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Topical treatment of glaucoma: established and emerging pharmacology

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Abstract

Introduction—Glaucoma is a collection of optic neuropathies consisting of retinal ganglion cell death and corresponding visual field loss. Glaucoma is the leading cause of irreversible vision loss worldwide and is forecasted to precipitously increase in prevalence in the coming decades. Current treatment options aim to lower intraocular pressure (IOP) via topical or oral therapy, laser treatment to the trabecular meshwork or ciliary body, and incisional surgery. Despite increasing use of trabecular laser therapy, topical therapy remains first-line in the treatment of most forms of glaucoma.

Areas covered: Novel glaucoma therapies are a long-standing focus of investigational study. More than two decades have passed since the last United States Food and Drug Administration (FDA) approval of a topical glaucoma drug. Here, the authors review established topical glaucoma drops as well as those currently in FDA phase 2 and 3 clinical trial, nearing clinical use.

Expert opinion: Current investigational glaucoma drugs lower IOP, mainly through enhanced trabecular meshwork outflow. Although few emerging therapies show evidence of retinal ganglion cell and optic nerve neuroprotection in animal models, emerging drugs are focused on lowering IOP, similar to established medicines.

Keywords

Adenosine Receptor; Neuroprotection; Norepinephrine Transporter Inhibitor; Nitrous oxide; Primary Open Angle Glaucoma; Rho-associated Protein Kinase Inhibitor; Ribonucleic Acid Interference; Trabecular Meshwork; Uveoscleral Outflow

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1. Introduction

Glaucoma is a collection of optic neuropathies consisting of retinal ganglion cell (RGC) and axonal death with corresponding visual field loss. Many forms of glaucoma exist, with unique pathophysiologies and targets for treatment. Glaucoma currently remains the leading cause of irreversible vision loss worldwide, and its global prevalence is forecasted to sharply rise in the coming years; when all forms are considered, prevalence in 40–80 year-olds is estimated to increase from 76 million in 2020 to 111.8 million in 2040 [1]. Primary-open angle glaucoma (POAG), the most common type of glaucoma, was estimated to afflict 57.5 million individuals in 2015. 65.5 million are to be affected by 2020, [2] with 5.9 million having bilateral blindness [3].

Many risk factors for POAG development have been found, including elevated intraocular pressure (IOP), advanced age, family history, African-American race, axial myopia, thin central corneal thickness, and low cerebrospinal fluid pressure [4]. However, other factors likely exist. Altered retinal vascular autoregulation, oxidative stress and free radical formation, alteration in local cytokines, RGC glutamate stimulation, aberrant local immunity [4], irregular optic nerve perfusion [5], or inadequate drainage and exchange of waste products and neurotoxins along optic nerve glymphatic pathways [6] have all been implicated. To date, elevated IOP is the only clinically modifiable target in glaucoma prevention and treatment, and it remains the sole target of current glaucoma therapy.

Treatment options aimed at lowering IOP include topical therapy, oral therapy, laser treatment to the trabecular meshwork (TM) or ciliary body, and incisional surgery. Clinical decision-making and treatment algorithms are often multifactorial and depend on disease severity, rapidity of progression, treatment side effect profile, and patient preference. Although laser treatment of the TM is gaining in popularity as effective first-line therapy in ocular hypertension (OHTN) or mild to moderate forms of open-angle glaucoma [7–9], topical monotherapy largely remains first-line treatment for most forms of glaucoma.

As the rise in glaucoma prevalence looms, new therapy continues to be a focus of investigational study. Two decades have passed since the United States Federal Drug Administration (FDA) last approved a topical agent for OHTN and glaucoma (Table 1), and many drugs are currently in preclinical and clinical study. Here, the authors review established topical pharmacologics available in the United States as well as active agents with completed FDA Phase 2 or 3 study, nearing clinical use.

2. Established Topical Monotherapy Agents

Topical glaucoma therapy has its roots loosely intertwined the calabar bean, a natural source of the parasympathomimetic physostigmine, native to the Calabar river delta of Nigeria and Cameroon. In the 1800s, natives used it as a judiciary ritual in cases of alleged crime. Accused individuals were forced to ingest potentially lethal amounts of the bean, leaving survivors to be deemed innocent [10]. European missionaries in the area witnessed the ritual and the bean was ultimately brought back to Europe for scientific study. In 1863, Scottish ophthalmologist Argyll Robertson published on the miotic effects of the bean extract. [11].

Shortly thereafter it was utilized in filtering surgery, and by 1877 its IOP-lowering effects were discovered [12–13].

2.1 Parasympathomimetics

Parasympathomimetic agents lead muscarinic receptor activation by increasing levels of acetylcholine via cholinesterase inhibition (ecothiopate, carbachol), or by direct receptor agonism (pilocarpine, carbachol). Within the ciliary body, muscarinic activation leads to muscle contraction and increased tension of the scleral spur, facilitating aqueous outflow through filtering TM.

Although this drug class is beneficial in certain forms of glaucoma, its adverse effect profile, especially in phakic individuals, often limits its use. Ocular side effects include pupillary miosis, refractive myopia, cataract formation, accommodative spasm and brow ache, iridocorneal angle closure, dampening of the blood-ocular-barrier, and rhegmatogenous retinal detachment. Systemic side effects include vomiting, nausea, diarrhea, tachycardia, bronchospasm, sweating, and change in mentation [14].

2.1.1 Indirect Parasympathomimetics: *Ecothiopate (currently available in 0.125% solution)*—Despite use in aphakic or pseudophakic individuals with certain forms of glaucoma, indirect acting parasympathomimetics are used sparingly due to their high side effect profile. Unique ocular side effects of the indirect-acting agents include iris cyst formation. Formulations are preserved with the alcohol chlorbutanol.

2.1.2 Direct Parasympathomimetic: *Pilocarpine (1%, 2%, 4%)*—The most commonly used parasympathomimetic drug, pilocarpine, is a direct-acting muscarinic agonist. IOP reduction from pilocarpine has been estimated around 20–30% [15], with a dose-dependent effect [16].

2.1.3 Mixed direct and indirect parasympathomimetic: *Carbachol (1.5%, 3%)*—Carbachol works by direct muscarinic receptors agonism as well as inhibition of cholinesterase [14]. Its IOP effect is stronger than that of pilocarpine; however, its local and systemic side effect profile is also more potent, limiting its use. Further, carbachol is very hydrophilic, preventing adequate topical penetration with an intact corneal epithelium [17].

2.2 Sympathomimetics

In 1901, experimental studies of adrenal gland extracts led to the eventual discovery of the second oldest class of IOP lowering agents- sympathomimetics. However, it took another 50 years from its discovery for epinephrine to be commercially available for topical use [12].

Sympathomimetics activate α_1 , α_2 and β_2 receptors within the eye leading to lowering of IOP through various mechanisms, which have not been fully clarified. α_1 receptors within the pars plicata lead to vasoconstriction and decreased aqueous production. β_2 receptors within the TM [18] and ciliary body [14] lead to increased outflow. Inhibitory presynaptic α_2 receptors negatively regulate overall catecholamine state.

