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NOTEWORTHY EFFECTS OF RIPASUDIL, A RHO-KINASE INHIBITOR, ON OPHTHALMIC PATHOLOGIES

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ABSTRACT
Ripasudil, a rho-associated protein kinase (ROCK) inhibitor, is a coil-coiled protein kinase inhibitor that was first approved in Japan in 2014. ROCK has two isoforms ROCK1 and ROCK 2. Their pathway controls myosin-actin interactions and endothelial function. It has since been used to lower ocular pressure (IOP) by increasing aqueous flow accomplishing a better target intraocular pressure as compared to standard available drugs including B-blockers, carbonic anhydrase inhibitors, alpha 2 agonists, and use of prostaglandins. It has, therefore, been demonstrated as efficacious for the treatment of glaucoma. Due to its activity on tight junctions, it has also been stated useful in treating diabetic macular edema as well as in corneal healing. The efficacy of ripasudil is indirectly related to damage to trabecular meshwork making it less efficacious on irreversible damage and hence, better to start early. Here, we will elaborate on the ophthalmic effects of ripasudil. We also shed light on the side effects of ripasudil use like conjunctival hyperemia and blepharitis.

KEYWORDS: Ripasudil, ROCK inhibitors, Glaucoma, Diabetic macular edema, Intraocular pressure.

INTRODUCTION
Rho-associated protein kinase (ROCK) is a serine-threonine molecule that displays multifunctional purpose including that on neurons.[1] Rho kinase/ROCK is a downstream effector of the small GTP-binding protein named Rho.[2] Many previous studies have described them to have demonstrated a critical role, such as in apoptosis, formation of reactive oxygen species, and chemotaxis.[3] Furthermore, ROCK has been shown to be accountable for the lack of neuronal regeneration. Alternatively, the inhibition of ROCK has been demonstrated to have antiapoptotic effects on retinal ganglion cells after optic nerve axotomy.[4] More than 170 ROCK inhibitors are currently present and many were intensely studied, with efforts being made to clinically test them for different indications. These indications included chronic kidney failure, atherosclerosis, glaucoma, spinal cord injury, diabetic retinopathy, psoriasis, and many more. However, only two: fasudil and ripasudil have been approved for clinical use to date.[5] Ripasudil was developed in Japan as an ophthalmic solution having Rho-associated coiled-coil containing protein kinase inhibitor. It was developed as Glantec 0.4 % solution by Kowa Company as means of treating glaucoma and ocular hypertension (OH).[6] Ripasudil, K-115, is a ROCK inhibitor that possesses significant properties of lowering the intraocular pressure by modifying the outflow of aqueous.[7] Further, topical ripasudil has been demonstrated to safely reduce IOP in uveitis glaucoma (UG) patients after noting elevated expression of ROCK in UG.[8] It has also been noted to attenuate activation of human fibroblasts present in the conjunctiva, and was, therefore, also suggested as a therapeutic utility in preventing excessive scarring in glaucoma patients undergoing filtration surgery as seen in most surgical failures in patients with glaucoma. This was mostly observed due to the formation of scarring and fibrosis activation, induced as a response to healing.[9] ROCK is also responsible for angiogenesis and its inhibition was also reported to be beneficial for diabetic retinopathy and diabetic macular edema.[10-13] A study reported Ripasudil to have effects on retinal edema and nonperfusion areas of a retinal vein occlusion murine model.[14] Another study reported ripasudil to have helpful during intraocular surgery as it showed corneal endothelial wound healing in rabbits.[15] Here, the various ophthalmic effects of ripasudil will be detailed with collected data, along with its safety profile and essential use at present.

DISCUSSION

Reduction of intraocular pressure

Development of glaucoma from increased intraocular pressure (IOP) has only one reliable cure, which is decreasing the pressure using IOP-reducing eye treatments. However, despite the availability of many such medications such as B-blockers, carbonic anhydrase inhibitors, alpha 2 agonists, and the use of prostaglandins, a percentage of patients with glaucoma are not able to accomplish the target IOP.[16] For this reason, Ripasudil was developed, a Rho-kinase inhibitor, along with others to alter the outflow of aqueous humor by acting on the cytoskeleton.[17,18]

