Rhokinase Inhibitors novel Potential Treatment Modality for Glaucoma

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Abstract

Rhokinase inhibitors is a new class of drug under trial that improve the outflow facility through conventional path way by inhibiting the contractile tone of actin cytoskeleton. They additionally protect trabecular meshwork from oxidative stress, improve Optic Nerve head blood flow, facilitate corneal endothelium wound healing, increase ganglion cell survival and reduce scarring in glaucoma surgery.

Keywords: glaucoma, rhokinase, ROCK, trabecular meshwork

Glaucoma is the second leading cause of irreversible and potentially preventable blindness worldwide with an estimated 60.5 million sufferers. It is a group of conditions causing chronic progressive optic neuropathy with characteristic visual field loss and is usually associated with elevated IOP. Raised pressure is the only modifiable risk factor which has been targeted by pharmacological and surgical measures to manage the disease. There is considerable work in progress with regard to developing alternative treatment modalities like neuroprotection and newer drugs and delivery systems. Medical management works by decreasing aqueous production or increasing outflow but so far there has been a lacunae in dealing with the actual pathology; the resistance to outflow by the conventional pathway. The primary site responsible for 75% of the resistance to outflow is believed to be the juxtanacanicular region and Schlemm canal’s inner wall that modulate cellular contractility and tension. Rhokinase is a serine/threonine kinase whose activity increases actomyosin contraction in smooth muscle cells, including the smooth muscle-like cells of the TM. On activation by binding to GTP (guanosine triphosphate), Rho activates it’s effector molecules ROCK (rhokinase) which polymerize actin fibers inducing vasoconstriction and decrease cell migration. ROCK inhibitors depolymerize filamentous actin leading to enhanced TM outflow presumably by wider empty spaces in the juxtacanicular region and increased vacuoles in endothelial cells.

Additional Benefits to Ocular Tissues

1. Protect trabecular meshwork cells from oxidative stress: Cell culture studies have shown that human TM cells treated with RKI Y-27632 exhibit reduced expression of IL-6 and IL-8 mRNA after oxidative stress, which suggests that ROCK inhibitors may have a protective effect on human TM cells.

2. Improve blood flow to the optic nerve: Fasudil is used in many countries for the treatment of acute and/or chronic cerebral ischemic stroke and vasospasm as it induces vasodilatation and improves cerebral circulation. Vasospasm and altered haemodynamics are known to be relevant in glaucoma pathogenesis especially normal tension glaucoma. Systemic and topical instillation of fasudil improved impaired optic nerve head perfusion in studies indicating role of rhokinase inhibitors in addressing this presumed pathogenic factor in certain types of glaucoma.

3. Facilitate corneal endothelium wound healing: RKI Y-27632 has been shown to increase corneal endothelial cell density and restore function in animals with partially injured cornea, suggesting a role for rhokinase inhibitors as a potential therapeutic treatment for certain forms of corneal endothelial cell dysfunction in humans.

4. Increases ganglion cell survival: Rhokinase inhibitor Fasudil has been shown to protect retinal ganglion cells from the neurotoxic effects of N-methyl-d-aspartate (NMDA) in rats. Glutamate and NMDA have been implicated in retinal ischemia and optic neuropathy and thus Rhokinase
inhibitors have a potential neuroprotective benefit.25,26

5. Reduce bleb scarring in glaucoma surgery: Topical RKI Y-27632 has been shown to decrease subconjunctival scarring after filtration surgery in rabbits.27 This indicates a future role of ROCK inhibitors as wound modulators in glaucoma surgery.

Potential Drawbacks

1. Considering their mechanism of action, they are likely to benefit those glaucomas where the primary site of damage is the trabecular meshwork i.e primary open angle glaucoma, pseudo exfoliation glaucoma, pigmented and juvenile glaucoma. They may not be effective in angle closure glaucoma.