2.2.1 Non-selective sympathomimetics: *Phenylephrine (2.5%, 10%)*—

Phenylephrine stimulates α_1 , α_2 , as well as β_2 -adrenoceptors. The drug causes a dose-dependent decrease in anterior uveal blood flow [17], however aqueous production has been shown to rise for a few hours after instillation [14]. Twice daily dosing can lower IOP by 15–25% in most patients [14], however up to a third do not get IOP lowering effects [17]. Clinical use is limited by high rates tachyphylaxis and many adverse side effects including pupillary mydriasis and visual blur, follicular conjunctivitis, cystoid macular edema, adrenochrome deposits of the conjunctiva, lacrimal punctal stenosis, and increased risk of pupillary block and acute angle-closure glaucoma. Systemic effects include hypertension, tachycardia, cardiac arrhythmia, tremor, and anxiety.

2.2.2 Selective Sympathomimetics

2.2.2.1 α_1 , α_2 Selective: *Apraclonidine (0.5%, 1%)*: In the 1950s, clonidine was discovered and utilized for its systemic hypotensive properties. Its topical use as an IOP lowering agent was limited due to its high lipophilicity and crossing of the blood-brain barrier, with secondary systemic hypotension; it was also found to worsen visual field loss in glaucomatous patients [14]. Less lipophilic alternatives were investigated, and with the addition of an amide group apraclonidine was developed. Apraclonidine's vasoconstrictive effects and possible prevention of intraocular hemorrhagic with laser iridotomy procedures was studied, [19] showing that it actually prevented IOP spikes and lowered intraocular pressure. In 1987, it was FDA approved for prevention of post laser IOP spikes, and by 1993 it was formulated for short-term IOP control [12]. Despite estimates of IOP reduction around 20% [20,21], high rates of tachyphylaxis have limited its long-term clinical use in glaucoma treatment. Further, its potential systemic hypotensive effects may prevent its use in cardiovascular patients [17].

2.2.2.2 α_2 Selective: *Brimonidine (0.15%, 0.2%)*: In 1996 brimonidine was developed and approved for management of OHTN [12]. A quinoxaline double-ring differentiates this drug from clonidine and apraclonidine, perhaps accounting for its thousand fold selectivity for α_2 receptors than α_1 [17]. Furthermore, brimonidine is more lipophilic than apraclonidine, allowing lower concentration formulations and less class-specific local side effects including allergic blepharoconjunctivitis. Studies have shown up to 20–27% reduction in IOP [22–24] via reduction of aqueous production [14] and enhancement of uveoscleral outflow [25, 26]. Peak effects occur 2 hours after drop instillation, with a trough 12 hours after instillation [26]. Importantly, effects are lessened overnight, similar to timolol (see section 1.3.1), although with slightly improved trough IOP than timolol [14].

Of note, compared with clonidine and apraclonidine, it does not seem to negatively affect ocular perfusion pressure or visual field indices [17]. Animal models have suggested neuroprotective effects [27,28], however this has yet to be substantiated in humans.

The most significant local adverse reaction is allergic blepharoconjunctivitis, while systemic effects most commonly include dry mouth and dry nose [14, 26]. It is contraindicated in patients on monoamine oxidase inhibitors as well as in young children [17], as its

lipophilicity may allow it to cross the blood-brain-barrier and cause central nervous system depression.

Lower dose trade formulations exist with the preservative Purite® (Allergan, Inc), as a preservative alternative to benzalkonium chloride, commonly employed in topical glaucoma therapy. Purite® is a sodium chlorite complex that degrades to chloride ions and water upon exposure to ultraviolet light.

2.3 Sympatholytics (beta blockers)

Propranolol, the first systemic beta-blocker, was found to have IOP lowering in studies of intravenous administration [29]. However, development as a topical agent was thwarted due to deleterious corneal side effects [12]. Other agents were subsequently developed but similarly limited by local side effects. Timoptic®, FDA approved in 1978, showed a more tolerable side effect profile with IOP lowering upwards of 35% [30–33].

Beta-blockers reduce aqueous production [34], however the mechanism through which this is achieved is not well known. It has been suggested that inhibition of β_2 receptors and downregulation of adenylate cyclase in the ciliary processes may be involved.

2.3.1 Non-selective sympatholytics: *Timolol (0.25%, 0.5%), levobunolol (0.25%, 0.5%), metipranolol (0.3%), carteolol (1%)*—Timolol and other non-selective beta-receptor blocking agents inhibit both β_1 and β_2 receptors. They are dosed once or twice daily, however their overnight IOP lowering ability have been shown to be blunted in healthy individuals [35]. Preservative free formulations are available.

Local side effects of this class include conjunctival hyperemia, ocular surface discomfort, reduction in tear flow and worsening of dry eye. Systemic side effects include bradycardia, heart block, and arrhythmia, bronchospasm and worsening of underlying asthma or chronic obstructive pulmonary disease. Further, this class of drug can lead to worsening of myasthenic symptoms, masking of hypoglycemic symptoms in patients with diabetes mellitus, alterations in cholesterol profiles, and may lead to anxiety, depression, impotence, and fatigue [14].

Levobunolol has similar effectiveness and side effect profile as timolol [14].

Metipranolol has been reported to cause corneal anesthesia. Furthermore, various reports of a granulomatous anterior uveitis have been reported with long-term use [14]. Still, the drug has comparable IOP lowering effects to timolol 0.25 and 0.5% and levobunolol 0.5%. It has also shown to possess powerful antioxidant properties [17].

Although a non-selective β -adrenergic blocker, carteolol has been shown to have sympathomimetic activity through partial β receptor agonism. It has also been shown to have less effect on systemic lipid profile than timolol [36]. Still, its use is limited in patients with cardiopulmonary insufficiency [14].

2.3.2 Selective sympatholytics: *Betaxolol (0.25%, 0.5%)*—Betaxolol is a selective β_1 blocker, allowing less respiratory side effects. It has also been found to have less cardiovascular side effects, perhaps from high protein binding affinity in the plasma [14].

IOP lowering is estimated to be 18–26%, less than that of timolol [37–40]. Although it also reduces aqueous production [41], its exact mechanism of action is unknown. As there is a paucity of β_1 receptors within the ciliary body, it has been posited that betaxolol contains weak β_2 antagonism [14].

Of note, studies of betaxolol in normal patients as well as those with normal tension glaucoma have shown improvements in ocular blood flow and visual function in both groups, suggesting a neuroprotective effect [17].

2.4 Carbonic Anhydrase Inhibitors: *Dorzolamide (2%), Brinzolamide (1%)*

Sulfonamide drugs were discovered in the late 1930s and utilized for antibacterial and diuretic purposes. By the 1950s, the sulfonamide-derived acetazolamide was discovered [12] and found to also have IOP lowering effect [42]. Acetazolamide's inhibition of carbonic anhydrase, an enzyme that catalyzes the hydration of carbon dioxide, decreases aqueous production from active filtration in the non-pigmented epithelium of the pars plicata, where carbonic anhydrase isozyme II is present in large quantities [43].

Despite its acetazolamide's effectivity via systemic administration, topical formulations were ineffective at lowering IOP, and for the next few decades testing of multiple topical carbonic anhydrase inhibitor agents similarly failed. After over 1,000 candidate molecules were studied this search was nearly abandoned, until Trusopt® gained FDA approval in 1995, followed by Azopt® shortly thereafter [12].

