It has been several years since we have welcomed a novel molecule and pathway to our armamentarium of medical treatments for glaucoma. Although our current therapies can be very effective, we are always looking for a few extra millimeters of mercury of IOP lowering in our most challenging cases. Are we clinicians ready to embark on the use of the next generation of medications?

The initial discovery of nitric oxide (NO) as a signaling mediator involved the cardiovascular system. NO is generated endogenously from L-arginine by a family of enzymes (nitric oxide synthase [NOS]) and activates the second messenger cyclic guanidine monophosphate (cGMP), which is involved in several homeostatic processes of the eye. Initial studies indicated that the inducible isoform of nitric-oxide synthase (iNOS, NOS-2) is present in astrocytes of optic nerve heads from glaucomatous eyes of humans and is increased in the trabecular meshwork (TM) with elevated perfusion pressure in vitro.

**ROLE OF NO**

The role of NO in IOP control has been studied in human patients and animal models. In the healthy eye, the aqueous humor outflow pathway and ciliary muscle are sites of endothelial NOS (eNOS) activity, which is decreased in the TM, Schlemm canal, and ciliary muscle in glaucomatous eyes. In addition, lower levels of end products of both NO and cGMP have been found in the aqueous humor.

Further investigation of NO donors (eg, nitroglycerin, sodium nitroprusside) has revealed IOP lowering in several animal models as well as in humans. NO induction increases outflow facility in nonhuman primates, with additional cellular targets in the TM and Schlemm canal; the process alters the cytoskeletal network and cell adhesion system of the cells of the conventional outflow pathway. This leads to relaxation of the TM and the inner wall of Schlemm canal. Downstream cellular effects, including Rho-kinase inhibition, are also triggered. Relaxation of the longitudinal ciliary muscle alters the uveoscleral (unconventional) pathway. There may also be effects on the regulation of episcleral blood flow, thus lowering episcleral venous pressure.

The potential neuroprotective effects of NO are not well understood. In the DBA/2J mouse glaucoma model, neuronal NOS was elevated in the retina, and an NOS inhibitor prevented apoptosis. Neufeld et al showed that NOS-2 inhibition had a neuroprotective effect on retinal ganglion cells in a glaucoma rat model. Because NO may have neurodegenerative or neuroprotective properties, depending on the dosage, selected inhibition or enhancement of NO synthesis in various parts of the eye may be used for future glaucoma therapy. Caution is warranted, because the manipulation of NO homeostasis may have deleterious effects on vascular autoregulation.

**LATANOPROSTENE Bunod**

Latanoprostene bunod (LBN; Bausch + Lomb and NicOx) is an NO-donating prostanoid FP receptor agonist that is metabolized by esterases to three byproducts: (1) latanoprost acid, the active metabolite of latanoprost, (2) a prostaglandin
F2-α agonist (Xalatan; Pfizer), and (3) butanediol mononitrate, an NO-donating moiety that is further metabolized to 1,4-butanediol and NO. In vitro studies of human TM cells treated with LBN induced dose-dependent increases in cGMP and relaxation of endothelin-1 mediated contraction. Latanoprost had no effect on these changes (Figure).

PHASE 1 TRIAL

The aforementioned preclinical findings led to a phase 1 proof-of-principle trial (KRONUS) in Japan that confirmed LBN’s preliminary safety and tolerability.

PHASE 2 TRIALS

Subsequent phase 2 randomized, controlled studies of 1-month treatment duration included VOYAGER, which compared LBN to latanoprost, and CONSTELLATION, which compared LBN to timolol.

- VOYAGER, a multicenter, investigator-masked study, revealed a dose-dependent IOP lowering (maximal with 0.024% dose) that was greater than achieved with latanoprost treatment.
- In CONSTELLATION, a single-center, open-label crossover study, both LBN and timolol decreased IOP. LBN produced a greater mean reduction in nighttime IOP, however, and improved diurnal ocular perfusion pressure compared with both baseline and timolol.

PHASE 3 TRIALS

Two phase 3 randomized, multicenter, double-masked, parallel-group, noninferiority trials have been completed to date. The APOLLO study, which included centers in Europe and North America, randomized 417 patients with open-angle glaucoma (OAG) or ocular hypertension (OHT) who had a baseline IOP higher than 25 mm Hg but lower than 36 mm Hg in a 2:1 fashion to treatment with LBN 0.024% once daily in the evening or timolol 0.5% twice daily for 3 months, followed by treatment with LBN (open label). IOP was measured at 8:00 AM, 12:00 PM, and 4:00 PM at baseline, weeks 2 and 6, and months 3, 6, 9, and 12. Mean IOP with LBN was significantly lower compared with timolol at all time points, a finding maintained during the open-label phase and confirmed in the crossover group from timolol to LBN.

The LUNAR study included 414 patients with OAG or OHT with the same IOP entry criteria. Patients were randomized 2:1 to treatment with LBN 0.024% once daily in the evening or timolol 0.5% twice daily for 3 months, followed by 3 months of open-label treatment with LBN 0.024%. IOP was measured at 8:00 AM, 12:00 PM, and 4:00 PM at baseline, weeks 2 and 6, and months 3 and 6. Mean IOP with LBN was significantly lower compared with timolol at all time points except the 8:00 AM week-2 time point. IOP lowering was maintained during the open-label treatment and confirmed in the crossover group.
JUPITER was performed in Japan as a single-arm, open-label study in 130 subjects with OAG or OHT who had a baseline IOP higher than 14 mm Hg that was significantly lower compared to the other studies. All subjects used LBN 0.024% once daily for 12 months. IOP was measured at 10 AM every 4 weeks. By week 4, IOP had decreased by 22%, and this effect persisted for 1 year.

SAFETY AND TOLERABILITY

Adverse events in all of the clinical trials discussed herein were mild and transient. The most common ocular events were eye irritation/discomfort, conjunctival hyperemia, and eyelash growth. These findings were similar to those in the latanoprost group.

FUTURE THERAPY

Valeant Pharmaceuticals first submitted a new drug application for LBN to the FDA in July 2015. On August 8, in a complete response letter to Valeant, the FDA did not approve the new drug application for LBN ophthalmic solution, 0.024% (Vesneo), citing Current Good Manufacturing Practice issues for the new drug application for LBN ophthalmic solution, 0.024%

This drug has a novel dual mechanism of action—a prostaglandin backbone (increasing uveoscleral outflow) and an NO-donating moiety that relaxes TM and Schlemm canal (improving conventional outflow). It shows great promise for glaucoma treatment.

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