape JP, Waldock A. Spirometry for patients prescribed topical beta-blockers. Nurs Stand. 2000 Oct 11-17;15(4):35-8.

24. Hepsen IF, Yildirim Z, Yilmaz H, Kotuk M. Preventive effect of lacrimal occlusion on topical timolol-induced bronchoconstriction in asthmatics. Clin Exp Ophthalmol. 2004 Dec;32(6):597-602.

25. Waisbourd M, Pruzan NL, Johnson D, et al. The Philadelphia Glaucoma Detection and Treatment Project: Detection Rates and Initial Management. Ophthalmology. 2016 Aug;123(8):1667-74. doi: 10.1016/j.ophtha.2016.04.031.