Dorzolamide and brinzolamide have IOP reductions in the 20% range, with synergistic effect with most other classes of topical antihypertensive agents [14, 43]. Peak effect occurs at 2 hours after instillation with trough at 8 hours; importantly, the possibility for 24-hour IOP lowering effect makes it a good adjunctive therapy in many patients [44]. In addition, these agents have shown to improve ocular blood flow [43].

Ocular side effects include stinging, burning, itching, rarely blepharoconjunctivitis [14], and altered corneal endothelial function [45]. Ocular surface discomfort has been found to occur less commonly with Brinzolamide.

2.5 Prostaglandin Analogues: *Latanoprost (0.005%), travoprost (0.004%), bimatoprost (0.01%, 0.03%), tafluprost (0.0015%)*

While studying mediators of ocular inflammation, researchers found that prostaglandins, lipophilic derivatives of arachidonic acid, were found to have IOP-lowering effect [14]. Of the naturally occurring D2, E2, F2 α , I2 and thromboxane A2 prostaglandins, E2 and F2 α have shown high expression in ocular tissues [43]. In 1982 the first topical prostaglandin F2 α receptor agonist, latanoprost, was developed. It ultimately gained FDA approval in 1996 [12]. Latanoprost and others in this class reduce intraocular pressure via alterations to uveoscleral outflow, although its exact mechanism is unknown. It is thought that stimulation

of prostanoid receptors within the ciliary body relaxes the muscle and stimulates matrix metalloproteinases proteins that remodel extracellular matrix between muscle fibers [46], lowering resistance to aqueous flow [35]. Latanoprost studies have found up to 39% reduction in IOP [46–48] with 24-hour coverage via daily dosing [49, 50]. It has been suggested that administration at night offers slightly better efficacy [51].

Ocular side effects for prostaglandins include conjunctival hyperemia, ocular surface discomfort, increased iris pigmentation, periorbital skin hyperpigmentation, orbital fat atrophy, hypertrichosis, anterior uveitis, reactivation of herpetic keratitis, and cystoid macular edema in pseudophakic patients with a history of existing maculopathy or complicated cataract surgery [14, 36]. Systemic side effects are infrequent and may include headache or upper respiratory symptoms [36].

Travoprost exhibits full agonism at prostaglandin F2 α receptor, unlike others prostaglandins which exhibit partial agonism [36, 43]. Further, its molecular stability does not require refrigeration prior to use [36].

Trade formulations of travoprost exist with the preservative SofZia[®] (Alcon Laboratories, Inc), marketed as a less irritating antimicrobial ionic solution containing zinc, borate, propylene glycol and sorbitol.

Tafluprost is a preservative free prostaglandin with similar efficacy to others in this class.

Bimatoprost contains a unique amide group and is often referred to as a prostamide; it is unclear whether this compound is hydrolyzed by corneal esterases like other prostaglandins or passes unaltered, activating a different receptor than prostaglandin F2 α analogues [36,43]. There is suggestion that non-responders to latanoprost may show effectivity with bimatoprost [43]. Bimatoprost lowers IOP via enhanced uveoscleral outflow, as well as increased filtration via TM. It is a stable compound that does not require refrigeration prior to use [36].

3. Investigational Agents

In adults, a large majority of aqueous humor outflow is dependent on percolation through the filtering TM, a porous structure composed of interlaced collagen fibrils, endothelial-like cells, and extracellular matrix. Beyond the TM, flow continues into Schlemm's canal (SC) and then into collector channels and episcleral veins, ultimately draining into the central venous system. Resistance to flow through this pathway is encountered at many points. Cells within the TM possess smooth muscle-like function and may relax and contract with stimulation, allowing regulation to aqueous flow [52]. Trabecular cellular density, cell-cell adhesions and rate of formation of extracellular matrix also create resistance. Importantly, resistance to outflow may also occur in SC, collector channels, and beyond.

As will be described, many current investigational agents target trabecular outflow as a complement to established pharmacologics that reduce aqueous formation or enhance uveoscleral outflow (flow through ciliary muscle and into the supraciliary and suprachoidal

space, with eventual drainage into the choroid or through the sclera via emissary channels and simple diffusion).

3.1 Nitrous Oxide Agents

3.1.1 Latanoprostene bunod (Bausch and Lomb/ NicOx), formerly BOL-303259-X.

Current Status: Completion of Phase 3 Study: Latanoprostene bunod (LBN) is a combination compound of latanoprost and butanediol mononitrate, a nitric oxide (NO) donating molecule. NO is a short-lived, soluble gas normally created through conversion of L-arginine to L-citrulline, with further conversion to NO and citrulline by nitrous oxide synthase (NOS). In the early 1900s, investigations of systemic NO agents in humans reported secondary increases in IOP. When NO agents later gained attention for their vasodilatory properties and benefits in coronary disease, its ocular effects were again revisited. In the 1970s, systemic NO agents were shown to conversely lower IOP [53]. By the 1990s, topical NO agents were created and shown to have IOP lowering efficacy in animal studies [54–56] and human volunteers [52].

NO mediates multiple tissue responses in the eye via guanylate cyclase and cyclic GMP pathways. NO and NOS have been found in human TM, SC, ciliary body and various retinal layers and vasculature [57–59]. Therefore, they are posited to play an important role ocular homeostasis and IOP control. Within the TM, NO alters actin cytoskeletons and actomyosin contractility, allowing decreased resistance to aqueous outflow within the TM and inner wall of SC [60]. In animal studies, NO has also been shown to relax ciliary muscle [59].

Alterations in NO have been implicated in the development of POAG [61]. NOS activity has been found to be reduced in TM, SC, and ciliary muscle in human eyes with POAG [62], and lower levels of NO end products and cyclic GMP have been found in the aqueous humor in POAG [63].

In a 2005 study of rabbits with OHTN induced from intravitreal injection of saline, Orihashi and colleagues reported on the hypotensive effects of topical nitroprusside, a NO-releasing compound, and nipradilol, a β -adrenergic antagonist with weak α .1 blocking ability and NO releasing ability. Latanoprost monotherapy and combinations of the agents were also studied for comparison. Both nitroprusside and nipradilol lowered IOP in ocular normotensive and hypertensive rabbits, however the effect was enhanced when combined with latanoprost [64].

In 2009, a study of prostanoid FP-receptor knockout mice showed effectiveness of a combination NO-latanoprost agent but not latanoprost alone, showing NO's unilateral effectiveness, even formulated with a prostaglandin analogue [65]. In 2010 [57] and 2011 [66], combined NO donating and prostaglandin topical drugs were reported to have more effective IOP lowering than prostaglandin alone in rabbit, dog, and non-human primate models.

In 2011, BOL-303259-X reported similar effects in these animal models [61]. Cynomolgus monkeys with unilateral OHTN created via photocoagulative destruction of the TM were

given BOL-303259-X or vehicle, followed by the alternative 3 days later. BOL-303259-X was studied at doses of 0.012%, 0.030%, and 0.12%. A dose depending IOP decrease was found, with 35% reduction from baseline with 0.12% drug. In contrast, latanoprost 0.1% was only able to lowering IOP by 25.8%. Beagles with naturally occurring POAG were analyzed and randomly assigned to 0.036% BOL-303259-X versus vehicle, with IOP measurements taken up to 6 hours after administration. IOP decreased from baseline by 44% with BOL-303259-X, versus equimolar latanoprost which reduced IOP by 27%. Finally, 0.036% BOL-303259-X or equimolar 0.030% latanoprost was studied in New Zealand rabbits with OHTN created by intravitreal injection of saline. BOL-303259-X was able to dull the hypertensive effects of saline injection, with a maximal 30% mean reduction between 0.5 and 1.5 hours after injection; latanoprost was unable to blunt the induced OHTN.

