2023

Rho kinase inhibitors for the treatment of glaucoma

BOSTON UNIVERSITY

ARAM V. CHOBANIAN & EDWARD AVEDISIAN SCHOOL OF MEDICINE

Thesis

RHO KINASE INHIBITORS FOR THE TREATMENT OF GLAUCOMA

by

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Submitted in partial fulfillment of the

requirements for the degree of

Master of Science

2023

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He that is strucken blind cannot forget

The precious treasure of his eyesight lost

Shakespeare. *Romeo & Juliet*: Act 1, Scene 1. Lines 227-228

DEDICATION

I dedicate this work to Hagar, who treasures the sight she so nearly lost.

ACKNOWLEDGMENTS

Thank you to Dr. Haiyan Gong for her inspiration and consistent support. My gratitude to Dr. Andrew Taylor for his valuable input. Thanks also to Dr. Gwynneth Offner for her wise counsel. Heartfelt appreciation to the friends who encouraged me along the way. Special thanks to Thembi, Diana, and Ben, my work buddies. Inexpressible thanks to my parents, whose patient support has made this achievement possible, and to my siblings for their unshakeable faith in me.

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ABSTRACT

Glaucoma is a degenerative disease that contributes greatly to vision loss and blindness worldwide. There are several treatments that focus on alleviating its symptoms, but few address the underlying pathophysiology, the blockage of aqueous outflow, and the onset of neuroretinal damage. Novel drugs under investigation have aimed to address this deficiency. Two of these Rho kinase inhibitors have been approved by national health agencies, and several are in clinical trials. This work investigates the promise of inhibitors of the Rho kinase signaling pathway to treat primary open-angle glaucoma.

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LIST OF ABBREVIATIONS

ACG ..... Angle-closure glaucoma

AQH ..... Aqueous humor

AV ..... Aqueous veins of Ascher

CC ..... Collector channels

CH ..... Conjunctival hyperemia

GTP ..... Guanosine triphosphate

IOP ..... Intraocular pressure

JCT ..... Juxtacanalicular tissue

LMICs ..... Low- and middle-income countries

MIGS ..... Minimally-invasive glaucoma surgery

MLC ..... Myosin light chain

MSVI ..... Moderate or severe visual impairment

NET ..... Norepinephrine transporter

NTG ..... Normal-tension glaucoma

OAG ..... Open-angle glaucoma

OHT ..... Ocular hypertension

PACG ..... Primary angle-closure glaucoma

POAG ..... Primary open-angle glaucoma

QD ..... Once daily

RGC ..... Retinal ganglion cell

RKI ..... Rho kinase inhibitor

ROCK..... Rho kinase

ROCK/NET..... Rho kinase/norepinephrine transporter

SC..... Schlemm's canal

SD .....Standard deviation

TM .....Trabecular meshwork

US .....United States

INTRODUCTION

Background

Glaucoma is the leading cause of permanent blindness in the world and the second-leading cause in the United States (US) (Flaxman et al., 2017; Goldberg et al., 2023). It affects more than 64 million people aged 40 to 80 worldwide and at least 2.9 million people over age 40 in the US alone (Gupta et al., 2016; Mathur et al., 2023). This is undoubtedly an undercount because glaucoma frequently remains undiagnosed (Mohammed et al., 2023). In the US, Ireland, and Australia, 50% or more of those who have glaucoma do not know it (Mohammed et al., 2023). That percentage rises to more than 90% for Japanese, Korean, Indian, and African populations (Mohammed et al., 2023). Within national populations, there is also disparity. In the US, minority and elderly populations generally have higher rates of undiagnosed glaucoma (Shaikh et al., 2014). For example, 62% to 75% of Hispanic Americans with glaucoma are unaware of their condition (Mohammed et al., 2023). As of 2022, more than 70 million people worldwide have glaucoma, and its prevalence is expected to rise to 112 million worldwide by 2040 (Brusini et al., 2022; Mohammed et al., 2023).

Glaucoma is a collection of neurodegenerative eye diseases which can destroy the visual system by causing the loss of retinal ganglion cells (RGCs) and the associated deterioration of the optic nerve (Barrett et al., 2019; Sharif, 2023). It results in a characteristic pattern of visual field loss from peripheral to central associated with deformity of the optic nerve head (Goldberg et al., 2023). It is

insidious because it typically begins as an asymptomatic “silent” disease, and in the absence of regular screening, substantial damage to the visual field can occur before it is detected (Sharif, 2023). There are multiple subtypes of glaucoma, and their causes are incompletely understood. However, the most strongly-associated risk factor (and the only one that is currently modifiable) is heightened intraocular pressure (IOP), which was once considered a diagnostic factor (Barrett et al., 2019; Freddo et al., 2021; Goldberg et al., 2023). One reason why it is no longer diagnostic is that some sufferers with statistically normal or low IOP still develop the pattern of vision loss typical of glaucoma (Freddo et al., 2021; Goldberg et al., 2023). Still other people experience statistically high IOP, or ocular hypertension (OHT), without the symptoms or damage of glaucoma (Freddo et al., 2021; Goldberg et al., 2023). Both open-angle glaucoma and closed-angle glaucoma seem to be associated with heightened IOP in both their onset and worsening (Barrett et al., 2019; Goldberg et al., 2023). Despite this uncertainty about the contribution of heightened IOP, all therapeutic interventions for treating glaucoma currently in use are aimed at lowering the pre-treatment pressure, whether it was high or low (Freddo et al., 2021).

IOP depends on the balance between production and drainage of aqueous humor (AQH) (Gong & Swain, 2020). Options for lowering IOP include decreasing the rate at which AQH is synthesized, decreasing the resistance to AQH outflow of the conventional pathway, or increasing the aqueous outflow via the unconventional pathway (Tanna & Johnson, 2018).

Current treatments for glaucoma include surgical intervention and several classes of drugs which take aim at different ocular structures and processes. Until recently, pharmaceutical solutions have tended to focus on reducing the production of AQH, with less emphasis on improving AQH outflow through the trabecular meshwork (TM) and uveoscleral pathway (Goldberg et al., 2023; Sharif, 2023). Novel drugs under investigation have aimed to address this deficiency. Several are in the pharmacological pipeline—most in a preclinical investigation, but several are in current clinical trials. Two have been approved in Japan, China, and the US.

SPECIFIC AIM

The aim of this text is to evaluate the therapeutic promise of novel Rho kinase inhibitors (RKIs) for the treatment of glaucoma and explore their mechanisms of action. Their innovation lies in addressing the causative factors of primary open-angle glaucoma (or hypertension-related glaucoma) as opposed to merely relieving its symptoms. This is to say they target the problem of obstructed aqueous drainage due to heightened outflow resistance instead of relying on workarounds such as reducing the production of aqueous humor. It will be interesting to see if they are more effective than drugs with different therapeutic targets.

The drugs ripasudil and netarsudil, which have been approved for use in Japan, China, and the US, will be evaluated for efficacy and safety in clinical trials and post-marketing use. Patient data from RKIs still in the phase II or III clinical phases of investigation will be described. These drugs hold promise to reduce the morbidity of glaucoma and the global burden of avoidable blindness and vision loss.

REVIEW OF LITERATURE: WHAT IS KNOWN?

Description of Glaucoma

Introduction

Glaucoma is a disease whose course comprises a progressive degeneration of the retinal ganglion cell layer of the eye and the optic nerve, featuring characteristic structural changes, such as optic disc cupping and thinning of the inner retinal layers, that lead to the diminishment of the visual field (Goldberg et al., 2023; Mohammed et al., 2023). Over the course of years, the disease, asymptomatic at first, may lead to blindness if elements such as ocular hypertension and glaucomatous optic neuropathy are not detected with an in-depth eye exam and consistently treated (Sharif, 2023).

There are several types of glaucoma. The two commonest types are open-angle and closed-angle (Mohammed et al., 2023). Open-angle glaucoma (OAG), which is more common overall and seems to have a genetic component, can be thought of as a chronic type developing over a long period of time (Barrett et al., 2019). It occurs when AQH flow into the TM is not obstructed, but has trouble leaving the eye because it faces increased outflow resistance due to decreased permeability (Barrett et al., 2019; Tanna & Johnson, 2018). This leads to heightened IOP, or ocular hypertension (OHT) (Sharif, 2023). Angle-closure glaucoma (ACG) can also take a chronic course, but sometimes it is an acute, emergent condition in which a sudden narrowing of the anterior chamber angle obstructs access to the trabecular

meshwork through which the bulk of aqueous humor leaves the eye, which allows ocular pressure to rise quickly and cause damage to the structures of the eye (Mohammed et al., 2023). Some people have normal-tension glaucoma (NTG), with normal angles of the drainage area of the anterior chamber and apparently normal IOP despite the initiation of glaucoma's characteristic pattern of nerve damage and visual field loss (Goldberg et al., 2023). Once that damage is observed, the disease is still classified as primary open-angle glaucoma (POAG), after checking for diurnal variations in pressure (Goldberg et al., 2023). OHT can also occur without accompanying signs of such damage. Hence, an outlying value for ocular pressure is no longer considered a requirement for the diagnosis of glaucoma (Goldberg et al., 2023). Both NTG and OHT are fairly prevalent (Goldberg et al., 2023). Finally, glaucoma can be classified as primary or secondary; it is primary if the heightened pressure is of unknown etiology and secondary if it develops in response to an identifiable causal factor (Goldberg et al., 2023). Secondary glaucomas can be caused by pseudoexfoliation, occlusions of the veins, diabetes, uveitis, trauma, and other factors (Mohammed et al., 2023). Most research on mechanisms and pharmaceutical treatments for glaucoma has focused on POAG and OHT, since IOP is the most clearly modifiable biomarker (Mohammed et al., 2023; Sharif, 2023).

Burden & Consequences

Glaucomatous optic neuropathy is a major contributor to blindness throughout the world (Goldberg et al., 2023). It causes fewer cases of blindness and

moderate-to-severe visual impairment than cataracts and uncorrected refractive error, but the visual impairment it causes cannot be reversed by either corrective lenses or surgery (Flaxman et al., 2017; World Health Organization, 2022). Rates of bilateral blindness vary overall, but in developing countries where there is poor access to eye care and in areas where primary angle-closure glaucoma (PACG) predominates, it is a frequent cause of bilateral blindness (Goldberg et al., 2023). Areas with older populations also see higher rates of blindness. The predicted rise in the burden of glaucoma is expected to fall more heavily on Asian and African populations. As the world's population grows and ages, glaucoma is expected to contribute proportionally more to blindness as cataracts and trachoma contribute less (Goldberg et al., 2023). Men are more likely than women to suffer vision impairment due to glaucoma (Flaxman et al., 2017).