2. They are potent vasodilators and when used topically cause hyperemia, albeit temporary and in some cases subconjunctival hemorrhages.28

3. The vasodilatation also causes greater systemic absorption of concomitantly administered drugs and consequently decrease their ocular potency and increase chances of their systemic side effects. For example, RKI Y-27632 reduced intraocular penetration of timolol maleate that presumably was due to increased systemic elimination through the conjunctival vasculature.29

4. In higher doses, these ROCK inhibitors can also affect other protein kinases although in published clinical trials on using ROCK inhibitors for glaucoma treatment, few clinically significant side-effects have been reported.30

5. Vasodilatation can also presumably worsen uveitis, although not yet reported in clinical trials.

Rhokinase Inhibitors In The Pipeline

The most exciting thing about this therapeutic class is that it is already being evaluated in human trials. At least two companies have ROCK inhibitors in clinical trials: Amakem Therapeutics and Aerie Pharmaceuticals.

Ripasudil (K511)

Ripasudil is currently used as a second line drug in the medical management of glaucoma in Japan (approved for use as adjust to prostaglandin) as a recommended twice daily drop in dosage 0.4%.31 A prospective 52 week study of glaucoma patients (POAG, ocular hypertensives and pseudoexfoliation glaucoma) showed an IOP lowering of -2.6 and -3.7mmHg at trough and peak as monotherapy. It was also shown to be effective in combination therapy. The most frequent side effect was conjunctival hyperemia (74%), blepharitis (20.6%) and allergic conjunctivitis (17.2%). The conjunctival hyperemia was mild (97%), transient and showed spontaneous resolution (78%).32,33

Rhopressa (AR13324)

Rhopressa is a triple action drug

(i) It increases aqueous outflow by means of ROCK inhibition
(ii) It decreases aqueous production by norepinehrin transporter inhibition and
(iii) It has been demonstrated in a preclinical study to decrease episcleral venous pressure, an important component of IOP, particularly at low pressures. Phase IIb trial (June 2013) demonstrated that AR13324 successfully brought down IOP by 5.7-6.2mmHg by once daily application in patients with elevated IOP (approximately 1mmHg lower than latanoprost). However this difference was not statistically significant in the subgroup with baseline IOPs less than 26.34 Clinical results suggest that Rhopressa produces consistent IOP-lowering activity regardless of baseline pressure unlike the available categories of anti glaucoma medication which are more effective in higher IOP ranges.

Rocket 1 (phase 3 trial) studied pateints with IOP range 20-27mmHg and proved non inferiority to timolol in subjects with baseline IOP less than 27 although it did not meet it’s primary endpoint of non inferiority to timolol 0.5% dosed BD. Rocket 2 phase 3 trial studied efficacy in IOP range 20-25mmHg and showed non inferiority to timolol at all time points evaluated. Aerie expects to file Rhopressa for U.S. regulatory approval in mid-2016.

Rocklatan

Aerie Pharmaceuticals have worked out a fixed combination of Rhopressa and Latanoprost (Rocklatan/ PG32) dosed once a day with quadruple action attacking the IOP on all fronts. Rocket 1 (a phase 2 clinical trial on 300 patients) demonstrated a decrease in IOP by 34% which was an average 2mmHg greater than that achieved by latanoprost alone.35

AMA0076 (AMAKEM)

Amakem reports that AMA0076 produced an mean IOP drop of 3.7mmHg with little and transient hyperemia although the results are not yet published. The unique quality of AMA0076 versus the other under trial Rhokinase inhibitors is that the drug outside the aqueous quickly gets converted into an inactive form thereby potentially reducing off target activity and adverse effects like hyperemia.36

Conclusion

It has been two decades since the launch of prostaglandin analogs had revolutionized the medical management of glaucoma. With the upcoming Rhokinase inhibitors with their novel mechanism of action, we may be at yet another historical milestone. ROCK/ NET have multiple beneficial ocular effects and have been reported to offer at least four distinct applications relevant to glaucoma management, including significant IOP-lowering effects, improvement in ocular blood flow, inhibition of postoperative scaring, and promotion of retinal ganglion cell survival and axon regeneration. Although clinical trials at present show modest IOP lowering, there is hope that a new class of glaucoma medication will be born.
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