In 2014, study of human TM cell contractility revealed enhanced relaxation with LBN versus latanoprost [67].

In 2015 and 2016, multiple phase 2 and phase 3 clinical trials of LBN were completed (Table 2). In a Phase 2 randomized trial of 413 patients with open-angle glaucoma or OHTN, 0.024% LBN was shown to have mean diurnal IOP lowering of 9 mm Hg versus 7.8 with latanoprost 0.005% [60]. A prospective, multicenter, randomized Phase 3 trial of 0.024% LBN evening dosing and timolol 0.5% twice daily dosing showed IOP reduction of >25% from baseline or < 18 mm Hg in 31% and 17.7% of LBN patients, compared to 18.5% and 11.1% in timolol patients [68]. Another multicenter, randomized Phase 3 trial similarly compared LBN and timolol. Mean diurnal IOP was significantly lower in the LBN 0.024% patients compared with timolol 0.5% (18.2 mmHg vs. 19.5 at week 2; 18.1 vs. 19.3 mmHg at week 6; 18.2 vs. 19.4 mmHg at month 3). At all study time points, the percentage of subjects with mean IOP <18 mmHg was significantly higher in the LBN group (22.9% vs. 11.3%), similar to IOP reduction >25% from baseline (34.9% in LBN vs. 19.5% timolol) [69].

In a single arm, multi-center open label study by Kawase et al. [70], LBN 0.024% was administered once daily in the evening for 52 weeks, in Japanese subjects over age 20 with open-angle glaucoma or OHTN. Mean IOP reduction of 22.0% from baseline was achieved by week 4 in study eyes and maintained through week 52.

The ocular side effect profile of LBN appears similar to prostaglandins and includes conjunctival hyperemia, hypertrichosis, ocular irritation, punctate keratitis, foreign body sensation, ocular pain or photophobia.

3.2 RHO-associated Protein Kinase Inhibitors

In 1954, investigation of biological functions of normal and neoplastic tissue led to the discovery of kinases, enzymes that transfer the terminal phosphate from adenosine triphosphate (ATP) to substrate [71]. Within the human genome, over 500 protein kinases have been mapped.

A subgroup of the Ras superfamily of guanosine triphosphate binding proteins, Rho are small signaling proteins involved in cell proliferation, apoptosis, and motility and are activated by many molecules including endothelin-I, thrombin, angiotensin II, transforming growth factor- β , interleukin-1, and cytokines [72, 73]. In 1996, two types of Rho effector molecules were discovered in the human body- Rho-associated protein kinase (ROCK) 1 and ROCK 2 [74].

ROCK activation and its downstream effector molecules lead to alterations of cellular growth, shape, apoptosis, migration, adhesion, as well as smooth muscle contraction via calcium sensitization and actin cytoskeletal organization [73]. ROCK-mediated pathways have also been found to negatively regulate endothelial NO and NOS levels throughout the body. Given their protean effects, ROCKs have been implicated in multiple pathophysiologic processes encompassing angiogenesis and vascular remodeling, hypertension, kidney disease, cerebral ischemia, myocardial remodeling, erectile dysfunction, and pulmonary hypertension [73, 75]. As such, inhibition of Rho and ROCK-mediated pathways has garnered significant pharmaceutical interest.

Within the eye, ROCK expression has been found in TM, SC, ciliary muscle, and the optic nerve head [75, 76]. Animal studies in the 1970s through the 1990s led to the development of a nonspecific kinase inhibitor that improved aqueous outflow in monkeys [76]. Eventually, a specific ROCK inhibitor, Y-27632, was developed and tested in normotensive rabbits in 2001, showing IOP lowering via topical [77, 78], intracameral and intravitreal application [77]. Since then, Y-27632 and other Rho-kinase agents (H-1152, HA-1077) have been tested in various normotensive, ocular hypertensive and glaucoma animal models, showing significant improvements in aqueous outflow and IOP reduction [79–83]. A light microscopy study by Gong and Yang [52] showed monkey eyes perfused with Y-27632 had separation between the inner wall of TM and SC and separation between cells of SC and associated their extracellular matrix, perhaps explaining the mechanism of increased aqueous outflow.

Of great interest, animal studies of ROCK inhibitors have reported benefits in glaucoma treatment other than IOP reduction [73]. Studies of topical Y-39983 [83] and intravenous and topical Fasudil® (Asahi Kase Corporation) [84] in rabbits have shown improvements in optic nerve head blood flow. Intravitreal injections of Fasudil [85] and Y-39983 [83] in rats have shown protection against glutamate-related excitotoxicity in RGCs as well as regeneration of axons; injection of Y-39983 has similarly shown axonal regeneration in crushed optic nerve heads of cats [86]. Y-27632, when injected intravitreally within three hours of induced retinal ischemia in rats, has shown decreased apoptosis of RGCs and attenuated leukocyte infiltration and endothelial dysfunction compared to controls [87].

In studies of human TM and SC cells, application of Y-27632 was shown to alter cellular morphology, cell-to-cell adhesions, and actomyosin morphology, suggesting the improvement in trabecular outflow [77, 82] seen in animal models. Furthermore, Y-27632 has been thought to drop resistance between the inner wall of TM and SC via alterations in pore density and size within SC cells and adjacent spaces [52].

3.2.1 Ripasudil, manufactured by Kowa; formerly, K-115

Current Status: Completion of Phase 3 Study: Ripasudil is a fluorinated derivative of fasudil, a systemic ROCK inhibitor marketed for cerebral vasospasm and ischemia. Initial reports of the IOP lowering effects of K-115 in monkeys and rabbits in 2007 and 2008 led to increased study, showing short-lived (3 hour) dose-dependent IOP lowering in rabbits via increased trabecular outflow, with IOP levels close to episcleral venous pressures. In monkeys, IOP lowering occurred to a lesser degree, however its effects were more potent than 0.005% latanoprost and with equivalent duration of action [88].

In 2013, a Phase 1 clinical trial in 50 healthy Japanese male volunteers with 0.05%, 0.1%, 0.2%, 0.4% or 0.8% K-115 at daily or twice daily dosing showed IOP lowering up to 4.3 mm Hg with 0.8% dosed daily (peak effect 1–2 hours after instillation)[89]. A follow up Phase 2 trial of 210 patients (Table 3) also revealed dose-dependent IOP lowering up to 4.5 mm Hg two hours after instillation with 0.4%. IOP lowering effects were still found 8 hours after administration [90].

An open-label investigation of twice daily 0.2%, 0.4% K-115 and placebo in 28 patients with OHTN and open-angle glaucoma showed IOP lowering of 6.8, 7.3 and 4.1 mm Hg respectively 2 hours after the second instillation, with a similar a trend up to 7 hours after instillation [91]. 0.4% K-115 was later studied in phase 3 randomized trials (Table 3), in patients already on latanoprost 0.005% and timolol 0.5%. Effective IOP lowering in both groups was seen [92]. In a retrospective review of patients with multiple forms of glaucoma on medical therapy, including maximal medical therapy, benefit was again shown with the addition of 0.4% ripasudil (up to 17% further reduction in POAG patients) [93].