This is achieved by a sophisticated mechanism. Generally, the cells of the trabecular network have G-protein coupled receptors on which the agonist bind. The binding initiates the Rho guanine nucleotide exchange factor (RhoGEF) which activates Rho by catalyzing GDP-GTP exchange. Activated Rho binds to ROCK1 and ROCK2, activating them, which in turn phosphorylate myosin light chain and Lin-1/Isl-1/Mec-3 kinase (LIMK). This promotes remodeling of the cytoskeleton and synthesis of the extracellular matrix which results in increased tissue contraction as shown in Figure 1.[19,20,21] ROCK inhibitors prevent this mechanism. In a study where trabecular meshwork cells were cultured and treated with ROCK inhibitors, morphological changes were noted which included disassembly and disruption of actin bundles along with an increase in permeability of cultured Schlemm's canal endothelial cells.[22]

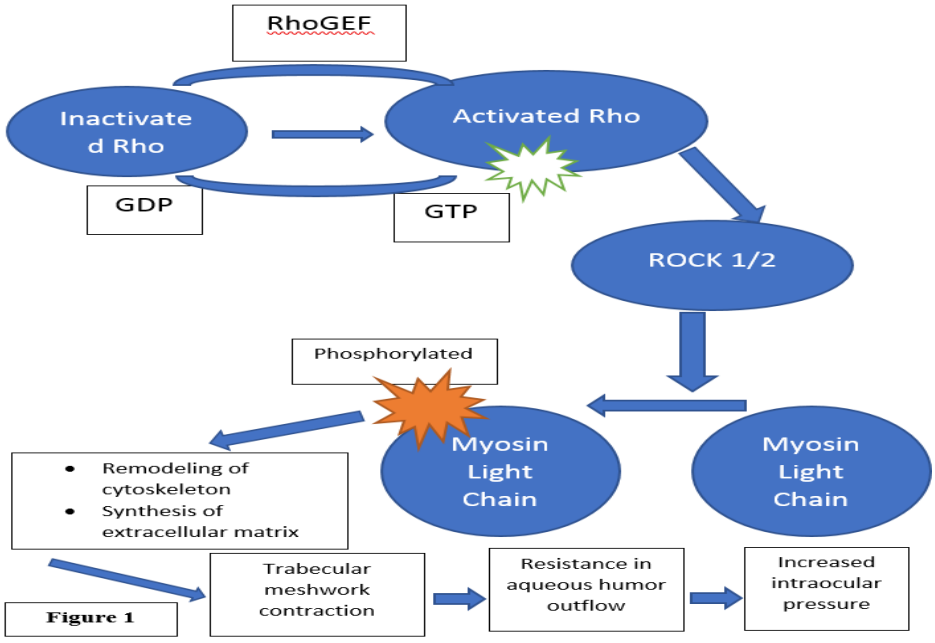

Figure 1

In previous studies, there were diurnal and nocturnal differences noted in the IOP lowering effects of medications which are considered significant for the treatment of glaucoma. This difference was said to be partially caused by the circadian rhythm of aqueous humor production.[23]

For example, in previous studies, latanoprost (a prostaglandin analog) was noted to provide a circadian reduction in IOP, and beta-blocker timolol was noted to be less effective at night time.[24] Additionally, a study shows that carbonic anhydrase inhibitors contribute to the lowering of IOP nocturnally.[25,26] Another study noted them to be insignificant in terms of effectiveness for IOP reduction during nighttime.[27] We do not have information on whether ROCK inhibitors have variations in the nocturnal IOP-lowering effect. However, ripasudil was demonstrated to have maximum and prolonged IOP lowering effect in combination with different agents.[28]

Effect on diabetic macular edema

Diabetic macular edema has many risk factors and pathologic processes. These include inflammation, oxidative stress, dysfunction of endothelial lining and blood-retinal barrier, and retinal neurodegeneration. Vascular endothelial growth factor (VEGF) plays a major role, due to which, intravitreal anti-VEGF has been the main goal of DME treatment.[29] This, however, was not cost-effective for patients requiring repetitive injections for a prolonged time.[30] It was then suggested that ripasudil regulates tight junctions in the retina, thereby, effectively reducing macular edema.[14] It was further suggested that ROCK inhibitors protect vascular endothelial cells significantly, helping in treating DME due to dysfunction of capillary endothelium.[31,32] Another study was conducted which included a study group having DME with primary open-angle glaucoma with no prior ocular surgical history. Foveal thickness and IOP were measured before ripasudil administration. As result, there was a significant reduction noted in FT

from baseline to 1 month in the group with ripasudil administered as compared to the control group. Further, the mean IOP was noted to have more reduction than the control group from baseline.[33]