Blindness is a devastating loss, individually and societally. Even mild visual impairment and its consequences can lead to personal struggles with loneliness, helplessness, and alienation that in turn lead to isolation and social disengagement (Sharif, 2023). Independence and quality of life are both compromised (Misra et al., 2023; Sharif, 2023).

Anatomy and Pathophysiology

The eye is an enclosed tissue defined by a blood-ocular barrier containing an anterior and posterior chamber, surrounded by the sclera, an opaque white outer protective layer of the eyeball (Barrett et al., 2019; Freddo et al., 2021). The whole

structure of the eyes sits within bony sockets called the orbits, which protect the eye from injury (Barrett et al., 2019). The cornea, at the front of the eye is a clear avascular tissue that allows light to pass through it (Barrett et al., 2019). The ocular surface of the eye that is contiguous with the cornea is the conjunctiva, which is covered by a clear mucous membrane (Barrett et al., 2019). On the inner surface of the sclera is the choroid, a vascular layer that allows oxygen and nutrients to diffuse through the eye's blood barrier (Barrett et al., 2019). The retina is the neural tissue containing the photoreceptors which detect light and convert it to neurological signals, the neurons that transmit the signal to the ganglion cells and then to the brain via the optic nerve (Barrett et al., 2019). The retina lines two-thirds of the posterior cavity and rests on a monolayer of retinal pigment epithelial cells that provide the retina with nourishment and is part of the blood-ocular barrier (Barrett et al., 2019; Schubert, 2023). The posterior cavity, also called the vitreous chamber, is a space between the lens and the retina and is filled with vitreous humor, a clear, gelatinous fluid (Barrett et al., 2019).

Understanding the progression of glaucoma and treating it requires an understanding of structures from both the anterior and posterior segments of the eye. The anterior segment can be further subdivided into the anterior chamber and posterior chamber (Figure 1) (Barrett et al., 2019). The structures of the anterior cavity include the crystalline lens, the circular lens suspensory ligament (or zonule) that holds the lens in place, the ciliary body into which the zonule is anchored, and the iris (Barrett et al., 2019). The space between the cornea and the iris, the colored

portion of the eye, is the anterior chamber (Barrett et al., 2019). The space between the iris, lens, and zonule is the posterior chamber, a narrow space containing aqueous humor (Barrett et al., 2019). The uvea is the collective term for the iris, ciliary body, and choroid (Barrett et al., 2019). The whole structure of the eyes sit within bony sockets called the orbits, which protect the eye from injury (Barrett et al., 2019).

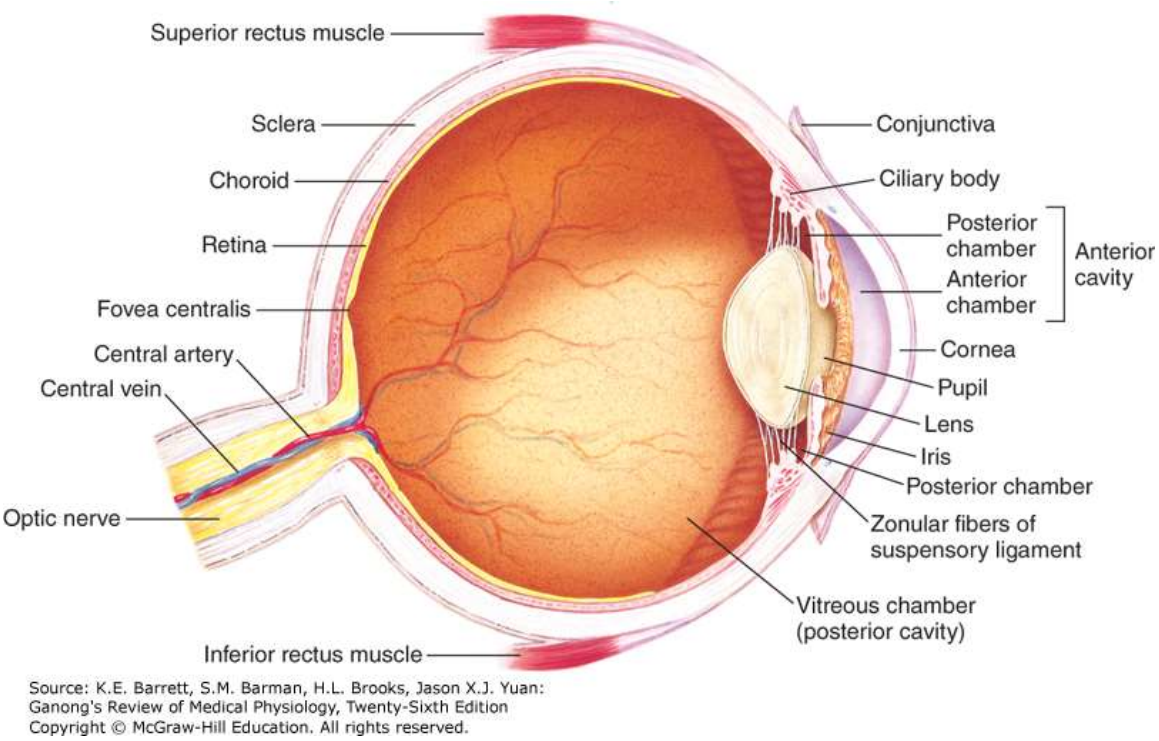


Figure 1. A schematic of the anatomy of the eye.

Reproduced from Barrett et al. (2019).

Maintaining consistent pressure within the eye is important for ensuring the elements of the visual system are spaced a nearly-constant distance from each other (Freddo et al., 2021). The formation and regulation of aqueous humor fulfills this

function by maintaining pressure in the eye, which lacks rigid infrastructure (Freddo et al., 2021). AQH is a substance that resembles protein-free plasma, though it is also higher in ascorbate, lactate, and certain amino acids than plasma (Freddo et al., 2021; Goldberg et al., 2023). It forms by transferring solute into the posterior chamber, which sets up an osmotic gradient that draws water in (Goldberg et al., 2023). It flows into the anterior chamber of the eye, where it nourishes the avascular tissues of the lens, cornea, and TM and helps maintain the sphericity of the eye (Freddo et al., 2021; Goldberg et al., 2023). Elements of the AQH help maintain ocular immune privilege (Freddo et al., 2021). The ciliary body secretes AQH into the posterior chamber; it flows through the pupil in a one-way direction into the anterior chamber and circulates in a convective manner according to the temperature difference between the iris and cornea (Freddo et al., 2021). From there, it drains out of the eye, ultimately into the vasculature, by two pathways: the "conventional" trabecular meshwork pathway and the "unconventional" uveoscleral pathway (Freddo et al., 2021).

There are two ways that AQH flows out of the anterior chamber: the "conventional" trabecular outflow pathway, which accounts for 80—90% of drainage, and the "unconventional" uveoscleral outflow pathway that accounts for the remaining flow (Freddo et al., 2021; Gong & Swain, 2020). Trabecular drainage is pressure-dependent (though not absolutely) (Goldberg et al., 2023). Anatomical elements of this pathway are the uveal and corneoscleral portions of the TM, the juxtacanalicular tissue (JCT), SC, the collector channels (CCs), the scleral venous

plexus, and the aqueous veins of Ascher (AVs) (Goldberg et al., 2023; Gong & Swain, 2020). Of these, the main contributor to outflow resistance in normal function is thought to be in the JCT and inner Schlemm's canal (SC) wall (Goldberg et al., 2023). When aqueous humor flows into the trabecular meshwork, the scleral spur divides the flow (Freddo et al., 2021). The bulk of it passes anterior to the spur, from the anterior chamber to smaller and smaller TM channels into SC, from where it passes into external CCs through the venous plexus into the episcleral vasculature (Freddo et al., 2021; Gong & Swain, 2020). No active transport is involved in this system (Gong & Swain, 2020). The AQH, which passes posterior to the spur, enters the uveoscleral outflow pathway, which seems to be mostly pressure-independent (Freddo et al., 2021). In this pathway, after AQH reaches the potential space between the outer surface of the ciliary muscles (at the root of the iris) and the inner surface of the sclera, it leaves the eye by diffusing through the sclera (uveoscleral) or diffusing through the vortex veins (uveovortex) (Freddo et al., 2021; Goldberg et al., 2023).

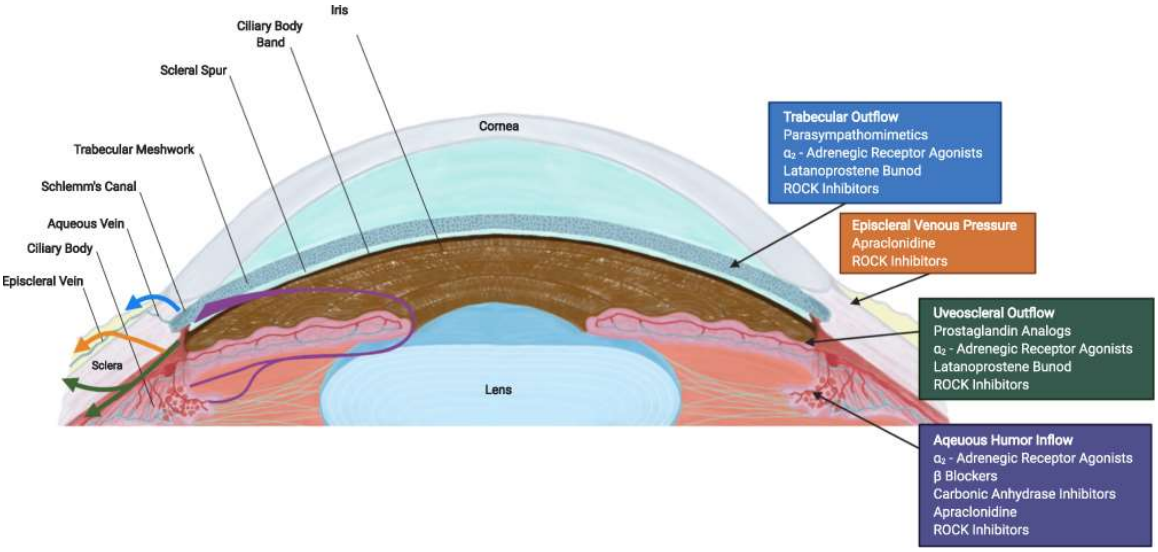


Figure 2. Cross section of an eye illustrating AQH pathways and site of action of antiglaucoma medications.