Transient conjunctival hyperemia, hypothesized to be secondary to vasodilation from smooth muscle relaxation, was commonly seen in patients. Less commonly found was follicular conjunctivitis, eye irritation, blurred vision and punctate keratitis. Rarely, pharyngitis, laryngopharyngitis, and altered blood and liver laboratory studies were reported [89].

3.2.2 SNJ-1656, manufactured by Novartis AG/Senju Pharmaceutical Company; formerly Y-39983

Current Status: Completion of Phase 2 Study: Topical Y-39983, a selective, potent ROCK inhibitor, showed increase in animal trabecular outflow (65.5% in rabbits) with a dose dependent reduction in IOP up to 13 mm Hg in rabbits and 2.5 mm Hg in monkeys [83].

In phase 1 study of 45 healthy Japanese males, SNJ-1656 concentrations of 0.003%, 0.01%, 0.03%, 0.05% and 0.1% were tested against placebo. After single instillation, dose-dependent reductions in IOP were seen up to 3 mm Hg with 0.1% drug at 4 hours (versus 0.63 mm Hg with placebo). Repeated instillation of drug also showed IOP reduction [94].

In multicenter, randomized, Phase 2 testing, 63 adult subjects with OHTN or POAG were randomized to placebo or 0.03%, 0.05% or 0.1% twice-daily drug for 7 days. Two hours after final instillation, IOP was lowered in all groups by 1.5, 5, 4.4, and 4.5 mm Hg, respectively, highlighting similar IOP lowering at any drug concentration tested. Commonly

cited side effects included conjunctival hyperemia, while punctate keratitis was rare. One patient was noted to have mild hepatic dysfunction after 0.05% drug instillation [95].

3.2.3 Verusodil, manufactured by Aerie; formerly AR-12286. Precursor to AR-13324 (Section 2.3.1)

Current Status: Completion of Phase 2 Study: A 2009 study of the Rho-kinase inhibitor AR-12286 in monkeys revealed IOP lowering effect via enhanced trabecular outflow. By 2011, a Phase 2a study of AR-12286 in patients with OHTN and glaucoma revealed significant IOP lowering at doses of 0.05%, 0.1%, and 0.25% when compared to vehicle, with maximum mean lowering up to 28% with 0.25% twice daily dosing (Table 3) [96]. Continued pharmacological study led to development of AR-12286 in new vehicle media with increased stability, which was tested in a Phase 1 double-masked single-center randomized a study of 18 normal human volunteers. Healthy subjects with baseline IOP 14–20 mm Hg were given 0.5% drug in newer versus older formulation. Both formulations led to reductions in IOP from baseline ranging from 3 to 7 mm Hg, with the newer formulation reducing mean IOP by 42 % at peak (4 hour) and 20% at trough (24 hour) [97].

When studied in patients in OHTN, open-angle and pseudoexfoliation and pseudoexfoliation patients in a prospective, double-masked randomized trial, 0.5% and 0.7% AR-12286 were shown to be similarly effective, approximately reducing IOP 30% from baseline [98].

The most commonly cited side effects included transient mild to moderate ocular and conjunctival hyperemia (secondary to vascular smooth muscle vasodilation). Rarely, eye irritation, pain, swelling, increased lacrimation and transient visual blur were reported. Systemic side effects were rarely reported and included gastrointestinal disorders, abdominal pain, neck pain, headache, dry throat, oropharyngeal pain, and pruritus [97].

3.3 RHO-associated Protein Kinase Inhibitors / Norepinephrine Transporter (NET) Inhibitor

After discovery of AR-12286, other derivatives were investigated to find an effective agent with longer IOP-lowering effect and more effective once daily dosing. Some agents were also found to also have inhibitory activity against the norepinephrine transporter (NET) [99]. NET inhibition blocks reuptake of norepinephrine at adrenergic synapses and is hypothesized to reduce aqueous production via mechanisms similar to the sympathomimetics (see section 1.2), namely activation of presynaptic α_2 receptors and α_1 activation within the ciliary body, leading to vasoconstriction and reduced aqueous formation.

3.3.1 Netarsudil, manufactured by Aerie; formerly AR-13324

Current Status: Completion of Phase 2 Study: When studied in 7 normotensive monkeys, AR-13324 was found to have significant IOP lowering effect (25% reduction) from enhanced conventional aqueous outflow as well as reduced aqueous production [100]. To further investigate mechanisms of IOP lowering, AR-13324 was studied in a rabbit model, showing significant lowering of episcleral venous pressure as well, accounting for 42% of the total IOP lowering effect [101].

Initial tests of 0.01% to 0.04% AR-13324 in humans showed significant IOP reductions lasting 24 hours; the 0.02% concentration appeared to reach peak dose response. A phase 2b non-inferiority study was subsequently created to investigate IOP lowering of daily 0.01% and 0.02% AR-13324 versus 0.005% latanoprost in adults with OHTN or POAG (Table 3). On day 28 of the trial, mean diurnal IOP was reduced in all 3 groups (−5.5, −5.7, and −6.8 mmHg for 0.01%, 0.02% AR-13324 and latanoprost groups, respectively), and AR-13324 did not meet non-inferiority criteria against latanoprost. Despite potential vasoconstrictive effects from NET inhibition, mild to moderate conjunctival hyperemia was the most cited in around 50% of patients [102].

A double-masked study of fixed combination of 0.01% and 0.02% AR-13324 and 0.005% latanoprost (PG324) were evaluated to see if complimentary actions of each drug could further enhance IOP lowering. 292 patients with OHTN or POAG were randomized to the above combination drugs, or 0.02% AR-13324 or 0.005% latanoprost monotherapy and followed for 28 days. At the end of the study, mean diurnal IOP decreased 7.8 mm Hg with 0.01% PG324, 8.6 with 0.02% PG234, 7.6 with 0.005% latanoprost and 6.3 with 0.02% AR-13324. Both 0.01% and 0.02% PG234 met superiority criteria over latanoprost or AR-13324. Similar to other ROCK inhibitors and latanoprost, mild to moderate conjunctival hyperemia was the most commonly cited side effect and occurred in approximately 40% of PG234 patients [103].

Of importance, similar to the aforementioned neuroprotective findings of Rho and ROCK inhibitors, AR-13324 was also found to have protective and regenerative effects on RGCs and axons when applied topically in rat studies with optic nerve crush injury [104].

3.4 Adenosine Receptor Agents

Adenosine is a purine nucleoside that is involved with nucleic acid and ATP synthesis [105]. It can also directly stimulate many cellular receptors throughout the body. Four subtypes of adenosine receptors have been discovered: A₁, A_{2A}, A_{2B}, and A₃. All adenosine receptors modulate signaling via G protein-coupled pathways, however differences exist. A₁ and A₃ subtypes inhibit adenylyl cyclase and decrease cyclic AMP levels, whereas A_{2A} and A_{2B} conversely activate adenylyl cyclase and increase cyclic AMP levels. Phospholipase C, calcium, mitogen-activated protein kinase and other pathways are also involved with adenosine signaling [106].

