News

Rho-Associated Kinase Inhibitors: Potential Future Treatments for Glaucoma

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Glaucoma is the second-leading cause of vision loss in the world: the so-called "silent thief of vision" is globally the most common cause of preventable, irreversible blindness. It is estimated that the disease affects more than 60 million people worldwide, and this number is projected to increase to about 80 million by 2020.[1] Moreover, it is proposed that nearly 8.4 million people are bilaterally blind due to glaucoma and this number will be increased to 11.1 million by 2020.

To date, although intraocular pressure (IOP) is no longer an essential element for the diagnosis of glaucoma, it is regarded as the mere modifiable risk factor for the disease. The clinical management of patients suffering from various types of glaucoma has historically focused on reduction and tight control of elevated IOP through different pharmacological and surgical interventions.[2-6]

In open angle glaucoma, tissues of the conventional outflow pathway are diseased and are the underlying cause of elevated IOP. It is hypothesized that the cells in this pathway could not appropriately change their shape to decrease resistance to aqueous outflow and compensate the pathologically increased resistance.[7-10] Greater amounts of endogenous contractility mediators, such as endothelin-1 and transforming growth factor-beta 2, in the glaucomatous eye could be a contributing factor.[8,11-15]

Considering these pathophysiological aspects of open angle glaucoma, medical and surgical treatments that specifically target and treat the diseased tissues of the conventional outflow pathway have long been aimed for its management.[16] Several surgical procedures, including laser trabeculoplasty,[17] canaloplasty,[18,19] iStent microshunt (Glaukos Corporation, Laguna Hills, CA, USA) implantation,[20,21] Trabectome (Neomedix Inc., Tustin, CA, USA) assisted ab-interno trabeculotomy,[22] and excimer laser trabeculostomy (AIDA Excimer Laser System; TuiLaser AG, Germering, Germany)[23] have been introduced in recent years to directly alleviate the increased resistance in conventional outflow pathway. However, drugs that specifically treat the diseased trabecular meshwork (TM)/Schlemm canal complex have not yet been marketed. Indeed, during the past decades and since the introduction of prostaglandin analogs in 1996, little progress has been made in medical management of glaucoma, and no new class of drugs has been introduced. None of the currently available antiglaucoma drugs, directly targets the conventional outflow pathway [Table 1]. In recent years, new horizons emerged with the introduction of Rho-associated kinase (ROCK) inhibitors as a potential class of ocular hypotensive drugs.

The Rho family includes a series of small G-proteins, including Rho (RhoA, RhoB, RhoC), Rac, and CDC42. Rho molecules when bounded to guanosine triphosphate, activate its effector molecules (ROCK-1 and ROCK-2). Activated ROCK, in turn, stimulates a series of downstream molecules, which finally translate into actin stress fiber polymerization, focal adhesion formation and calcium-independent smooth muscle contraction.[24] Moreover, ROCK-signaling system is involved in regulation of cellular growth, migration and life cycle through control of muscle cell contractility

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Table 1. Main classes of antiglaucoma medications in clinical use

Drug class	Main drug	Mechanism of action	Year of introduction
Parasympathomimetcs	Pilocarpine	↑Conventional outflow; indirect	1875
Alpha-agonists	Brimonidine	↓Production; ↑uveoscleral outflow	1900
Carbonic anhydrase inhibitors	Dorzolamide	↓Production	1954
Beta-blockers	Timolol	↓Production	1967
Prostaglandins	Latanoprost	↑Uveoscleral outflow	1996

and the nonmuscle cellular actin cytoskeleton.[25-28] Impairment in ROCK pathway and resultant impaired cell contractility could contribute to disease in different organs, including cardiovascular, respiratory and renal systems.[24] Hence, ROCK inhibitors are potential therapeutic agents for hypertension,[29,30] ischemic heart disease,[31,32] chronic obstructive pulmonary disease,[33] asthma,[34,35] erectile dysfunction,[36,37] diabetic renal failure,[36] chronic nephritis and glaucoma.

