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Rho-kinase Inhibitor: A Potential Alternative to Current Glaucoma Therapy

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ABSTRACT

Glaucoma is a group of progressive and irreversible optic neuropathies linked to intraocular pressure-related damage of the optic head. It is the second leading cause of blindness with estimation of 76 million people affected. Among many types of glaucoma, Primary Open-Angle Glaucoma (POAG) is the most common. Management of POAG primarily focus on lowering IOP with a variety of topical, oral, intravenous therapy, and surgery. Prostaglandin Analogue and Beta-blocker have long been the first line therapy for POAG with proven efficacy and safety profile. Rho-kinase Inhibitor is a novel class of drug with IOP lowering property through its ability to increase aqueous humor drainage via trabecular meshwork. Rho-kinase Inhibitor is proven to have mild local adverse effects and rare systemic drug reaction. This might be beneficial for patients with contraindication to Prostaglandin Analogue and/ or Beta-blocker use.

Keywords: glaucoma, rho-kinase inhibitor

INTRODUCTION

Glaucoma is a group of optic neuropathies linked to intraocular pressure (IOP)- related damage of the optic nerve head, subsequently leading to ganglion cell axon loss.[1] Glaucoma is the second leading cause of blindness after cataract with an estimation of 76 million people affected.[2] It is progressive and irreversible which possess major public health concern.[3] There are two main types of Glaucoma; primary and secondary; and are further classified into two major subtypes of open-angle and angle-closure according to the pathophysiology.[3]

Primary Open-Angle Glaucoma (POAG) is the most common type of glaucoma with global prevalence of 2.2%.[3] Risk factors include increased IOP, older age, race (more prevalent in African-Caribbean descent), myopia, thinner central cornea (which suggests less rigid support around optic nerve head thus increase susceptibility to Optic Nerve Head/ ONH damage), first-degree family history, diabetes mellitus, and hypertension.[1]

Both IOP-dependent and independent mechanisms have been proposed as cause for ONH damage in POAG. Structural changes such as Trabecular Meshwork/ TM obstruction by foreign material, trabecular endothelial cell loss, loss of trabecular phagocytic activity, loss of giant vacuoles from Schlemm's canal endothelium, and reduced pore size and density of Schlemm's canal wall may precipitate IOP elevation, inducing mechanical changes at lamina cribosa and/ or vascular dysfunction leading to ischemia of ONH.[1,4] On the other hand, reduced ocular perfusion pressure, excitotoxic damage from excessive glutamate, autoimmune-mediated nerve damage, loss of neurotrophic factors, failure of cellular repair mechanisms, abnormal autoregulation of retinal and choroidal vasculature are some of possible

mechanisms for ONH damage which is IOP-independent.[1]

Diagnosis of POAG includes assessment of IOP using tonometer, examination of anterior chamber angle showing normal/ open irido-corneal angle, sign of optic disc damage such as high cup/ disc ratio (C/ D), C/ D asymmetry, vertical elongation of cup, neuro-retinal rim thinning/ notching, vessel bayoneting, peripapillary atrophy, and disc haemorrhage, visual field examination findings characterized by defect in horizontal meridian, nasal step, and arcuate scotoma.[1] Most patient with symptomatic POAG are in late-stage disease, in which significant constricted visual field and blurred vision already occurred.[4]

Managements of POAG are mainly focused on lowering the IOP.[5] American Academy of Ophthalmology recommends reduction of IOP for at least 20-30% as reasonable initial goal and more aggressive lowering IOP goal for patient with advanced condition. Advanced Glaucoma Intervention Study/ AGIS demonstrate reduction in disease progression in patient with consistent IOP below 18 mmHg. Multiple approach in therapy as ways to reduce IOP; medical (topical and systemic), laser therapy, and surgical procedures.[1,5]

First line therapies usually involve using topical IOP reducing agent such as prostaglandins analogue, beta blocker, alpha agonist, carbonic anhydrase inhibitor, and miotics[5]. Prostaglandins Analogues (PA) and Beta-blockers (BB) are typical first line therapies for POAG.[1]

Prostaglandin F2-alpha Analogue

Prostaglandin F2-alpha analogue such as Latanoprost reduces IOP by inducing ciliary smooth muscle relaxation and increases matrix metalloproteinases, through remodeling of extracellular matrix of uveoscleral pathway.[6] PA is the most effective single topical agent for lowering IOP, capable of lowering the IOP by greater than 30% from baseline, achieving greater effect in IOP >24 mmHg with an average of 30-35%.[1,5,6] Latanoprost is administered once daily at night and may be used with other antiglaucoma agents to further reduce IOP. Some of side effects such as conjunctival hyperemia, hypertrichosis, pigmentation in iris, eyelid, lashes, and periorbital tissue; intraocular inflammation, macular oedema aggravation, reactivation of herpetic keratitis, and superficial punctate keratopathy may happen while using PA.[6]