Cross section of an eye illustrating aqueous humor (AQH) pathways (left) and site of action of antiglaucoma medications (right). AQH formation occurs in the ciliary body and flows from the posterior chamber through the pupil to the anterior chamber angle. The drainage of AQH is mainly facilitated by the conventional [trabecular meshwork (TM), Schlemm's canal, and episcleral veins] pathway and the non-conventional (uveoscleral-uveovortex) pathway. The current glaucoma hypotensive medications and their sites of action are shown on the right. Reproduced from Al-Humimat et al. (2018).

Changes in vascular volume can influence IOP, but the most important contributor is the "back pressure" introduced by tissue resistance to AQH drainage (Freddo et al., 2021). Regulatory mechanisms contribute to the maintenance of IOP, which varies cyclically with each heartbeat and with diurnal cycles (Freddo et al., 2021).

Various subtypes of glaucoma have differing causes of impaired AQH outflow (Goldberg et al., 2023). In PACG, physical blockage occludes the outflow pathway near the anterior chamber angle. In some of the common secondary forms of OAG,

particulate matter clogs the TM. By contrast, in POAG, there is no clinically visible explanation for the increased outflow resistance (Goldberg et al., 2023). Both pathways do undergo age-related changes that might contribute to glaucoma's association with older age, such as extracellular material deposition and loss of TM elasticity, which is significant because the TM cytoskeleton is known to regulate AQH outflow (Goldberg et al., 2023).

The Rho Kinase Pathway in Glaucoma Pathophysiology

In the late 20th century, a hypothesis developed that cells of the AQH outflow pathway could control aqueous drainage (Saha et al., 2022). Exploration of this theory led to the discovery that certain substances that affect the cytoskeleton were able to decrease AQH outflow resistance and highlighted the possible role of Rho kinase (Saha et al., 2022). This suspicion was strengthened when glaucomatous eyes were found to contain higher concentrations of RhoA protein in the optic nerve head than age-matched controls (Moura-Coelho et al., 2019). Rho kinase, through its effects on cytoskeletal elements, increases cell contractility and stiffness while regulating their processes, especially those used in movement and smooth muscle contraction (Tanna & Johnson, 2018).

Rho kinase (ROCK) molecules are expressed in all cells, though the degree sometimes varies by cell tissue, and they are activated by various integrins or secreted cytokines (Moura-Coelho et al., 2019). Therefore, ROCK inhibitors (RKIs) have been developed and tested for many disease processes (Tanna & Johnson,

2018). The ROCK signaling pathway, involved in both normal ocular physiology and the glaucomatous state, exerts effects on many cytoskeletal elements and is thus an key regulator of trabecular meshwork (TM) outflow (Moura-Coelho et al., 2019). Rho proteins (RhoA, RhoB, and RhoC) are GTPases, and the binding of guanosine triphosphate (GTP) leads to their association with effector molecules, including ROCKs. Humans are known to have two isoforms of ROCK, ROCK-1 and ROCK-2, which are serine/threonine kinases and share some downstream substrates in common. ROCK-1 and ROCK-2 share 65% sequence homology overall, which goes up to 87% for the kinase domain (Tanna & Johnson, 2018). They activate some of the same downstream targets, suggesting some redundancy, but are also able to yield somewhat differing effects (Moura-Coelho et al., 2019; Tanna & Johnson, 2018). Activation of ROCKs leads to downstream phosphorylation of substrates responsible for, among other things, modulation of the actin skeleton, microtubule dynamics, cell migration, smooth muscle contraction, regulation of polarity, vesicular transport pathways, cell proliferation, gene transcription, cell cycle progression, and several enzymatic activities (Moura-Coelho et al., 2019). Hence Rho proteins regulate cell morphology, polarity, motion, cytokinesis, proliferation, adhesion, and apoptosis along with neurite elongation and smooth muscle contraction (Tanna & Johnson, 2018).

When activated, Rho kinase phosphorylates the myosin light chain, driving the formation of stress fibers and focal adhesion complexes as myosin interacts with actin (Tanna & Johnson, 2018). It also phosphorylates Lin-11/Isl-1/Mec-3 kinase,

decreasing the disassembly of actin filaments and thereby increasing their density, rigidity, and stability (Tanna & Johnson, 2018). Rho kinase also depolymerizes intermediate filaments and modulates microtubule movement and polarity, increasing cells' contractility and stiffness (Tanna & Johnson, 2018). It also regulates cell processes involved in movement and smooth muscle contraction. (Tanna & Johnson, 2018).

Rho kinase inhibitors can likewise have a broad range of effects. On the systemic level, they have antitumor activity, reducing tumor cell invasion and metastasis likely by reducing cell motility and division (Tanna & Johnson, 2018). They can increase blood flow via vasodilation mediated by vascular smooth muscle relaxation (Tanna & Johnson, 2018). They also prevent axonal degeneration and actively promote regeneration (Tanna & Johnson, 2018). Most known RKIs, including fasudil, ripasudil, netarsudil, and several others in various stages of pharmaceutical development, inhibit both ROCK1 and ROCK2 (Tanna & Johnson, 2018). The only one currently known to be selective for ROCK2 is KD-025 (Tanna & Johnson, 2018). In the context of glaucoma and OHT, ROCK signaling is involved in many aspects of the cytoskeletal structure, which in turn influences outflow resistance. Their vasodilatory effects (though likely therapeutically useful) can cause conjunctival hyperemia and other adverse effects (Tanna & Johnson, 2018).

One of the determinants of AQH outflow is the pore density of the inner wall endothelial cells in Schlemm's canal. The pores themselves are large and numerous, meaning they do not generate much outflow resistance themselves, but AQH is

forced to “funnel” through the extracellular matrix of the JCT to reach these pores (Tanna & Johnson, 2018). The overall stiffness of the canal is associated with a greater number of pores, which results in lower outflow resistance (Tanna & Johnson, 2018). RKIs’ promotion of actin depolymerization is likely what enables higher AQH outflow with treatment and could be related to pore formation (Tanna & Johnson, 2018).

Current Treatment Options for Glaucoma

Non-ROCK Inhibitors; or All

There are three general approaches to glaucoma treatment: topical medications, surgical procedures, and aqueous humor drainage devices (Sharif, 2023). One approach frequently used in both pharmacological and surgical interventions is to inhibit the production and inflow of AQH (Goldberg et al., 2023). Another is to increase aqueous outflow. These are all effective ways to lower IOP (Goldberg et al., 2023).

Medical management of glaucoma aims to lower IOP with eyedrops or systemic medications (McMillan & Gross, 2023). Different classes of glaucoma medications address different contributors to IOP (McMillan & Gross, 2023). The classes of medication currently in use for chronic treatment include prostaglandin analogues; β-blockers, selective and nonselective; α-adrenergic agonists; carbonic anhydrase inhibitors (topical or oral); miotics; and rho kinase inhibitors (McMillan & Gross, 2023). Classes of medication used for acute reduction of IOP include oral or

intravenous osmotics and intravenous carbonic anhydrase inhibitors (McMillan & Gross, 2023). β-blockers, α-adrenergic agonists, and carbonic anhydrase inhibitors decrease AQH production (McMillan & Gross, 2023). Prostaglandin analogues promote uveal outflow of AQH. Still others, including miotics, nitric oxide donors, and RKIs promote AQH drainage through the trabecular pathway. Then there are combinations of the foregoing that work through multiple pathways.

Topical prostanoids (prostaglandin analogues) are the first line treatment for POAG and are considered the most effective class of treatments (Freddo et al., 2021; McMillan & Gross, 2023; Ruiz-Lozano et al., 2023). They have been used in the US for more than two decades (McMillan & Gross, 2023). They shift the balance between matrix metalloproteases and tissue inhibitors of matrix metalloproteases, which regulates the extracellular matrix such that the metabolism of the interstitial matrix surrounding ciliary muscle cells is altered and uveoscleral outflow increases (Freddo et al., 2021; McMillan & Gross, 2023). Relaxation of the ciliary body muscle and dilation of the space between its fibers also contributes to uveoscleral outflow (McMillan & Gross, 2023). This yields therapeutically effective reductions in IOP (Freddo et al., 2021). Latanoprost, bimatoprost, travoprost, and tafluprost are among the prostanoids available in varying concentrations and formulations to improve convenience and mitigate side effects (McMillan & Gross, 2023). Latanoprost, in particular, seems to be especially helpful for angle-closure glaucoma and normal-tension glaucoma (McMillan & Gross, 2023). Common side effects of this class of drugs include conjunctival hyperemia, burning and stinging, blurred vision,

itching, foreign body sensation, tearing, and eye pain. Irreversibly increased iris pigmentation, which tends to occur over a period of months, is also fairly common, depending on eye color. Few systemic adverse effects have been noted (McMillan & Gross, 2023).

Beta-blockers reduce IOP by decreasing production of AQH by the ciliary body (McMillan & Gross, 2023). Their effect might only occur during the day, leaving the risk of disease progression if they are used by themselves (McMillan & Gross, 2023). Nonselective β-blockers tend to be more effective than β_1-selective blockers (McMillan & Gross, 2023). Lower concentrations seem to be just as effective as higher ones, but do not offer relative relief from side effects (McMillan & Gross, 2023). Locally-applied β-blockers are fairly well-tolerated, but systemic ones have a host of potentially serious side effects that make them contraindicated in some people with chronic respiratory, cardiac, or diabetic disease (McMillan & Gross, 2023).

