

Rho Kinase Inhibitors – A Potential New Class of Glaucoma Drugs

Recent ocular perfusion studies with drugs that inhibit the Rho-associated kinase (ROCK) pathway in animal models have shown enhanced drainage of aqueous humor through the trabecular meshwork (TM), which has led to exploration and development of a promising new class of drugs for treatment of ocular hypertension (OHT) and primary open-angle glaucoma (POAG): Rho-Kinase Inhibitors (RKIs).

RKIs work at the cellular level by inhibiting the ROCK signaling pathway. The ROCK signaling pathway promotes cell contractility and adhesion of fibroblast cells (e.g., juxtacanalicular (JCT) cells). Simply put, RKIs induce structural changes to the cytoskeletal framework of fibroblast cells that make them more flexible. Although the exact mechanism is unknown, studies suggest RKIs lower intraocular pressure (IOP) by inducing cellular relaxation and disrupting focal adhesions in the TM and the inner wall endothelial lining of Schlemm's canal.

The IOP-lowering effects of topical RKIs have been documented in a

number of human studies. Topical administration of RKI AR-12286 with a BID dosage of 0.25% has been shown to decrease IOP by 28%, with the only adverse side effect of note being trace to moderate conjunctival hyperemia that lasted less than four hours. Another study combined 0.25% AR-12286 and 0.5% Travoprost and showed an ocular hypotensive effect that was clinically and statistically greater than Travoprost alone, which suggests that a combination therapy of RKI/prostaglandin analog may be a highly effective ocular hypotensive treatment. However, this may not be the case with other combinations of RKIs and ocular hypotensive drugs. In one study, RKI Y-27632 reduced intraocular penetration of Timolol maleate that presumably was due to increased systemic elimination through the conjunctival vasculature. RKIs are potent vasodilators and, when administered topically to the eye, have been shown to induce conjunctival hyperemia, which may decrease the effect of concomitantly administered topical drugs by rapidly increasing extraocular clearance from the ocular cavity to the systemic circulation. Therefore, a multi-drug regimen of RKIs and other ocular

hypotensive drugs may require the clinician and the patient to be mindful of the order and timing of RKI administration.

In addition to lowering IOP, RKIs may have other benefits for the eye that include: protection of TM cells from oxidative stress, improved blood flow to the optic nerve, facilitation of corneal endothelial wound healing, protection of retinal ganglion cells, and decrease subconjunctival fibrosis following glaucoma filtration surgery.

Although RKIs are not yet commercially available, RKIs in early clinical trials appear to be safe and highly effective in lowering IOP, and may even provide neuroprotection to retinal ganglion cells at increased risk in patients with OHT and POAG. RKIs to be on the lookout for are Y-27632, AR-12286, ATS907, ATS8535, AR-13324 and AMA0076.

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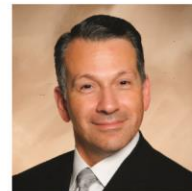
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