Beta-blocker

Beta blockers are another IOP lowering agent that works by activating beta-adrenergic receptor on nonpigmented ciliary epithelium and blood vessel, limiting active transport of aqueous humor (AH), thus reducing production of AH.[7] Timolol is the most common BB agent used in POAG. It is a nonselective beta-adrenergic blocker which inhibit both β1- and β2-adrenergic receptor. Although having fewer local side effects compared to Latanoprost, timolol shows more systemic side effects due to its non-selective beta-adrenergic blocking nature. It is contraindicated in patients with bronchial asthma, Chronic Obstructive Pulmonary Disease/ COPD, cardiovascular condition such as bradycardia, heart block, or syncope.[8] Selective beta-1 adrenergic blocker such as Betaxolol hypothetically have lower systemic cardiopulmonary side effect. However, studies show comparable cardiopulmonary effect of Betaxolol and Timolol with less IOP lowering effect of Betaxolol compared to Timolol.[9,10]

Rho-kinase Inhibitor

Rho-kinase inhibitor is a novel glaucoma drug which works by inhibiting Rho-kinase pathway. Rho-kinase (ROCK) are serine/ theorine kinase which work on smooth muscle contraction. There are 2 isoforms of ROCK, ROCK1 and ROCK2, located in chromosome 18 and 12 respectively. Both isoforms are expressed in majority of tissue in human body, including in TM. ROCK mediating actin cytoskeletal changes and inducing vasoconstriction by inhibiting myosin light chain phosphatase. These changes influence the contractile properties

of TM outflow tissue, demonstrated in loss of ROCK function causing micromechanical relaxation of cells and disassembly of stress fibers and focal adhesion complexes.[11]

Rho kinase inhibitor alter the cell morphology and interactions of TM, increasing AH drainage through TM tissue, thus lowering IOP.[11,12] Other effects such as increased ocular blood flow through vascular endothelial smooth muscle and prevention of ocular blood flow impairment by NO synthase inhibitor have been observed in animal studies.[13,14] Stress fibre-altering property of Rho-kinase inhibitor is shown to prevent postoperative scarring after glaucoma filtering surgery by limiting transformation of fibroblast to myofibroblast which is essential in wound healing process. Neuroprotective ability of Rho-kinase inhibitor is also demonstrated in several animal studies, showing increased neuron survival and axon regeneration improvement in ganglion cells of retina.[11]

Currently, Ripasudil and Netarsudil are the only Rho-kinase inhibitor approved as glaucoma therapy in Japan and US respectively. Aside from inhibiting Rho-kinase, Netarsudil has norepinephrine transport inhibitor property, decreasing reuptake of norepinephrine and causing vasoconstriction in ciliary process as a result of its effect on alpha-adrenergic receptor.[15] This results in reduced AH production, further lowering IOP.[11,12] Dose-dependent conjunctival hyperemia and non-dose dependent conjunctival hemorrhage were observed as adverse effects on both Ripasudil and Netarsudil. Some of the subjects also develop corneal verticillate and site pain while using Netarsudil. Both Ripasudil and Netarsudil have minimal systemic adverse effect and milder local adverse events compared with PA.[16,17]

Ripasudil vs Prostaglandin Analogue and/ or Beta-blocker

In a multicenter, prospective, randomized, open-label, 3 period, Latin-square crossover clinical study, IOP-lowering ability of 0.2% and -0.4% Ripasudil from 1 to 7 hour after instillation was observed, with optimal result found in 0.4% Ripasudil solution. Both 0.2% and 0.4% Ripasudil showed significant IOP- reduction compared to placebo.[18] Another phase 2 randomized clinical study have been conducted to determine optimal dosage for Ripasudil. 0.1%, 0.2%, 0.4% and placebo are tested in 210 patients with POAG or ocular hypertension after washout periods. Drugs were given twice daily for 8 weeks and IOP measured before instillation, 2 hours, and 8 hours after instillation. Optimal efficacy was found in Ripasudil 0.4% solution with dose dependent IOP lowering effect was statistically significant at all time points.[19]

There is no direct comparison between Ripasudil and other topical antiglaucoma drug to date, however there are several studies that observed the efficacy of Ripasudil as an additive therapy. In a study conducted by Tanihara et al. in 2015, two multicenter, randomized, double-masked, parallel group studies of Ripasudil-Timolol and Ripasudil-Latanoprost were established in 29 and 36 Japanese clinical centers, respectively. After a period of using Timolol or Latanoprost, 208 and 205 patients with IOP >18 mmHg were admitted in Ripasudil-Timolol and Ripasudil-Latanoprost groups in which placebo group was given to each division. IOP measurements were done before instillation at 9 a.m. (at through) and 11 a.m. (peak level) and analyzed in week 4, 5, and 8. Ripasudil-Timolol group showed statistically significant IOP lowering effect compared to placebo at through and peak level, whereas Ripasudil-Latanoprost group showed significant advantage over placebo at peak level.[16,20]