Considering glaucoma, ROCK inhibitors have favorable roles in glaucoma management, owing to their reducing effect on IOP as well as some neuroprotective and antiscarring effects.[24] ROCK inhibitors, similar to some other cytoskeletal drugs, could increase matrix metalloproteinase expression in TM cells and may induce extracellular matrix reorganization and widening of empty spaces in the TM.[38] Moreover, the ROCK inhibitors could weaken cell attachment to its extracellular matrix, which results in relaxation of the whole of TM tissue and hence, wider empty spaces.[24] It is also probable that ROCK inhibitors enhance outflow through unknown mechanisms by inducing some "washout effects" in the human TM. It seems that the effect of ROCK inhibitors on TM cells is through a calcium-independent pathway, which is not prominent in ciliary muscle cells.[24]

Rho-associated kinase inhibitors relax smooth muscle tone in brain vasculature and could potentially increase optic nerve head perfusion. Thus, ROCK inhibitors could have neuroprotective effects on ganglion cells.[39] Moreover, in animal models, ROCK inhibitors decrease fibrosis following trabeculectomy and could have similar preventive effect in TM and optic nerve (ON) and decrease fibrosis and stiffening.[40,41]

There are some limitations for using ROCK inhibitors in clinical practice. First, these drugs would be effective in trabecular glaucomas; in other words, in those glaucomatous cases where TM is the main site of pathology, including primary open angle glaucoma (POAG), pseudoexfoliative glaucoma, pigmentary glaucoma and juvenile glaucoma. Considering their mode of action, it is unlikely that these drugs are effective in angle closure glaucoma. In addition, despite their beneficial effects, ROCK inhibitors are not ROCK specific in higher concentrations and can modulate other protein kinase activity[29] resulting in unwanted side-effects. However, in published clinical trials on using ROCK inhibitors for glaucoma treatment, few clinically significant side-effects have been reported.

Most interestingly, smooth muscle cells in conjunctival, episcleral and iris blood vessels are responsible for maintenance of vascular tone; ROCK inhibitors can dilate such vessels and result in some side-effects. The most common side-effect is conjunctival hyperemia and vasodilation[42,43] which is important from a cosmetic standpoint and could reduce patient compliance. In addition, conjunctival hyperemia could reduce bioavailability of other drops.[44] It seems rational to use the ROCK inhibitors after other hypotensive drops. Another possible sequel is iris vasodilation and aggravation of uveitis; however, this was not observed in clinical trials. Conjunctival punctate hemorrhage was reported in animal studies with ROCK inhibitors; but, similar finding has not been observed in the human trial of ROCK inhibitors for the management of glaucoma.[45] Finally, it is noteworthy that knockout mice with ROCK deficiency breed generations with eyelid developmental defect (open eye birth) and insufficient ventral body closure (omphalocele).[46]

Initially, there were some concerns on endothelial safety of ROCK inhibitors;[16] however, there is evidence that ROCK inhibitors could improve corneal endothelial cell adhesion and wound healing.[47,48] Hence, these drugs may be not only safe for patients with compromised corneal endothelial cell function, but also a potential therapeutic agent for conditions such as Fuch's endothelial dystrophy and corneal edema.[16] There is evidence that ROCK inhibitors can convert corneal endothelial cells into a phenotype capable of regenerating endothelial cells.[47,49,50]

First reports on the effect of Rho-kinase inhibitor on IOP were published in early 2001.[51-53] Since then, various ROCK inhibitors, including Y-27632, Y-39983, H-1152P, AR-12286, AMA0076, HA-1077 (fasudil), and K-115, have been used in several human and animal eye studies.[43,45,50,52-64] Among these, K-115 passed phase 1 and phase 2 clinical trials and had favorable results.[63,64] In a recent phase 2 clinical trial on the effect of K-115 in POAG and ocular hypertensive patients, Tanihara et al have reported a 20% IOP reduction on average with twice daily instillation of K-115 0.4%.[63]

In future, more specific ROCK inhibitors targeting explicitly the TM, corneal endothelium, or optic nerve are expected to be introduced, which would increase drug

efficacy and reduce potential side-effects. Moreover, until now, the ROCK inhibitors used in clinical trials were used at least twice daily; however, intensive efforts are underway to produce once-daily dosing of these medications to improve patient adherence and compliance. An interesting alternative is direct genetic modulation of ROCK-signaling pathway, which is a potential novel target for glaucoma gene therapy.[24]

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