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SOME NEW PHARMACOLOGIC OPTIONS FOR OPEN-ANGLE GLAUCOMA

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ABSTRACT

Glaucoma is the second leading cause for irreversible bilateral blindness worldwide. Open-angle glaucoma is multifactorial chronic disease of the optic nerve, characterized by damage of the retinal ganglion cells and visual field impairment. Raised intraocular pressure is one of the strongest risk factors for development and progression of glaucoma and is the primary target of treatment. The aim of this review is to present the exiting pharmacological options for glaucoma therapy and to reveal new coming tendencies. The review is based on published information about the available and investigational pharmacological options for open angle glaucoma therapy. The articles were retrieved through systematical search of PubMed, Google Scholar, Scopus. Currently six classes of drugs are used to treat glaucoma, acting by either decreasing aqueous humor production or by increasing aqueous outflow. New classes of drugs are being clinically tested: a novel compound with dual EP3 and FP agonist activity, ONO-9054 and Rho kinase inhibitors, like ripasudil (K-115). More efficient pharmacologic therapy for patients with primary open-angle glaucoma and ocular hypertension may be available soon.

KEYWORDS: Open angle glaucoma, pharmacology therapy, Rho kinase inhibitors, prostaglandin analogues, dual EP3 and FP agonist activity, ONO-9054, like ripasudil (K-115).

INTRODUCTION

Glaucoma is the second leading cause for irreversible bilateral blindness worldwide.[1,2] Open-angle glaucoma is multifactorial chronic disease of the optic nerve, characterized by damage of the retinal ganglion cells and their axons. The loss of vision is painless, progressive, and permanent, starting from the periphery and moving towards the central

vision. Usually patients do not realize any visual field deficits until permanent damage has occurred.[3] Early diagnosis and proper treatment are of high importance.[4]

The theories of glaucoma pathogenesis are numerous, however it remains largely unknown.[3,5] Most theories of the glaucoma pathogenesis concede that the trabecular meshwork, the part of the drainage system of the eye in which any morphological, biochemical and functional changes may lead to increased resistance to aqueous humor outflow. That is why this anatomical area is the target of many of the current methods for glaucoma treatment.[5] Recently Endothelin-1, a potent vasoconstrictor, is considered to have a key role in the regulation of ocular perfusion and glaucoma pathogenesis. High ET-1 and ETA-receptor levels are reported in patients with primary open-angle glaucoma.[6]

Glaucoma is not defined by raised intraocular pressure (IOP), however it is one of the strongest risk factors for both development and progression of glaucoma and is the primary target of treatment.[2,3,7] Glaucoma treatment includes medication eye drops, laser treatment to the trabecular meshwork, or surgery.

Currently six classes of drugs are used to treat glaucoma: miotics, beta-blockers, alpha-agonists, epinephrine derivatives, carbonic anhydrase inhibitors, and prostaglandin analogues. They act by either decreasing aqueous humor production or by increasing aqueous outflow.[3]

The aim of this review is to present the exiting pharmacological options for glaucoma therapy and to reveal new coming tendencies.

MATERIALS AND METHODS

The review is based on published information about the available and investigational pharmacological options for open angle glaucoma therapy. The articles were retrieved through systematical search of PubMed, Google Scholar, Scopus.

RESULTS

Prostaglandin analogues

Prostaglandin analogues (PGAs) are commonly prescribed IOP-lowering medications. The most effective PGs for lowering IOP are derivatives of PGF2 α modified structurally to enhance ocular penetration and, after metabolism to the free acid, specifically activate the FP-prostanoid receptor.[8] Latanoprost, travoprost, and bimatoprost target the prostanoid F (FP) receptor and lower IOP mainly by increasing outflow of aqueous humor through the

uveoscleral pathway. In monkeys prostanoid EP3 receptors found in the trabecular meshwork and ciliary muscle augmented the reduction in IOP after the application of FP agonists.[2,8] A novel modified prostaglandin analoug with dual EP3 and FP agonist activity, ONO-9054 is a prodrug that is hydrolyzed to its active form ONO-AG-367 by the action of esterases, which are present in the cornea. PGAs are high-affinity FP agonists, while ONO-9054 has equivalent high agonist activity at both the human EP3 and FP receptors. Preclinical data of ONO-9054 show more potent and longer-lasting IOP- lowering effects in monkeys, suggesting greater efficacy in humans than currently available PGAs. IOP is reduced by increase in trabecular outflow in addition to the increase in uveoscleral outflow from PGAs.[2,7]

Rho kinase inhibitors

Rho kinase inhibitors are a new class of glaucoma drugs, which are still under development. Rho kinase inhibitors modulate the cytoskeleton and the focal adhesions in trabecular meshwork cells. The actin cytoskeleton is one of the main regulators of aqueous humor outflow in the trabecular meshwork outflow pathway. Rho kinase inhibitors decrease resistance in the trabecular meshwork outflow pathway and reduce IOP. Such a drug is ripasudil (K-115).[7,9] Ripasudil (K-115) is approved for ocular use in Japan since 2014. Tanihara et al. investigated the IOP lowering effects and safety of 0.4% ripasudil (K-115), administrated twice daily for 52 weeks, in patients with open-angle glaucoma or ocular hypertension (OHT). In this multicentre, prospective, open-label study, 388 patients with primary open-angle glaucoma, OHT or exfoliation glaucoma were enrolled and 354 of them were divided into groups of ripasudil monotherapy and additive therapy to prostaglandin analogs, beta-blockers, and fixed-combination drugs. The IOP reduction at trough and peak from baseline and adverse events was investigated. The mean IOP reductions at trough and peak at week 52 were -2.6 and -3.7 mmHg for monotherapy, and -1.4 and -2.4, -2.2 and -3.0, and -1.7 and -1.7 mmHg, respectively, for additive therapy. Adverse events were observed: conjunctival hyperaemia (n = 264, 74.6%), blepharitis (n = 73, 20.6%) and allergic conjunctivitis (n = 61, 17.2%). Most of the conjunctival hyperaemia findings were mild (97.0%), transient and resolved spontaneously (78.0%). Although 51 patients discontinued from the study due to blepharitis and/or allergic conjunctivitis, all the events resolved with or without treatment after the discontinuation of ripasudil administration.[7,10]

Results from recent clinical study have now supported and expanded findings of ripasudil's additive effects of IOP reduction to other prostaglandin analogs, beta blockers, fixed

combination drugs over a longer treatment period. Additionally, ripasudil's effectiveness was confirmed at IOP reduction even in monotherapy compared to current first-line anti-glaucoma drugs[7,10], adding to previous findings of ripasudil's IOP-lowering effects compared to second-line medications such as carbonic anhydrase inhibitors and brimonidine.[7]

Recent clinical studies confirm that ripasudil has the potential to become effective new drug for the reduction of intraocular pressure in patients with primary open-angle glaucoma and ocular hypertension.[7]

CONCLUSION

Glaucoma is a disease of social importance. First line therapy is pharmacologic treatment for reduction of intraocular pressure in order to slow the progression of the disease and delay the visual field loss.[7] In recent years, new drugs are being developed for IOP reduction in patients with primary open-angle glaucoma and ocular hypertension. Among them are Rho kinase inhibitors, such as ripasudil (K-115) and modified prostaglandin analogs, like ONO-9054. We hope that new, more efficient pharmacologic therapy for patients with primary open-angle glaucoma and ocular hypertension will be available soon.

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