Alpha-adrenergic agonists include apraclonidine and brimonidine (McMillan & Gross, 2023). Apraclonidine is typically used in acute applications, such as preventing IOP spikes after laser surgery and treating cases of acute angle-closure glaucoma (McMillan & Gross, 2023). It decreases production of AQH and is also associated with increases in outflow facility and decreases in episcleral venous pressure (McMillan & Gross, 2023). Brimonidine also prevents postoperative IOP spikes after laser surgery (McMillan & Gross, 2023). Unlike apraclonidine, brimonidine is used more often in chronic treatment (McMillan & Gross, 2023). It is

also more selective, and it works by reducing AQH production and increasing uveoscleral outflow (McMillan & Gross, 2023). Brimonidine may also have neuroprotective effects on RGCs and the optic nerve, based on extensive animal studies and a single clinical trial in humans (McMillan & Gross, 2023). Apraclonidine's tendency to provoke allergic reactions is one reason why it is limited to acute application; apart from that, systemic use is well tolerated (McMillan & Gross, 2023). Dry mouth is an adverse effect of both drugs, while brimonidine is also associated with fatigue and drowsiness (McMillan & Gross, 2023). In local application, there are several irritant and allergic adverse effects, such as conjunctival blanching, burning and stinging (Freddo et al., 2021). These are somewhat mitigated when the drug concentration is lowered or Purite preservative is used in place of benzalkonium chloride (McMillan & Gross, 2023).

Carbonic anhydrase inhibitors reduce AQH production by at least half by reducing the generation of bicarbonate ions, which are normally actively transported into the posterior chamber, establishing an osmotic gradient that pulls water into the chamber and promotes AQH production. This can be a powerful way to reduce IOP, but it requires the inhibition of nearly all the carbonic anhydrase present. This requirement meant that formulation of oral carbonic anhydrase inhibitors that could suppress the enzyme activity that powerfully without excessive systemic side effects took a long time. Dorzolamide and brinzolamide are topical formulations, with brinzolamide causing less stinging upon application but causing temporary blurred vision (McMillan & Gross, 2023). Oral acetazolamide is

somewhat more effective than topical dorzolamide and brinzolamide, but both topical medications are appropriate choices for monotherapy or adjunct therapy when there is a reason other, more effective drugs may not be used (McMillan & Gross, 2023). The carbonic anhydrases may not be preferred because of their wide range of adverse effects, including malaise, fatigue, anorexia, depression, and gastrointestinal distress for the oral forms. Less frequent side effects include metabolic acidosis in patients with severe kidney or liver disease or kidney stones. Blood dyscrasias are still rarer but are associated with significant risk of mortality. Topical carbonic anhydrase inhibitors have fewer side effects. There are minimal effects on blood pressure or heart rate, and the principal systemic side effect was a bitter taste experienced by about a quarter of patients, which could be mitigated with a few minutes of gentle eyelid closure or nasolacrimal occlusion after eyedrops had been instilled (McMillan & Gross, 2023). About a third of patients who took dorzolamide experienced ocular burning, stinging, or discomfort, but fewer who took brinzolamide experienced that. Superficial punctate keratitis was also found in a tenth of patients who took dorzolamide.

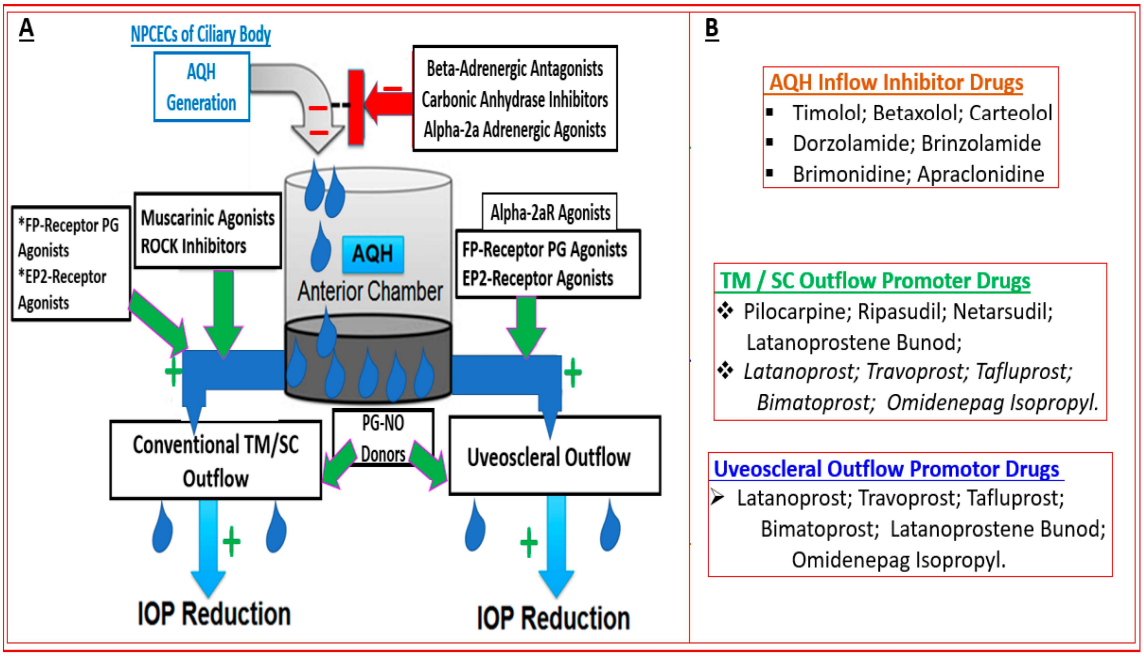


Figure 3. Processes of AQH production and removal and mechanisms of key medications.

The schematics illustrate the processes of AQH production and its removal from the anterior chamber of the eye via the conventional IOP-dependent outflow pathway (TM/SC) and the uveoscleral pathway. Furthermore, the mechanism of action of key approved medications to lower IOP by influencing the latter process and pathways is depicted in both (A) and (B). The red minus symbol denotes inhibition, and the green plus symbol indicates stimulation or activation. Reproduced from Sharif (2023).

Miotics, which also reduce IOP by increasing AQH outflow facility, imitate parasympathetic agonists like acetylcholine or inhibit its degradation (Freddo et al., 2021; McMillan & Gross, 2023). The main mechanism for their effect seems to be opening the corneoscleral trabecular meshwork; by contracting the longitudinal bundle of the ciliary muscle fibers, which separates its layers (Freddo et al., 2021). Another theory is that the contraction of the ciliary muscle effected by miotics helps Schlemm's canal resist the collapse that occurs when IOP increases (Freddo et al.,

2021; McMillan & Gross, 2023). An example of a miotic is pilocarpine (Freddo et al., 2021). Miotics were the first drugs used to treat glaucoma and have been around for a long time, but these days they are prescribed less frequently because other medications have more advantageous side effects profiles (McMillan & Gross, 2023). By themselves, they reduce IOP by 20-30%, and they can be used alongside β-blockers, adrenergic agonists, and carbonic anhydrase inhibitors for an additive effect (McMillan & Gross, 2023). They have very few, infrequent systemic cholinergic side effects, but they can be difficult to tolerate topically. Pupillary miosis, burning upon application, headache and brow ache soon after application, alteration in lens accommodation that results in a myopic shift of refractive error, and added opacity of the lens are all undesirable side effects. Pseudocholinesterase inhibitors can even promote cataract formation in adults. However, patients who have previously had cataract surgery may tolerate miotics more easily (McMillan & Gross, 2023).

The ROCK inhibitors currently approved for the treatment of glaucoma are netarsudil and ripasudil (Sharif, 2023). Fasudil is another RKI that is approved in oral form in Japan to treat vascular diseases, and others remain in the research pipeline, not yet approved for use in humans (Al-Humimat et al., 2021). They will be discussed in further detail below. RKIs have the advantage of targeting multiple contributors to OHT at once (Al-Humimat et al., 2021).

Combination drugs use components from multiple classes of glaucoma medications to devise a single therapy that is more effective, more convenient, safer,

or otherwise advantageous. Examples are Vyzulta and Rocklatan. Vyzulta (latanoprostene bunod) is a conjugated drug consisting of a prostaglandin analogue and a nitric oxide (NO)-donating moiety (Hoy, 2018; Sharif, 2023). It is a newer drug, approved by the Food and Drug Administration in 2017 for use in OAG and OHT. Once instilled, it is broken down into the metabolites latanoprost acid and butanediol mononitrate (Hoy, 2018; McMillan & Gross, 2023). Latanoprost acid mediates the increase of AQH outflow via the uveoscleral pathway, while the NO molecule released by butanediol mononitrate facilitates AQH outflow through the TM pathway (Hoy, 2018; McMillan & Gross, 2023). NO, a naturally occurring signal molecule, is present in the normal TM and SC, but it is known to be reduced in glaucoma (McMillan & Gross, 2023). NO activates the guanylyl cyclase/cyclic guanosine monophosphate signaling pathway, which triggers a cascade that eventually involves ROCK signaling (McMillan & Gross, 2023). The result is relaxation in the cytoskeleton of TM cells (McMillan & Gross, 2023). Vyzulta is a highly effective combination that reduces IOP from a starting point of high or normal pressure and does not seem to lose efficacy over time (Hoy, 2018). It is well tolerated, with few ocular adverse effects as with other prostanoids (Hoy, 2018). Again, conjunctival hyperemia was the most frequently-reported adverse effect (Hoy, 2018). Rocklatan is a fixed-dose combination of netarsudil, an RKI, and latanoprost, a prostaglandin analogue, in eyedrop form (Sharif, 2023). It has enhanced ocular hypotensive activity compared to its individual components (Sharif, 2023). Rocklatan's effect on IOP is greater than the sum of its parts, yielding

31—37% reduction, apparently because it stimulates both aqueous outflow pathways and additionally lowers episcleral venous pressure and inhibits the norepinephrine transporter (NET) system (the ensuing disruption of norepinephrine signaling decreases AQH formation) (Batra et al., 2021; Sharif, 2023).

Table 1. Drugs Used to Manage Glaucoma.

Reproduced from McMillan & Gross (2023).