Creation of adenosine occurs with intracellular formation and subsequent transmembrane transport into the extracellular space, as well as by extracellular formation from multiple pathways. In the TM, for instance, ATP can be dephosphorylated to adenosine monophosphate (AMP), which is further metabolized into adenosine. Once created, adenosine can be rapidly phosphorylated back into AMP or it can be metabolized into inosine and hypoxanthine. As it is an unstable compound with a half-life of approximately 1.5 seconds, adenosine primarily functions as a paracrine and autocrine modulator.

Tissue concentrations of adenosine are in a constant state of flux and are sensitive to levels of oxygenation. Receptor binding affinities are also in constant flux. Under physiology conditions, A₁ and A₃ receptors are moderately active while A_{2A} is less so. A_{2B} receptors

are typically activated with pathologically increased levels of adenosine [107]. Of interest in glaucoma, A₃ has been shown to be upregulated in states of hypoxia, oxidative stress and in pseudoexfoliation syndrome, a cause of secondary open angle glaucoma [108]. Thus, depending on the tissue and physiologic status, basal stimulation of the four types of adenosine receptors vary [106].

Physiologic effects of adenosine date back to the 1920s, in which cardiac changes were seen after intravenous injection of various tissue extracts [108]. Since, adenosine has been found to influence circulatory tone, airway tone, bone formation, lipolysis, angiogenesis, pain, platelet aggregation, inflammation and immune function, and neurodegeneration [105]. Within the human ciliary epithelium, TM and SC, co-expression of the adenosine receptors have been identified with varying effects on ocular pressure status [107]. Studies have found that A₁ activation within the ciliary body leads to reduced aqueous formation in rabbits and monkeys [107, 110], while A₁ activation within the TM and SC increases release of metalloproteinase, leading to remodeling of extracellular matrix and improved outflow [107]. As such, selective A₁ agonism has been shown to reduce IOP in rabbit, monkey and cat models [110–115]. Conversely, A₃ agonism is thought to activate chloride channels in the ciliary epithelium, increasing aqueous production and raising IOP [110, 116].

3.4.1 Trabodenoson, manufactured by Inotek Pharmaceuticals; formerly INO-8875 (synonym PJ-875)

Current Status: Completion of Phase 2 Study: Trabodenoson is a potent A₁ receptor agonist. In preclinical study, it was shown to increase trabecular outflow in isolated porcine cornea-scleral shells. At doses of 10–1000 µg in normotensive cynomolgus monkeys, and 5–150 µg in rabbits, IOP was reduced up to 20–25% 1–2 hours after instillation [107].

In randomized, double-masked, placebo-controlled Phase 1 study of healthy patients aged 35–65 years, topical trabodenoson up to 3200 mcg per day was shown to be well tolerated with few reports of headache, eye pain, and transient ocular hyperemia [115]. In randomized, double-masked, dose-escalation Phase 2 study, 141 subjects aged 18–77 with OHTN or POAG were randomized to placebo or unilateral topical trabodenoson (50, 100, or 200 mcg) dosed twice daily for 14 days, or 500 mcg or placebo for 28 days. Trabodenoson produced dose-dependent IOP reduction. On day 28, the 500 mcg group had a mean IOP reduction of 4.1 mm Hg, compared to 1.6 for placebo. The drug was well tolerated- ocular hyperemia occurred in approximately 20% of subjects while no other clinically significant side-effect was noted [117].

3.5 Small interfering RNA

Ribonucleic acid interference (RNAi) pathways are natural post-transcriptional gene silencing mechanisms first discovered in nematode worms in 1998. These pathways, which have also been found in mammals, involve the creation of small RNA fragments from long pieces of double-stranded RNA. The RNA fragments ultimately incorporate into protein complexes and lead to messenger RNA cleavage and halting of protein synthesis. As RNA may be artificially produced, RNAi pathways have garnered considerable pharmacologic

attention. Further, given the relative ease of direct drug delivery, they have also garnered attention for ophthalmic use [118].

3.5.1 Bamosiran, manufactured by Sylentis; formerly SYL040012

Current Status: Completion of Phase 2 Study: Bamosiran is a double-stranded oligonucleotide that selectively inhibits ocular synthesis of β_2 -adrenergic-receptors. In a single center, open-label Phase 1 trial of 24 healthy subjects without OHTN, 600 μg SYL040012 was given to one eye in a singular dose; no change in IOP was subsequently seen. 600 μg or 900 μg was also given to one eye daily, over 7 days. On day 4 of the study, the 600 μg group showed a 20% decrease in IOP, not seen with the 900 μg group. By day 7, IOP was statistically significantly reduced in 15 out of 24 eyes with both doses, with a greater response seen in patients with higher baseline IOP. [CZ]. In the higher dose 900 μg group, the drug was well tolerated with few reports of itching, stinging or conjunctival hyperemia; furthermore, no destructive effects on other ocular parameters including corneal thickness, endothelial cell count, or refraction were seen. To assess potential systemic accumulation of the drug, 900 μg drop dosages were repeatedly administered and 5 minutes after the 7th administration, the drug was not detected in blood samples (lower limit of quantification, 44.2 ng/ml) [119].

Multi-center, randomized Phase 2 testing of 80 μg , 300 μg , and 900 μg doses versus placebo has preliminarily been reported. Results suggest IOP decrease at a 300 μg daily dose [120].

4. Conclusion

Emerging glaucoma drugs in phase 2 or 3 study have shown IOP lowering effect through different pathways than currently available drugs. Latanoprostene bunod, a nitrous oxide donating agent in combination with latanoprost, alters actin cytoskeleton elements and contractility, decreasing resistance to aqueous outflow within the TM and SC. In animal studies it has also been shown to relax ciliary muscle, potentially enhancing uveoscleral outflow. Phase 2 study showed reduction of IOP around 9 mmHg from baseline in patients with OHTN or open-angle glaucoma, slightly out-performing latanoprost monotherapy. Phase 3 studies showed non-inferiority to timolol, with increased number of subjects reducing IOP >25% from baseline or to <18 mm Hg compared to timolol. Side-effect profiles have appeared similar to latanoprost therapy.

RHO-associated Protein Kinase Inhibitors (Ripasudil, SNJ-1656) affect trabecular meshwork cellular shape, migration, adhesion, smooth muscle tone and cytoskeletal organization, thus relaxing multiple points of resistance within the TM and ciliary body. Furthermore, it has shown neuroprotective benefit in rat and cat models. Phase 2 study of Ripasudil showed approximately 4 mm Hg IOP lowering 2 hours after instillation with various drug concentrations, with effect shown at 8 hours. It was also shown to reduce IOP approximately 3 mm Hg in patients already on timolol or latanoprost, while studies have shown significant IOP lowering in glaucoma patients already on maximal medical therapy. Common local side effects include mild to moderate conjunctival hyperemia, thought to be secondary to vascular smooth muscle relaxation.

Combined ROCK/Norepinephrine Transporter Inhibition (Netarsudil) also blocks reuptake of norepinephrine at adrenergic synapses, reducing aqueous production and potentially episcleral venous pressure. Netarsudil did not achieve non-inferiority when compared to latanoprost, however combination formulations with latanoprost (PG324) did outperform latanoprost monotherapy. Commonly cited side-effects included mild to moderate conjunctival hyperemia (seen in up to 50% of patients).

Agonists of adenosine A₁ receptors decrease aqueous production and increase release of TM metalloproteinase, leading to remodeling of extracellular matrix and improved outflow. Phase 2 study in patients with OHTN or open-angle glaucoma showed up to 4 mm Hg IOP reduction, with few reports of ocular hyperemia.