Effect on fibroblasts

Several studies have been done appreciating the effects of ROCK inhibitors on fibroblast and their role in healing corneal endothelium. A study used topical ROCK inhibitor eye drops to demonstrate its in vivo effect on corneal healing in rabbit and monkey models.[34]

They conducted another research that demonstrated how ROCK inhibitors promote corneal epithelial cell proliferation in residual healthy cells and participation in the wound healing process.[35]

Later, another study was conducted where two different concentrations were taken on ripasudil eyedrops: 0.4% and 0.8%, administered 4 times and 2 times daily, respectively, into rabbit models having a partial corneal endothelial wound. The treated models were noted to have reduced haze in their corneas. These corneas also underwent Alizarinred stain which exhibited a smaller wound size in the ripasudil-treated eye (0.4% or 0.8%) than in the control group. Another finding that the study suggested, was that ROCK inhibitors did not induce cell proliferation once corneal epithelial cells form cell-cell contacts between adjacent cells.[15]

Effect on uveitic glaucoma

Tissue injury leading to vascular permeability and eventual inflammatory infiltration has a significant role in the onset of uveitis.[36] An investigation was planned to explain ripasudil properties on uveitis in rats in which lipopolysaccharide (LPS) endotoxin was used to induce uveitis, and retinal vessels and iris ciliary bodies were evaluated for infiltrating inflammatory cells. Ripasudil was noted to significantly reduce cell infiltration. This study showed that LPS-induced intracellular adhesion molecule-1 (ICAM-1) and monocyte chemotactic protein-1 (MCP-1) expression was noticeably blocked by ripasudil, in the aqueous humor, iris ciliary body, and retina. This suggested that there is a significant role of ROCK in ocular inflammation and ripasudil can inhibit this pathway causing a reduction in inflammatory cell infiltration by blocking ICAM-1 and MCP-1 expression.[37]

Another retrospective case series evidenced the use of ripasudil for uveitic glaucoma caused by several conditions including sarcoidosis and Behçet's disease. Ripasudil instillation showed that the median IOP which was 16 mmHg at 1 month and 18 at 12 months, went down to -3 mmHg at 1 month and -2 mmHg at 12 months.[38]

Safety/Side effects

Although ROCK inhibitors have been evidenced to lower lymphocyte count when administered systemically,[39] it is stated that ripasudil has not exhibited notable systemic side effects as compared to other agents that lower IOP. It was observed that ripasudil caused conjunctival hyperemia as a side effect. This is due to probable smooth muscle relaxation of blood vessels resulting from ROCK inhibition. However, the effect is recorded to be mild and transient.[22,40] In a multicenter prospective study, hyperemia caused by ripasudil was investigated to disappear within 60 minutes in half of the patients who had ripasudil instilled.[41] Conjunctivitis, blepharitis, and eye pruritis are other observed side effects in another analysis. Other than that, generalized headache, constipation, and nausea were also observed in less than 1% of cases.[42]

A multicenter, prospective, open-label study was conducted that consisted of 388 subjects in which ripasudil was used. However, discontinuation of the drug was recorded, the main reason being blepharitis and conjunctivitis (inflammatory reaction due to increased blood flow from ripasudil). 51 patients stopped the use due to allergic reactions (blepharitis and allergic conjunctivitis) which resolved without any treatment or with steroids and other drops once the ripasudil instillation was completely stopped.[43]

CONCLUSION

Although Rho-kinase inhibitors have various effects and are still being investigated to this day, the ophthalmic effects of ripasudil eye drops have been tested and applied. It is tolerated well and has been shown successful for subtypes of glaucoma. Further, they are noted to maintain the functional integrity of the corneal epithelium which undergoes intraocular procedures like cataract surgery. The side effects are minor except for the ocular adverse effect of conjunctival hyperemia which is also transient. More data by survey collection is going to be helpful to monitor it post-marketing, for ripasudil to be extensively considered. Not much data is available on its effects on use for a longer period. Long-term instillation of ripasudil into the eye has questionable effects on the corneal endothelium. Further, studies are needed to confirm its safety in long-term administration for it to be more widely used as a therapeutic modality. Additionally, it is essential to investigate the underlying cause of the few allergic events that were identified in the studies mentioned above.

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