Drug	Example	Mechanism of Action	Efficacy	Side Effects
Beta-blockers nonselective	Timolol Levobunolol Carteolol Metipranolol	Decreased aqueous production (waking hours only)	+++	Pulmonary: bronchoconstriction Cardiovascular: bradycardia/heart block Exacerbation of congestive cardiac failure Depression Impotence Death
Adrenergic agents nonselective	Epinephrine Dipivefrin	Outflow enhancement	+ (+)	External eye: toxic reaction
α-Adrenergic agents	Apraclonidine	Decreased aqueous production	++ (+)	External eye: allergic reaction
	Brimonidine	Also, uveoscleral outflow increase with brimonidine		Lethargy Dry mouth Allergic reaction
Miotics	Carbachol Pilocarpine Echothiophate	Increased conventional aqueous outflow	+++	Eye ache Headache Dim vision
Carbonic anhydrase inhibitors				
Systemic	Acetazolamide	Decreased aqueous production	++++	Malaise Blood dyscrasia Kidney stones

Drug	Example	Mechanism of Action	Efficacy	Side Effects
	Methazolamide			Depression Weight loss
Topical	Dorzolamide Brinzolamide		++	Metallic taste Eye irritation
Lipids (prostaglandin analogues, prostamides, decosanoids)	Latanoprost Travoprost Bimatoprost Tafluprost	Enhanced aqueous outflow (conventional and unconventional)	++++	Iris color change Hyperemia Periocular skin pigmentation Orbitopathy
Nitric oxide donating prostaglandin analogue	Latanoprostene bunod	Enhanced aqueous outflow (conventional and unconventional)	++++	Iris color change Hyperemia Periocular skin pigmentation Orbitopathy
Rho kinase inhibitors	Netarsudil Ripasudil (Japan)	Enhanced aqueous outflow (conventional), reduction of episcleral venous pressure	+++	Hyperemia Conjunctival hemorrhages Blurred vision

Other approaches to POAG and OHT treatment are surgical (McMillan & Gross, 2023). Surgical incision and laser ablation techniques are known to reduce IOP (Goldberg et al., 2023; Sharif, 2023). A small proportion of POAG patients undergo surgery due to failure to adhere to a medication regimen, incidental diagnosis during preparation for surgery for another condition, or multiple medication allergy; many patients with PACG or another cause of acute IOP

elevation also undergo surgery (Sugihara et al., 2022). Laser trabeculoplasty has been touted as an alternative to prostanoids for first-line treatment (McMillan & Gross, 2023; Ruiz-Lozano et al., 2023). Another tactic is minimally invasive glaucoma surgery (MIGS) (Gong & Swain, 2020). Procedures in this category encompass five characteristics: a microincision, "minimal tissue trauma, modest efficacy, rapid recovery, and a high safety profile." This is intended to be an intervention with fewer risks and shorter recovery times than traditional glaucoma surgery, but it comes at the cost of somewhat lower efficacy (Coulon et al., 2023). One MIGS option is implantation of miniature devices such as microshunts and tubes in the anterior chamber that allow AQH drainage (Sharif, 2023). Trabecular micro-bypass devices, including iStent and Microstent, are included in this class of intervention. These devices can be placed in varying locations, span a range of sizes and designs, and are made up of different biocompatible materials (Sharif, 2023).

Focus on ROCK Inhibitors

Rho kinase inhibitors are fairly novel medications approved for the treatment of POAG and OHT. They slow the progression of glaucoma in various ways lowering IOP by multiple avenues and displaying neuroprotection – and perhaps even regeneration (McMillan & Gross, 2023; Sharif, 2023). They decrease IOP by relaxing cytoskeletal elements of TM and Schlemm's canal cells; this increases their permeability and reduces resistance to AQH outflow (Al-Humimat et al., 2021). RKIs promote cell survival and reduce oxidative damage in TM cells, which is noteworthy

because increases in reactive oxygen species are found in glaucoma, as with other age-related diseases (Al-Humimat et al., 2021). Some RKIs also decrease AQH production by inhibiting NETs, acting via vasodilation in the uveoscleral pathway (Al-Humimat et al., 2021). Even perfusion of postmortem human eyes with adenoviral vectors that expressed a dominant negative Rho-binding domain of Rho kinase reduced outflow resistance (Tanna & Johnson, 2018). Inhibition of downstream effectors of the ROCK pathway, including myosin light chain (MLC), LIM kinase, and cofilin, which are all expressed in human TM, was also shown to significantly decrease outflow resistance without affecting unconventional flow (Tanna & Johnson, 2018).

The first RKIs to be investigated regarding ocular outflow were Y-27632 and fasudil, which both had dedensifying effects on the cytoskeleton of TM and SC cells. Others, including netarsudil, had favorable effects on pig and rabbit models of glaucoma. None of them affected unconventional outflow. Clinical trials have focused on a subset of RKIs, including ripasudil, netarsudil, SNJ-1656, and AR-12286 (Tanna & Johnson, 2018).

Fasudil (also known as HA-1077) is an RKI approved in Japan in oral form since 1995 for various vascular diseases, including cerebral vasospasm; it is currently being studied in topical form for glaucoma (Al-Humimat et al., 2021; Tanna & Johnson, 2018). A small case series demonstrated dose-dependent IOP reductions of 21.2% for 1.2% fasudil and 17.9% for 0.5% fasudil. It decreases the

density of actin stress fibers, relaxing the cytoskeleton of both TM and SC cells. In animal models, they greatly increased outflow facility (Tanna & Johnson, 2018).

SNJ-1656 (previously called Y-39983) was the first RKI tested in clinical trials for IOP reduction. In vitro and animal studies have yielded promising results. Phase I studies characterized its peak action at 4 hours post-instillation at 3.0±1.2 mmHg at the highest dose; transient conjunctival hyperemia was noted. Phase 2 comparison with placebo found a 3 to 3.5 mmHg peak reduction. Mild to moderate conjunctival hyperemia was noted (Tanna & Johnson, 2018).

Verosudil (AR-12286) was identified as a candidate by screening of aminoisoquinoline amides (Al-Humimat et al., 2021; Tanna & Johnson, 2018). A Phase 1 study found a significant decrease in IOP (about 7 mmHg at maximum) but also frequent side effects (ocular irritation, increased lacrimation, conjunctival hyperemia, and blurred vision) (Tanna & Johnson, 2018). A placebo-controlled Phase 2 trial using a lower maximum concentration found a 4.5 mmHg maximum average IOP reduction over three weeks. Again, the most common side effect was conjunctival hyperemia (Tanna & Johnson, 2018). Though it was found to have some efficacy in several small trials, it was abandoned in favor of netarsudil, which was deemed to have a longer duration of action (Al-Humimat et al., 2021).

Ripasudil (K-115), approved in 2014 for glaucoma and OHT in Japan, has been found to lower IOP within 2 hours of instillation in patients with both conditions in Phase I and II clinical trials (Tanna & Johnson, 2018). A noncomparative, open-label study confirmed this result (Tanna & Johnson, 2018).

Those trials established 0.4% concentration BID as a clinically useful dose which lowered IOP by 2 to 4.4 mmHg compared to placebo and maintained its action for at least 7 hours. It is structurally similar to fasudil but has a stronger and more specific RKI activity (Tanna & Johnson, 2018). The adverse effect of conjunctival hyperemia was found to be transient and dose-dependent, with peak intensity at 15 minutes post-instillation and slow return to baseline around 2 hours post-instillation. However, the adverse event of allergic conjunctivitis only appeared at 12 weeks in the long clinical trials at a rate of about 20% (Tanna & Johnson, 2018). Ripasudil was mainly considered as an adjunctive option to use with first-line agents, so the phase 3 randomized, placebo-controlled trials were conducted on a short-term basis with timolol or latanoprost. The addition of ripasudil lowered IOP further in the timolol group but not in the latanoprost group. Further studies of adjunctive use of ripasudil for patients already on maximum therapy found mean IOP reductions ranging from 2.6 to 3.1 mmHg, but design limitations make it difficult to interpret the results with regards to efficacy (Tanna & Johnson, 2018).

Netarsudil (AR-13324), approved in the US in 2017, is a Rho kinase/norepinephrine transporter (ROCK/NET) inhibitor (Al-Humimat et al., 2021). It increases AQH outflow animal models and in humans with glaucoma by various mechanisms (Gong & Swain, 2020; Tanna & Johnson, 2018). It expands the TM and JCT and dilates the episcleral veins, leading to enlargement of the active filtration area of the episcleral veins and of the TM near SC (Gong & Swain, 2020). It is unique among RKIs because, in addition to reducing outflow resistance, it

decreases AQH production and episcleral venous pressure. It is possible that those effects are due to its NET inhibitory activity (Tanna & Johnson, 2018). It was not noted to have any effect on the unconventional outflow pathway (Tanna & Johnson, 2018). A brief double-masked randomized clinical trial comparing two doses of netarsudil (0.01% and 0.025 both QD (once daily)) to latanoprost 0.005% QD did not find either dose as effective in lowering or maintaining IOP, except for patients with relatively low baseline IOP. Longer double-masked RCTs compared netarsudil 0.02% QD to timolol maleate BID and found netarsudil non-inferior in POAG and OHT patients with relatively low baseline IOPs but not in the overall study population (Tanna & Johnson, 2018). Ultimately, netarsudil was deemed inferior to PGAs and non-inferior to topical β-blockers for OAG/OHT (Gonzalez & Boylan, 2021). A significant number of study subjects ceased participation because of adverse events, including conjunctival hyperemia in almost half of those assigned to netarsudil and conjunctival hemorrhage in a smaller proportion. Corneal verticillata were also seen at higher rates than for the control group (Tanna & Johnson, 2018).

Again, Rocklatan's RKI and prostanoid elements enable it to lower IOP by enhancing both pathways of aqueous outflow, inhibiting the NE transporter, and reducing episcleral pressure by enlarging the active filtration area (Gong & Swain, 2020; Sharif, 2023). Clinical trials of the fixed-dose combination found statistically superior efficacy compared to netarsudil or latanoprost alone. Mean diurnal IOP was significantly lower after 12 months. Rates of discontinuation due to side effects were higher for the netarsudil and combination groups: around 6—7% at the 3-

month mark and about 20% at the 12-month mark, compared to 2% for the latanoprost-only group (Tanna & Johnson, 2018).

AMA-0076, also known as PHP 201, is a soft ROCK inhibitor, meaning it is designed to exert its effect locally but quickly become inactivated in the systemic circulation (Al-Humimat et al., 2021; Boland et al., 2015). This controlled metabolic inactivation is made possible by an ester moiety, and it is intended to reduce the risk of systemic adverse effects and thereby increase the therapeutic index (Al-Humimat et al., 2021; Boland et al., 2015). AMA0076 showed similar efficacy to latanoprost, with the added advantage of reducing IOP during the day as well as at night (Al-Humimat et al., 2021). Phase 1 trials showed it to be safe and well tolerated. The results of Phase 2 trials have not yet been published (Al-Humimat et al., 2021).