Finally, preliminary reports of small RNA interfering fragments that reduce β 2-adrenergic-receptor synthesis have shown reduction of IOP without significant local or systemic adverse effect.

5. Expert Opinion

IOP lowering remains the mainstay of current medical and surgical treatment for glaucoma. Contemporary medications focus on IOP control via reduction of aqueous humor synthesis or by increasing outflow through the uveoscleral pathway. Other locations for IOP control, such the TM, SC, collector channels or episcleral venous system are targeted less. While parasympathomimetics may enhance trabecular outflow, they concurrently reduce uveoscleral outflow and often have ocular and systemic side effects that limit their use. The prostamide bimatoprost has shown some effectivity at the trabecular meshwork. Still, most medications do not focus on the TM and distal outflow channels, a significant site of aqueous outflow. This, coupled with investigation of IOP-independent mechanisms for glaucoma treatment and management, highlights the need for developing new pharmacologics.

Two decades have passed since the FDA last approved a topical drug for glaucoma. Drugs currently in phase 2 or phase 3 FDA study demonstrate IOP reduction via enhanced trabecular outflow in multicenter, randomized clinical trial. What remains to be seen is whether any of these drugs will change clinical decision-making with regard to choice of first-line or second-line agent for IOP reduction. The well-trusted prostaglandin analogue class has been available for over two decades and is generally used as first-line therapy for many reasons: strong efficacy with 24-hour coverage, tolerability, safety, and affordability. It appears unlikely that current emerging drops would supplant the prostaglandins as first-line monotherapy for IOP control, yet if offered in formulation with prostaglandins, they may change current treatment algorithms. Agents such as LBN and Netarsudil have shown enhanced IOP reduction than prostaglandin alone, and with similar side effect profile (conjunctival hyperemia being the most commonly cited side effect). More experience with tolerability, long-term side effect profile, and cost would ultimately dictate its place within clinical decision-making.

Emerging drugs appear to have several important complimentary roles to the current therapy. They have been shown to be efficacious and safe when used in combination with existing drugs, and they have even shown utility in patients on current maximal medical therapy. Availability of such an agent would unequivocally strengthen the clinicians' armamentarium for medical management of glaucoma. Furthermore, some emerging agents have shown 24-hour IOP control. A diurnal variation in IOP exists in all individuals and is more dramatic in glaucomatous eyes. For many individuals, IOP naturally rises overnight and may be damaging, yet the lack of 24-hour IOP monitoring in clinical practice makes this aspect of glaucoma care difficult to assess. Agents that are effective overnight are therefore invaluable, and emerging drugs have shown 24-hour effectivity in contrast to some established drugs, such as timolol and brimonidine.

A review of the drugs in clinical trials highlights a lack of change in the approach to glaucoma treatment since IOP lowering drops were discovered in the late 19th century. As first-line therapy, treatment with current topical medications may sometimes be suboptimal, as seen in patients that continue to lose vision despite controlled in-office IOP. This highlights the need for better drug delivery systems as well as the ongoing need to better understand glaucoma and its mediators of vision loss. Other approaches to treating glaucoma including enhanced optic nerve blood flow and neuroprotection or neuroregeneration of RGCs and their axons may ultimately prove to be instrumental in slowing or halting disease. Admittedly, many barriers exist between studying neuroprotection in animal models and human subjects, and the longevity of study required to provide evidence of neuroprotection is a significant obstacle. If agents with neuroprotective properties are to be discovered, this would unequivocally change clinical practice, regardless of IOP lowering effect. This area appears to be of focus in the coming generation, yet for the time being pharmacologics with novel ways to lower IOP are on the immediate horizon.

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Abbreviations:

AMP	Adenosine monophosphate
ATP	Adenosine triphosphate
FDA	Food and Drug Administration
IOP	intraocular pressure
LBN	latanoprostene bunod
NET	norepinephrine transporter
NO	nitrous oxide
NOS	nitrous oxide synthase
OHTN	ocular hypertension

POAG	primary open-angle glaucoma
RNAi	Ribonucleic acid interference
RGC	retinal ganglion cell
ROCK	RHO-associated protein Kinase
SC	Schlemm's canal
TM	trabecular meshwork

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Article highlights box

- Glaucoma is the most common cause of irreversible vision loss worldwide and is expected to increase in prevalence in the coming decades
- Topical therapy of glaucoma is first-line for treatment in most patients
- Two decades have passed since the FDA last approved a topical drug for the treatment of glaucoma
- Current investigational drugs in phase 2 or phase 3 FDA study show effective intraocular pressure lowering through pathways different than current drugs—namely enhanced trabecular meshwork outflow.
- As emerging drugs are still focused on intraocular pressure control, a paradigm shift in the treatment of glaucoma has not yet been realized.

Table 1.**Established Topical Glaucoma Monotherapy**

Drug	Mechanism of Action	FDA approval date
Pilocarpine	Direct-acting muscarinic receptor agonist; increases trabecular outflow	*2010
Phenylephrine	Non-selective sympathetic agonist (α_1 , α_2 , β_2); increases trabecular and uveoscleral outflow	*#2013
Timolol	Non-selective beta receptor blocker (β_1 and β_2); decreases aqueous production	1978
Dorzolamide	Carbonic anhydrase inhibition; decreases aqueous production	1994
Brimonidine	Selective sympathetic agonist (α_2); decreases aqueous production	1996
Latanoprost	Prostaglandin F ₂ α analogue; increases uveoscleral outflow	1996

* = Used as a medically necessary unapproved marketed drug prior to FDA approval

= Not FDA approved for use in ocular hypertension or treatment of glaucoma

Table 2.**Latanoprostene Bunod Clinical Trials**

Study/Year	Study Type	Patients	Summary
Weinreb et al. [60] / 2015	-Phase 2 -Randomized -Investigator-masked -Parallel group -Dose-ranging	413	23 clinical sites (15 in United States, 8 in Europe). Patients aged > 18 years, with OHTN or OAG (including PDS or PXF). Washout of 28 days if previously on hypotensive drops. IOPs ranged 22–32 mm Hg at baseline. Excluded if CCT > 600 microns or corneal irregularities affected applanation, advanced glaucoma (C/D > 0.8 or fixation split on perimetry), or on any topical or systemic drug that could affect IOP. Patients randomly assigned to LBN 0.006%, 0.012%, 0.024% and 0.040%, compared with latanoprost 0.005%, 1 drop daily over 28 day period. IOP measured three times at 5 visits during 28 day study period. All study arms lead to decrease in mean diurnal IOP, with LBN showing dose-dependent lowering of IOP, plateauing at 0.24–0.4%. Mean diurnal change from baseline IOP at the end of the study was 9 mm Hg in LBN 0.024%, versus 7.8 in latanoprost.
Meideros et al. [68]/ 2016	-Phase 3 -Prospective -Randomized -Double-masked -Parallel-group -Noninferiority	387	46 clinical sites (40 United States, 6 Europe). LBN 0.024% (evening dose with vehicle in AM) versus timolol maleate 0.5% (twice daily dosing) was given for 3 months in patients with OHTN or OAG. Baseline IOP ranged from 22–36 mm Hg. Exclusion criteria similar to the Weinreb et al. [60]. IOP was measured 3 times a day on week 2, week 6, and month 3. Mean IOP reduction from LBN was noninferior to timolol, and greater than timolol at all but the first time point in the study (week 2, 8:00). 31% of LBN patients had IOP reductions >25% from baseline, and 17.7% had IOP < 18 mm Hg at all time points, compared to 18.5% and 11.1% respectively for timolol.
Weinreb et al. [69]/ 2016	-Phase 3 -Randomized, controlled -Multicenter, -Double-masked -Parallel-group	387	45 Clinical Sites in United States and Europe. Noninferiority study of LBN 0.024% evening dosing compared with timolol 0.5% twice a day; superiority evaluation also done after noninferiority determined. Subjects were required to have BCVA 20/100 or better in either eye; other inclusion and exclusion criteria similar to Meideros et al. [68]. Subjects completed 3 study visits: week 2 (±2 days), week 6 (±3 days), and month 3 (±10 days). IOP measured 3 times at each visit. Mean diurnal IOP was significantly lower in the LBN 0.024% group compared with the timolol 0.5% group at each visit (18.2 vs. 19.5 mmHg at week 2, 18.1 vs. 19.3 mmHg at week 6, and 18.2 vs. 19.4 mmHg at month 3). At all 9 time points, the percentage of subjects with mean IOP <18 mmHg was significantly higher in the LBN group (22.9% vs. 11.3%), as was patients with IOP reduction >25% from baseline (34.9% vs. 19.5%).