Another multicenter, prospective, open-label study observing the IOP reduction effect of Ripasudil monotherapy and Ripasudil as additive therapy to PA, BB, and fixed combination drug (PA and BB) in patient with POAG and ocular hypertension. After a proper washout period (4 weeks for PA and BB, 2 weeks for other antiglaucoma drug) for monotherapy group, 0.4%

Ripasudil was administered twice daily (at 9 a.m. and 9 p.m.) and IOP was measured at 9 a.m. (before administration of first dose) and 11 am (2 hours after administration). The IOP was evaluated for 52 weeks, every 2 weeks in first month and every 4 weeks thereafter. Ripasudil's IOP lowering effect was found to be statistically significant both in monotherapy group and additive group after 52 weeks compared to baseline.[21]

Netarsudil vs Prostaglandin Analogue and/ or Beta-blocker

Several studies have observed the IOP-lowering effect of Netarsudil compared to other anti-glaucoma drug as monotherapy. Two phase 3, double-masked, randomized noninferiority clinical trials: Rho Kinase elevated IOP treatment trial 1 and 2 (ROCKET-1 and ROCKET-2) comparing Efficacy of Netarsudil monotherapy to Timolol. After a proper washout of previously used anti-glaucoma drug, eligible subjects were put into 3 medication groups: Netarsudil 0.02% daily, timolol 0.5% twice daily, and (ROCKET-2) Netarsudil 0.02% twice daily. Data from 3 months observation was analyzed and showed that Netarsudil daily significantly reduced IOP from baseline IOP and was non inferior to Timolol in population with maximum IOP of <25 mmHg. IOP-lowering property of Netarsudil twice daily was also not inferior compared to Timolol.[22] ROCKET-2 study was further observed to 12 months which revealed that both Netarsudil daily and twice daily are not inferior to Timolol twice daily.[17]

Comparison between Netarsudil and Latanoprost has been observed in several studies, both as monotherapy and combination. A double-masked, randomized, dose-response study comparing Netarsudil to Latanoprost in patients with POAG or ocular hypertension has been reported in 2014. Patients with IOP between 22-36 mmHg have been included and further randomized to receive Netarsudil 0.01%, 0.02%, or Latanoprost 0.005% daily for 28 days. Mean diurnal IOP after 28 days were analyzed as primary efficacy endpoint. IOP-reduction from Netarsudil 0.02% did not meet noninferiority criteria to Latanoprost.[23]

Netarsudil/ Latanoprost combination has been investigated for its IOP-lowering property against Netarsudil or Latanoprost alone. MERCURY-1 and 2 are phase-3, double masked, randomized, parallel-group clinical studies which compared the IOP lowering effect of daily Netarsudil 0.02%/ Latanoprost 0.005% FDC, Netrasudil 0.02%, and Latanoprost 0.005%. The IOP lowering property of Netarsudil/ Latanoprost FDC revealed to be statistically superior compared to Netarsudil or Latanoprost alone in both Mercury-1 and 2.[24,25]

The most common side effect of Rho-kinase inhibitor found both in Ripasudil and Netarsudil is conjungtival hyperemia which is consistent across several studies.[18,19] Conjunctival hyperemia was also found as adverse event in Ripasudil as monotherapy and additive therapy of PA, BB, and FDC of PA and BB.[21] As for Netarsudil, conjunctival hyperemia is more prevalent compared to Timolol or Latanoprost groups. Other adverse events such as blepharitis, conjunctivitis, and conjunctival verticilata are relatively less prevalent and mild in nature. Systemic adverse drug reactions are relatively rare in both Ripasudil and Netarsudil study groups.[21,26]

CONCLUSION

Rho-kinase inhibitor is a novel therapy for glaucoma which offers different mechanism to reduce IOP. The efficacy of Rho-kinase inhibitor has been reported in multiple studies, showing IOP lowering property when used as monotherapy or additive therapy to other type of glaucoma drug. Ocular side effects, although more common than traditional glaucoma drug, are mild with rare occurrence of systemic adverse drug reaction. This could be beneficial compared to other topical glaucoma drug such as Latanoprost in which peri-orbitopathy is common and more noticeable

especially when used unilaterally and Timolol which may cause systemic side effects and are contraindicated in patients with asthma and cardiovascular disease (sinus bradycardia, cardiac failure, 2nd and 3rd AV block).

Declaration by Authors

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