H-1337 is another RKI that has shown long-lasting, powerful reduction of IOP in animals. It is thought to stimulate AQH drainage through the conventional pathway. A Phase 1/Phase2 clinical trial was completed in 2018, but its results have not been formally published (Al-Humimat et al., 2021).

Significance

Clinical trials have sought to establish whether RKIs can become a new standard for monotherapy or adjunct treatment (Saha et al., 2022). The clinical trials that have been performed so far have not shown RKIs to be superior to current first-line agents as a monotherapy for lowering IOP (Tanna & Johnson, 2018). They are likely to make the greatest impact as adjunctive therapy, partly

because their mechanisms of action complement those of medications that focus on reducing AQH production or aiding the uveoscleral outflow (Tanna & Johnson, 2018). Preclinical studies showed greater reductions in IOP than clinical trials, possibly for two reasons. First, animal studies sometimes used higher drug concentrations than human studies did. Second, glaucoma and OHT themselves may cause abnormalities in the outflow pathway that do not show up in animal models and are not responsive to RKIs (Tanna & Johnson, 2018).

Since glaucoma is not merely a disease of heightened IOP, it is important to consider the other effects RKIs might have on IOP-independent disease mechanisms. One reason RKIs are attracting attention is because they target the trabecular meshwork to improve aqueous humor outflow, instead of relying solely on restricting the production of AQH. They also promote wound healing following glaucoma surgery, improving recovery and inhibiting the mechanisms that lead to scarring that reduces vision (Al-Humimat et al., 2021; Saha et al., 2022). There is also evidence of neuroprotection from certain RKIs, which takes the possibilities of glaucoma treatment from merely addressing distal factors such as addressing OHT to the more direct prospect of preventing the optic cupping and nerve deterioration that contributes to glaucoma's long-term vision loss, while promoting axonal regeneration and blood flow (Saha et al., 2022; Tanna & Johnson, 2018). RKIs seem to contribute specifically to retinal and optic disc perfusion (Tanna & Johnson, 2018). If the promising results seen *in vitro* and in animal studies are borne out in

human trials, the RKIs have potential for protecting RGCs from glaucoma or OHT-associated damage and even promoting optic nerve regeneration (Sharif, 2023).

Moreover, combining RKIs with other classes of glaucoma drugs is demonstrating synergistic effects that reduce IOP beyond existing treatments. There has been some success in reducing IOP for patients whose condition was treatment-resistant. Certain formulations that pair RKIs with other pharmaceuticals in a single eyedrop are making it easier for patients to maintain their medication regimen.

Additional drug candidates continue to be investigated in preclinical research (Appendix, Table A1). Some nonselective RKIs in development are Y-27632, H-1152, Wf-536, Y-39983, AMA-0076, GSK-269962A, SB-772077-B, SAR-407899, and RKI-1447. The only known ROCK-2 inhibitor in development is KD-025 (Tanna & Johnson, 2018). Research is ongoing for targeting RKIs to cells of the outflow pathway and RGCs to specify their area of effect and reduce adverse effects (Tanna & Johnson, 2018).

Adverse Effects

Adverse effects are the primary obstacle to increased uptake of RKIs for glaucoma and include both local and systemic events (Al-Humimat et al., 2021). Local adverse effects include conjunctival hyperemia, subconjunctival hemorrhage, blepharitis, ocular irritation, increased lacrimation, and blurred vision. Conjunctival hyperemia and subconjunctival hemorrhage occur frequently with RKIs because they function as vasodilators (Al-Humimat et al., 2021). This trait also means

treatment with RKIs can increase the rate of elimination of other topical medications administered at the same time, which would reduce their therapeutic effects (Al-Humimat et al., 2021). Systemic adverse effects can include decreased blood pressure and a linked increase in heart rate as well as, rarely, reversible reduction in lymphocyte counts (Al-Humimat et al., 2021).

Nearly 50% of subjects treated with netarsudil QD in the ROCKET series of phase 3 clinical trials reported conjunctival hyperemia (Al-Humimat et al., 2021). 20.9% reported cornea verticillata, and 17.2% experienced subconjunctival hemorrhages (Al-Humimat et al., 2021). These events did not affect visual acuity and resolved following netarsudil cessation (Tanna & Johnson, 2018). Participants in a Phase 3 study of Rocklatan® (netarsudil 0.02% and latanoprost 0.005%) reported adverse effects, including conjunctival hyperemia (63%), pain at the site of instillation (23%), conjunctival hemorrhage (13%), and cornea verticillata (17.6%) (Al-Humimat et al., 2021). An open-label study of ripasudil noted side effects including conjunctival hyperemia that was dose-dependent and non-dose dependent conjunctival hemorrhage, along with rare (less than 1% frequency), mild occurrences of constipation, headache, dizziness, and nausea (Al-Humimat et al., 2021).

For drugs still in clinical trials, adverse effects are still noted. Topical administration of fasudil in a small case series was associated with conjunctival hyperemia at the higher dose and irritation at the site of instillation, but no systemic adverse effects were noted (Al-Humimat et al., 2021). A Phase 1/Phase 2 study of

latrunculin-B for early-stage POAG and OHT noted adverse effects of mild redness, irritation, a transient increase in corneal thickness, and conjunctival erythema/hyperemia (Al-Humimat et al., 2021). A phase 1 clinical trial of (Y-39,983, SNJ-1656 or RKI983) noted transient hyperemia at higher doses; conjunctival hyperemia was still the commonest AE in a Phase 2 trial, while one subject developed hepatic dysfunction that resolved when treatment stopped (Al-Humimat et al., 2021). LX7101, a dual LIM-kinase and RKI, seemed to be well tolerated in Phase 1/Phase2 clinical trials at both 0.125% and 0.25%, without any serious side effects reported or withdrawals from the study at the two-week mark (Al-Humimat et al., 2021). Verosudil, a selective RKI, was associated with transient adverse effects such as conjunctival hyperemia, blurred vision, instillation site reaction, ocular irritation, and headaches when tested for use in glaucoma and OHT (Al-Humimat et al., 2021). When it was studied for exfoliative glaucoma or exfoliation syndrome with OHT, conjunctival hyperemia was a frequent complaint (Al-Humimat et al., 2021).

The only noted adverse effect of AMA-0076 was mild, transient conjunctival hyperemia (Al-Humimat et al., 2021). Information on adverse effects for candidates still in a preclinical investigation is not available.

DISCUSSION

The disparities in the distribution of glaucoma prevalence and morbidity make it a public health issue. In poorer countries, glaucoma contributes more to permanent blindness than in wealthier ones. Across the globe, the different subtypes of glaucoma affect populations at varying rates. Some areas are more prone to hypertension-related glaucoma, others are prone to angle-closure glaucoma, and still others have pockets of NTG (Mohammed et al., 2023). Glaucoma is also an insidiously asymptomatic disease, at least in its early stages, leading it to be called the "silent thief of sight" (*What Is Glaucoma?*, 2022). Many people who have it do not know they have it, and much damage can occur before sufferers become aware of the disease (Mohammed et al., 2023; *What to Know After a Glaucoma Diagnosis*, 2023).

Medical management of glaucoma is still the cornerstone of glaucoma intervention, notwithstanding advances in surgical and laser procedures (Saha et al., 2022). However, established medications do not always succeed in lowering IOP to desired levels (Wu et al., 2022). The promise of RKIs lies in their ability to address different aspects of glaucoma's pathophysiology and combine with other therapies, pharmaceutical and non-pharmaceutical, to improve symptom relief, delay disease progression, and make the therapeutic regimen more bearable and effective for patients. So far, this anticipation seems to be borne out by studies on the first generation of RKIs.

ROCK inhibitors offer powerful IOP reduction for POAG and OHT on their own. They help decrease pressure when added to other ocular hypotensive medications such as prostaglandins and β-blockers (Moura-Coelho et al., 2019; Saha et al., 2022). This means that for people whose illness has resisted initial treatment, RKIs open up new avenues for relief. Furthermore, they can be combined with surgical interventions to improve outcomes by reducing scarring, preventing oxidative damage, and promoting wound healing (Al-Humimat et al., 2021; Moura-Coelho et al., 2019). They are also encouraging in the domain of neuroprotection and promote ocular blood flow; they may even support the regeneration of damaged neuroretinal tissue (Moura and other). To date, ripasudil and netarsudil are not known to interact with other medications or have any anticipated contraindications (Tanna & Johnson, 2018).

The barriers presented by the side effect profiles of RKIs make recommending them more complicated. Despite their substantial impact on IOP in combination with other medications, their use comes with higher rates of adverse effects than other commonly-used adjuncts (Tanna & Johnson, 2018). Moreover, the nature of the adverse effects can be particularly alarming to patients. Visible redness, hemorrhage, and pain soon after application are salient features that might make patients reluctant to continue using them. The adverse events are not all dangerous; in fact, many of the most frequently-reported ones are transient and self-limiting, but they might affect patients' attitude to continuing therapy (Saha et al., 2022). Subconjunctival hemorrhage, in particular, is a startling condition to

encounter, even if it tends to resolve by itself. Conjunctival hyperemia is highly noticeable to the patient and others. Pain and the aversion to it is self-explanatory; when contrasted with the absence of obvious symptoms typical of untreated POAG, it would take a lot of conviction and self-control to continue using medications that cause such side effects without an immediately perceptible benefit. Patients are less likely to adhere to a medication regimen if it causes painful or distressing effects, especially when the symptoms of the disease itself are subtle (Sharif, 2023).

Another concern is the potential for RKIs to hasten the elimination of concurrently-applied topical drugs. Many glaucoma patients require combinations of medications to manage the disease. Systemic effects of topical medications are also concerning, but there are attempts underway to reduce overall systemic exposure by incorporating drug design that takes metabolic considerations into account (Al-Humimat et al., 2021; Bodor & Buchwald, 2000).