Abbreviations: OHTN (ocular hypertension); OAG (open-angle glaucoma); PDS (pigment dispersion syndrome); PXF (pseudoexfoliation); IOP (intraocular pressure); CCT (central corneal thickness); C/D (cup/disc ratio); LBN (latanoprostene bunod); BCVA (Snellen best-corrected visual acuity); NTG (normal-tension glaucoma)

Table 3.

RHO-associated Protein Kinase Inhibitor Clinical Trials

Drug	Study/Year	Study Type	Patients	Summary
AR-12286	Williams et al. [96]/2011	-Phase 2a -Parallel comparison -Vehicle-controlled -Double-masked -Randomized controlled	87	Patients aged 18 and older with OHTN (IOP 21–36) or glaucoma were randomized to 0.05%, 0.1%, 0.25% AR-12286 or vehicle. Dosing was once daily in the morning for 7 days, then once daily in the evening for 7 days, then twice daily for 7 days. Exclusion criteria included recent ocular trauma, surgery, infection or inflammation, concomitant ocular medications, CCT >600 microns, and patients with prior glaucoma incisional or laser surgery, as well as a history of refractive surgery. Patients previously on ocular hypotensive agents had washout. Pregnant subjects and women of child-bearing age were excluded. All 3 concentrations of AR-12286 produced statistically significant reductions in mean IOP that were dose dependent, with peak effects occurring 2 to 4 hours after dosing. The largest IOP reduction occurred with 0.25% AR-12286 twice daily dosing (up to 6.8 mmHg lowering; 28% reduction). 0.25% evening dosing showed 5.4 to 4.2 mm Hg lowering the following day.
Ripasudil (K-115)	Tanihara et al. [90]/2013	-Phase 2 -Multicenter, prospective -Randomized, - -Placebo-controlled -Double-masked -Parallel group	210	20 clinical centers in Japan. Patients aged 20 years or older with POAG or OHT and baseline IOP 21–35 mm Hg. Pregnant women, patients of childbearing age planning pregnancy, eyes with narrow angles, and eyes with previous ocular surgery (aside from cataract more than 1 year prior, laser capsulotomy greater than 90 days prior, or eyelid surgery greater than 120 days prior) were excluded. Eyes with severe visual field defects were also excluded. Patients on IOP lowering drops had washouts prior to study initiation. Patients were randomized to 0.1%, 0.2%, and 0.4% or placebo twice daily for 8 weeks. IOP was reduced in dose-dependent fashion, at a peak 2 hours after instillation (–3.7 mm Hg, –4.2 mm Hg, –4.5 mm Hg, respectively). IOP was significantly lower at 8 hours after instillation (–3.2, –2.7, –3.1, respectively).
Ripasudil (K-115)	Tanihara et al. [92]/2015	-Phase 3 -Multicenter -Randomized -Double-masked -Parallel group -Comparison study	208	29 Clinical Centers in Japan. Inclusion and exclusion criteria similar to Tanihara et al. [90]. Twice daily ripasudil 0.4% in combination with timolol 0.5% versus placebo was studied over 8 weeks. Run-in period with timolol instillation was 4 weeks or more, prior to addition of ripasudil or placebo. IOP reductions were analyzed at weeks 4, 6, 7 at diurnal trough and peaks. Mean IOP reduction from baseline in the ripasudil and placebo groups were –2.9 and –1.3 mm Hg two hours after instillation, respectively.
Ripasudil (K-115)	Tanihara et al. [92]/2015	-Phase 3 -Multicenter -Randomized -Double-masked -Parallel group comparison study	205	36 Clinical Centers in Japan. Inclusion and exclusion criteria similar to Tanihara et al. [90]. Twice daily ripasudil 0.4% in combination with latanoprost 0.005% versus placebo was studied over 8 weeks. Run-in period with latanoprost instillation was 4 weeks or more, prior to addition of ripasudil or placebo. IOP reductions were analyzed at weeks 4, 6, 7 at diurnal trough and peaks. Mean IOP reduction from baseline in the ripasudil and placebo groups were –3.2 and –1.8 mm Hg two hours after instillation, respectively.
SNJ-1656 (Y-39983)	Inoue et al. [95]/2015	-Phase 2 -Randomized -Double Masked	63	Multicenter. Adult patients aged 20–74 with OAG or OHTN and IOP baseline 22–31 were included. BCVA was greater than or equal to 20/40. 0.03%, 0.05% or 0.1% of SNJ-1656 or placebo twice daily for 7 days was administered. Two hours after final administration, IOP was lowered to a similar degree at all drug concentrations- approximately 5 mm Hg for the 0.03% form (versus 1.5 for placebo).
Netarsudil (AR-13324) *	Bacharach et al. [102]/2015	-Phase 2b -Randomized -Double-masked -Parallel group comparison study -Noninferiority study	213	22 Clinical Sites in the United States. Adult patients with OHTN or OAG and baseline IOP 22–36 mm Hg were randomized to daily AR-13324 0.01% or 0.02%, or latanoprost 0.005% for 28 days. Exclusion criteria included a diagnosis of pigment dispersion syndrome or pseudoexfoliation, history of narrow angles and prior laser or glaucoma intraocular surgery, prior refractive surgery or central corneal thickness > 600 microns, history of herpetic keratitis, ocular trauma within the past 6 months, ocular or laser treatment within the past 3 months, or clinically significant ocular infection, inflammation, blepharitis or conjunctivitis at screening. On day 28, mean diurnal IOP reduction from baseline was 5.5, 5.7, and 6.8 mmHg for 0.01%, 0.02% AR-13324 and latanoprost groups, respectively. AR-13324 did not meet noninferiority criterion when compared to latanoprost.

Abbreviations: OHTN (ocular hypertension); OAG (open-angle glaucoma); IOP (intraocular pressure); CCT (central corneal thickness); BCVA (Snellen best-corrected visual acuity)

*
= combined Rho-kinase inhibitor/Norepinephrine transport inhibitor

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