On the other hand, the continued development of formulations that address barriers to patient use could make RKIs more tolerable. Once-a-day dosing of standalone RKIs and combined fixed-dose formulations with other medications could promote patient compliance by improving ease of use, reducing cost, and ameliorating the risk of exacerbating concomitant dry eye disease (Chaglasian & Than, 2018). Sustained drug delivery systems such as ocular implants, particles, and gels could deliver medications to patients who have trouble using eyedrops consistently or who lack regular access to ophthalmic care (Kaufman et al., 2018; Kompella et al., 2021). Research should attempt to develop RKIs with greater

specificity so that they can conceivably be targeted at cells of the trabecular meshwork and retina and have a narrower range of unintended effects (Saha et al., 2022). Patient counseling on the expected side effects, the threat posed by glaucoma progression, and the importance of the therapies the clinician has prescribed could be employed to improve acceptability and encourage adherence.

CONCLUSION

Blindness affected an estimated 43 million people worldwide in 2020, with 295 million suffering from moderate or severe visual impairment (MSVI) and 257 million from mild visual impairment. In this estimation, disparities based on socio-economic status, gender, and geography were apparent (*VISION 2020*, n.d.). Over the last 30 years, age-adjusted prevalence of blindness has gone down, but population growth and aging means that more needs to be done to maintain that trend (*VISION 2020*, n.d.). Considering its psychological impact and the disability it imposes on individuals and communities, it is important to address the preventable causes of blindness and visual impairment (Sharif, 2023). Vision loss due to glaucoma may be irreversible, but it is avoidable (Flaxman et al., 2017).

Glaucoma is one of the leading contributors of blindness and MSVI worldwide (Flaxman et al., 2017; Mohammed et al., 2023). While cataract and uncorrected refractive error lead to more cases of blindness, they are reversible with surgery and spectacle correction, respectively (Flaxman et al., 2017). The damage caused by glaucoma, however, cannot be undone. There is geographic variation not only in the prevalence of glaucoma, but also in its contribution to blindness. For instance, as of 2015, the proportion of blindness attributable to glaucoma is highest in southern sub-Saharan Africa (15.47%) and lowest in south Asia (5.81%) (Flaxman et al., 2017). As low- and middle-income (LMIC) countries undergo the epidemiological transition from acute, infectious diseases to noncommunicable chronic disease as the major contributors to disease burden,

glaucoma is one of the diseases whose prevalence is likely to increase as national populations age (Bourne, 2020).

According to the World Health Organization's (WHO) Global Action Plan to prevent avoidable blindness, the contribution of glaucoma to blindness and vision impairment is on already the wane (Bourne, 2020). Though the growth and aging of the population mean that overall numbers of people at risk for blindness are still rising, national and supranational organizations have already helped to raise public awareness of glaucoma and its consequences. This trend should be solidified with continued intervention to raise awareness of the causes of preventable vision loss and promote access to regular ophthalmic care. Ophthalmic care and access to medical and surgical interventions are not evenly distributed either worldwide or within countries. Increasing both the quantity and quality of care interactions around glaucoma will be important (Bourne, 2020). It is important to build up eye care that takes into account the factors of availability, accessibility, affordability, and acceptability. Shortages of trained health workers and their uneven distribution geographically and across socioeconomic levels and of ophthalmic equipment, supplies, and medication should be addressed, especially in the public sector of LMICs (World Health Organization, 2022). Sex and socioeconomic barriers to utilization of services should also be addressed, given that risk of glaucoma is unevenly distributed along those lines (Mohammed et al., 2023; World Health Organization, 2022). Costs of services and treatments should be better covered by insurance schemes to mitigate out-of-pocket expenses (World Health Organization,

2022). Acceptability of services will continue to develop as awareness of glaucoma, its risks, and treatment options are built up. Quality of services including surgery, data and monitoring frameworks is also important (World Health Organization, 2022).

Since glaucoma is typically asymptomatic until a large portion of the optic nerve and visual field have been destroyed, it is critically important to effect early screening and diagnosis (Mohammed et al., 2023). Early detection of glaucoma and OHT would allow patients to consider the full range of their and would ensure that RKIs could be used as early as necessary to reduce IOP and maintain the health of the visual system before degeneration has a chance to set in. Innovations in screening in high-resource settings have enabled early detection of asymptomatic glaucoma (Sun et al., 2022). Greater access to refractive correction and cataract services could potentially lead to better detection of asymptomatic glaucoma in low-resource settings. This advantage could be carried on with early treatment to slow disease progression (Sun et al., 2022). IOP measurement alone is not a good screening tool, since there is a lot of overlap between measured pressures in people with and without glaucoma. Even if attempted, there is no cutoff that yields an acceptable combination of sensitivity and specificity (Mohammed et al., 2023). Community screening for target populations or screening at the time of eye care appointments for moderate perimetric glaucoma would catch many cases of glaucoma before complete vision loss occurs (Misra et al., 2023). In addition, it could be performed with additional screenings for other causes of blindness and visual

impairment, such as cataracts, diabetic retinopathy, and macular degeneration (Bourne, 2020). Attention will need to be paid to the sustainability and cost-effectiveness of whichever screening programs are implemented (Bourne, 2020). Once screening has diagnosed glaucoma and determined the need for intervention, clinicians should work with public health bodies to ensure that patients are equipped with the knowledge and support to undergo a medication regimen that is effective and tolerable for them, taking into account the heterogeneous presentations of the disease, individual response to first-line medications, and lifestyle or environmental considerations.

Though IOP is limited in usefulness as a screening marker, it remains the only directly modifiable biomarker of glaucoma, it is important that those who are diagnosed initiate a medication regimen as soon as possible and adhere closely to it (Rosu et al., 2021; *What to Know After a Glaucoma Diagnosis*, 2023). Medications help arrest and control the disease process, thereby forestalling the damage (Rosu et al., 2021). Poor adherence can lead to greater vision loss or even blindness (Rosu et al., 2021). Unfortunately, the silent nature of the disease and the imperceptibility of the medications' action, in combination with the obvious and alarming side effects sometimes present, combine to reduce patients' sense of urgency to stick to the medications. Perhaps for these reasons, adherence to topical glaucoma medications is low even compared to treatment for other chronic conditions (Tapply & Broadway, 2021).

To promote adherence, health systems and clinicians should identify patients who are likely to become nonadherent to glaucoma medication and ascertain the barriers preventing them from adhering (Rosu et al., 2021). Some reasons that have been cited for nonadherence to glaucoma prescriptions are as follows: forgetfulness, low sense of self-efficacy, skepticism that a disease whose symptoms the patient likely had not noticed could lead to permanent visual impairment, lack of belief in the prescribed medications' ability to address the disease, and low levels of knowledge about glaucoma (Rosu et al., 2021). Whatever the specific reason is, the existence of these barriers has serious consequences for large numbers of people worldwide. Therefore, these barriers must be deliberately counteracted as far as possible in the clinician-patient relationship (Saha et al., 2022). In the broader public health context, ongoing health literacy and patient education efforts should make a special effort to discuss information on glaucoma, the silent nature of its destruction, the medications used to treat it, why it is important to use them consistently, and the implications of their adverse effects.

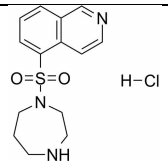
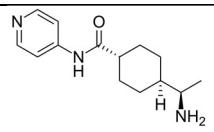
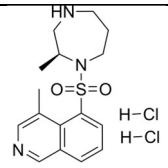
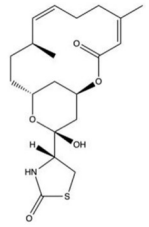
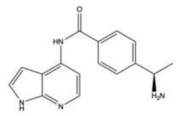
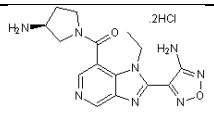
That is why the emergence of a novel class of drugs for glaucoma is significant; RKIs present an opportunity to decrease the global burden of irreversible blindness by addressing the leading preventable contributor. RKIs have been a major topic of discussion for the last few decades, and some of their contributions are encouraging for the prospect of reducing preventable vision loss worldwide. Mechanistically, their promise is undeniable, and three formulations have already been approved and seem to be performing well. Research has also

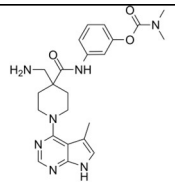
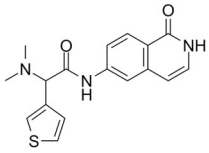
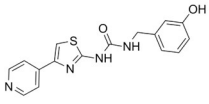
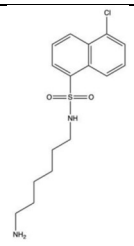
revealed some drugs in the pipeline that are more efficacious in vitro and in vivo than others. The issues that threaten to derail the contributions of RKIs are adverse effects and accessibility. Post-marketing research should continue to evaluate the safety and efficacy of those drugs which have been approved to date. Distribution and affordability should also be facilitated, particularly for LMICs. Clinical trials should continue for the sake of the approval process in additional countries, evaluating candidate drugs that have shown promise in animal models. Pharmaceutical screening and pipeline expansion should also continue in order to uncover medications with a higher therapeutic index and fewer, less distressing adverse effects. At all levels, investigation of this class of drugs will pay off by allowing clinicians to address heretofore unaddressed pathophysiological mechanisms. This will ultimately yield more powerful medications and more options for confronting the problem of preventable blindness worldwide.

APPENDIX 1

Table A1. Current Investigational Rho Kinase Inhibitors.

Adapted from Al-Humimat et al. (2021).

Agent and Reference	Chemical Formula and Structure	ROCK I IC50 (nM)	ROCK 2 IC50 (nM)	Effect on Other Receptors	Year Introduced	Current Phase
HA-1077 C14H17N3O2S		NA	NA	PKA, PKG, PKC	1995	Phase 1
Y-27632 C14H12N3O.2HCL		42	71	PKA, PKC, MLCK	1997	Preclinical
H-1152P C16H21N3O2S		NA	12	PKC, AMPK	1999	Preclinical
INS-115644 C20H29NO5S		5	14	NA	2004	Phase 1
Y-39983 C16H17C1N4O		3.6	3.6	NA	2005	Phase 2
SB772077BS C15H18N8O2		5.6	5.6	NA	2007	Preclinical

Agent and Reference	Chemical Formula and Structure	ROCK I IC50 (nM)	ROCK 2 IC50 (nM)	Effect on Other Receptors	Year Introduced	Current Phase
LX7101 C23H29N7O3		69	32	LIMK, Akt1	2007	Phase 1/ Phase 2
AR-12286 C17H17N3O2S		NA	NA	NA	2009	Phase 2
AMA-0076	NA	3.7	2.3	NA	2011	Phase 2
RKI 1447 C16H14N4O2S		14.5	6.2	NA	2012	Preclinical
AR-13533	NA	NA	NA	NET	2013	Preclinical
AMA0526	NA	5.7	3.1	NA	2013	Preclinical
H-1337		NA	NA	PKA, PKN2, PKD1, LRRK2	2015	Phase 2
ITRI-E-212	NA	NA	3.2	NA	2017	Preclinical
ITRI-E-247	Unavailable	NA	10.9	NA	2017	Preclinical

Note: IC50 is the half-maximal inhibitory concentration (the amount of drug needed to inhibit, in vitro, a given biological process or biological component by 50%).
Abbreviations: nM, nanomolar; NA, not available; PKA, protein kinase A; PKC, protein kinase C; MLCK, myosin light chain kinase; NET, norepinephrine transporter; LIMK, LIM kinase; GRK, G-protein coupled receptor kinase; LRRK, Leucine-rich repeat kinase 2; AMPK, 5' adenosine monophosphate-activated protein kinase.

APPENDIX 2

Table A2. Summary of Phase 2 and 3 Clinical Trials of Rho Kinase Inhibitors.

Adapted from Tanna & Johnson (2018).

Study	Study Design	Duration of Treatment	Diagnosis and Baseline IOP Inclusion Range (mmHg)	Drugs (number of subjects)	Baseline IOP mmHg (SD)	Efficacy mmHg (SD)		Frequent Adverse Events	Comments
SNJ-1656 Phase 2 Inoue et al (2015)	Multicenter RCT Double-masked Placebo control	7 days	POAG (37%) OHT (63%)		~22.5	Change from baseline at trough	Change from baseline at peak	CH	
				Placebo		−2.2 (1.9)	−1.5 (2.2)	Not reported	
			22≤ IOP ≤ 31	SNJ-1656 0.03% (16)		−3.8 (2.7)	−5.0 (2.4)	60%	
				SNJ-1656 0.05% (15)		−4.3 (2.3)	−4.4 (2.7)	100%	
				SNJ-1656 0.1% (18)		−4.0 (2.5)	−4.5 (1.9)	83%	

Study	Study Design	Duration of Treatment	Diagnosis and Baseline IOP Inclusion Range (mmHg)	Drugs (number of subjects)	Baseline IOP mmHg (SD)	Efficacy mmHg (SD)		Frequent Adverse Events	Comments
AR-12286 Phase 2 Williams et al (2011)	Multicenter RCT Double-masked Vehicle control	3 consecutive 7-day dosing periods: QD AM QD PM BID	OAG (58%) OHT (42%)		Mean diurnal	Mean diurnal IOP reduction from baseline		CH	
						QD AM Group	BID Group		
			24≤ IOP ≤ 36	Vehicle (22)	26.3 (2.47)	−1.9	−2.4	9.1%	
				AR-12286 0.05% (22)	26.0 (2.17)	−4.0	−4.1	27.3%	
				AR-12286 0.1% (23)	27.3 (3.18)	−5.0	−4.4	39.1%	
				AR-12286 0.25% (22)	26.9 (2.03)	−4.8	−6.0	59.1%	
Ripasudil Phase 2 Tanihara	Multicenter RCT Double-masked	8 weeks	POAG (41%) OHT (59%)		9 AM	Change from baseline at trough	Change from baseline at peak	CH	

Study	Study Design	Duration of Treatment	Diagnosis and Baseline IOP Inclusion Range (mmHg)	Drugs (number of subjects)	Baseline IOP mmHg (SD)	Efficacy mmHg (SD)		Frequent Adverse Events	Comments
et al (2013)	Placebo control			Placebo (54)	23.0 (2.1)	−2.2	−2.5	13%	
			21< IOP < 35	Ripasudil 0.1% (53)	23.3 (2.4)	−3.4	−3.7	43%	
				Ripasudil 0.2% (54)	23.2 (2.0)	−3.2	−4.2	57%	
				Ripasudil 0.4% (49)	23.2 (1.9)	−3.5	−4.5	65%	
Ripasudil Phase 3 Tanihara et al (2016)	Multicenter Non-randomized open-label clinical trial	1 year	POAG (65%) OHT (31%) XFG (4%)		9 AM	Change from baseline at trough	Change from baseline at peak	All Treatments: CH (75%) Blepharitis (21%) Allergic conjunctivitis (17%)	
				Ripasudil 0.4% BID (173)	19.3 (2.7)	−2.6	−3.7		
			15< IOP ≤ 35	Ripasudil 0.4% BID + PGA (62)	17.6 (2.0)	−1.4	−2.4		

Study	Study Design	Duration of Treatment	Diagnosis and Baseline IOP Inclusion Range (mmHg)	Drugs (number of subjects)	Baseline IOP mmHg (SD)	Efficacy mmHg (SD)		Frequent Adverse Events	Comments
				Ripasudil 0.4% BID + BB (60)	18.2 (2.3)	−2.2	−2.0		
				Ripasudil 0.4% BID + FC PGA and BB (59)	17.6 (2.0)	−1.7	−1.7		
Additive effect of ripasudil with timolol Phase 3 Tanihara et al (2015)	Multi-center RCT Double-masked Placebo control	8 weeks	POAG (47%) OHT (53%) IOP ≥ 18 on timolol		On timolol 9 AM	Change from baseline at trough	Change from baseline at peak	CH	
				Placebo (104)	19.7 (1.7)	−1.5	−1.3	5.8%	
				Ripasudil 0.4% BID (104)	19.9 (1.9)	−2.4	−2.9	65.4%	

Study	Study Design	Duration of Treatment	Diagnosis and Baseline IOP Inclusion Range (mmHg)	Drugs (number of subjects)	Baseline IOP mmHg (SD)	Efficacy mmHg (SD)		Frequent Adverse Events	Comments
Additive effect of ripasudil with latanoprost Phase 3 Tanihara et al (2015)	Multicenter RCT; Double-masked Placebo control	8 weeks	POAG (61%) OHT (39%) IOP ≥ 18 on latanoprost		On latanoprost 9 AM	Change from baseline at trough	Change from baseline at peak	CH	
				Placebo (103)	19.6 (1.9)	−1.8	−1.8	8.7%	
				Ripasudil 0.4% BID (102)	20.1 (1.9)	−2.2	−3.2	55.9%	
Netarsudil Phase 3 Bacharach (2015)	Multicenter RCT Double-masked	28 days	POAG (60%) OHT (40%)		Mean diurnal IOP	Change at trough	Change in mean diurnal IOP	CH	Netarsudil did not meet predetermined criteria for non-
				netarsudil 0.01% QD (74)	25.8	−5.4	−5.5	52%	

Study	Study Design	Duration of Treatment	Diagnosis and Baseline IOP Inclusion Range (mmHg)	Drugs (number of subjects)	Baseline IOP mmHg (SD)	Efficacy mmHg (SD)		Frequent Adverse Events			Comments
			24 ≤ IOP ≤ 36	netarsudil 0.02% QD (72)	25.6	−5.9	−5.7	57%			inferiority to latanoprost. Eyes with baseline IOP ≤ 26 mm Hg did meet those criteria
				latanoprost 0.005% QD (77)	25.5	−7.6	−6.8	16% increased lacrimation (5–7%) and CH (5–6%) also observed with netarsudil			
ROCKET-1 Netarsudil Phase 3 Serle et al (2017)	Multicenter RCT Double-masked	3 months	POAG (66%) OHT (34%)		Mean diurnal IOP	Change from baseline (diurnal range)		CH	HEM	VER	Netarsudil did not meet the non-inferiority criteria.
			20<IOP < 27 at 8 AM and	netarsudil 0.02% QD (202)	22.5	−3.3 to −5.0		53 %	13%	5%	
			17< IOP < 27 at 10	timolol 0.5% BID (209)	22.3	−3.7 to −5.1		7%	0.5 %	0%	

Study	Study Design	Duration of Treatment	Diagnosis and Baseline IOP Inclusion Range (mmHg)	Drugs (number of subjects)	Baseline IOP mmHg (SD)	Efficacy mmHg (SD)	Frequent Adverse Events			Comments
			AM & 4 PM							
ROCKET-2 Netarsudil Phase3 Serle et al (2017)	Multicenter RCT Double-masked	3-month Interim data reported for the 12-month trial	POAG (66%) OHT (34%)		Mean diurnal IOP*	Change from baseline (diurnal range)* *Primary efficacy population (maximum baseline IOP < 25 mmHg)	CH	HEM	VER	Netarsudil QD & BID met non-inferiority criteria in the primary efficacy population
			20< IOP < 27* at 8 AM and	netarsudil 0.02% QD (251)	21.4	−3.3 to −4.6	50 %	15%	9%	
			17< IOP < 27* at 10 AM and 4 PM	netarsudil 0.02% BID (254)	21.5	−4.1 to −5.4	59 %	17%	15%	
				timolol 0.5% BID (251)	21.5	−3.7 to −5.1	10 %	0%	0.4 %	
Fixed Combina	Multicenter	28 days	POAG (56%)		Mean diurnal IOP	Mean diurnal IOP	CH			Fixed combina-

Study	Study Design	Duration of Treatment	Diagnosis and Baseline IOP Inclusion Range (mmHg)	Drugs (number of subjects)	Baseline IOP mmHg (SD)	Efficacy mmHg (SD)	Frequent Adverse Events	Comments
tion netarsudil and latanoprost (PG324) Phase 2 Lewis et al (2016)	RCT Double-masked		OHT (44%)					tion formulations superior to latanoprost and netarsudil
			24≤ IOP < 36 at 8 AM and	latanoprost – netarsudil 0.01% QD (74)	25.1 (2.3)	17.3 (2.8)	41%	
			IOP ≥ 21 at 10 AM and 4 PM	latanoprost – netarsudil 0.02% QD (73)	25.1 (2.4)	16.5 (2.6)	40%	
				latanoprost QD (73)	26.0 (2.8)	18.4 (2.6)	14%	
				netarsudil 0.02% (78)	25.4 (2.7)	19.1 (3.2)	40%	

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