Medical Management of Open-Angle Glaucoma: Focus on Mechanisms of Action and Adverse Drug Reactions

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ABSTRACT

Glaucoma is an optic neuropathy characterised by optic nerve degeneration associated with visual field defects. It remains the world's number one cause of irreversible blindness and patients usually present at late stage of the disease since it is generally asymptomatic until severe. The disease is subdivided into primary and secondary with primary open-angle glaucoma (POAG) being the most common type. At present, lowering the intraocular pressure (IOP) remains the only proven efficient approach in delaying the onset or preventing the progression of the disease. Medical treatment with topical antiglaucoma agents is the treatment of choice in open angle glaucoma. The use of antiglaucoma drugs aims to reduce IOP by enhancing aqueous humour (AH) outflow, reducing AH production, or both. The choice to use any available treatment option should be carefully considered in an attempt to maximise benefits and reducing the risk of developing adverse drug reactions. This review highlights the six classes of ocular hypotensive agents currently in use for POAG treatment including prostaglandin analogues; β-adrenergic receptor blockers; α-2 adrenergic receptor stimulants; carbonic anhydrase inhibitors; muscarinic receptor stimulants; rho kinase inhibitors with regards to their mechanism/s of action and potential adverse drug reactions, and antiglaucoma fixed drug combinations.

KEYWORDS: antiglaucoma, intraocular pressure, trabecular meshwork, adverse effects, aqueous humour, primary open-angle glaucoma, ocular hypertension

INTRODUCTION

Glaucoma is a neurodegenerative condition affecting the optic nerve and is a leading cause of irreversible visual loss worldwide [1], [2]. The condition is characterized by damage at the optic nerve head and visual field defects due to loss of retinal ganglion cells (RGCs), which equates to both the structural and functional changes [3], [4]. This disease is classified into primary and secondary. Primary glaucoma refers to the presence of glaucoma in the absence of any other ocular condition and includes primary open-angle glaucoma (POAG), primary angle closure glaucoma (ACG) and primary congenital glaucoma. In POAG, diagnosis is made based on the exclusion of other types of glaucoma. ACG refers to glaucoma with occludable drainage angle of the anterior chamber and elevated IOP. Secondary glaucoma is secondary to underlying ocular or systemic illnesses such as uveitis and pseudoexfoliation (PEX) syndrome. Topical and systemic use of steroids is commonly associated with ocular hypertension, which, may progress to steroid-induced glaucoma.

At present, POAG accounts for more than half of the cases of glaucoma worldwide [5]. Elevated IOP has been identified as the main risk factor for the development and progression of POAG, thus making it the primary target of currently available antiglaucoma agents. Clinical studies such as Early Manifest Glaucoma Trial (EMGT) and Ocular Hypertension Treatment Study (OHTS) have demonstrated that elevated IOP is a predictive factor for the development

4

and progression of glaucoma and the use of topical ocular hypotensive agents delayed and prevented the onset of POAG [6]–[8]. Maintaining IOP within normal range depends on the critical balance between the rate of secretion and rate of drainage of aqueous humour (AH). The ocular hypertension in POAG is primarily due to increased resistance to AH outflow at the trabecular meshwork (TM) [9]. Increased deposition of extracellular matrix (ECM) within the TM has been shown to block the patency of the conventional outflow pathway and thus produce increased outflow resistance, hence ocular hypertension [9]. An imbalance between the rate of degradation and new synthesis of ECM within the outflow pathways leads to accumulation and blockage of AH drainage.

POAG

POAG is the most common type of glaucoma and it is defined as a progressive, chronic optic neuropathy that occurs in adults. It is a diagnosis by exclusion of other possible pathologies such as PEX, rubeosis iridis, peripheral anterior synachiae and others. Gonioscopic examination of POAG eyes demonstrates an open anterior chamber angle and is further subdivided into 'high tension glaucoma' and 'normal-tension glaucoma'. A study by Cho and Kee demonstrated that the calculated average prevalence of POAG in Southeast Asia is about 1 in 50 [10]. National Eye Survey done in 1996 looked at the prevalence of blindness and low vision in Malaysian population and observed that 1.8% of blindness in Malaysia is attributed to glaucoma [11]. National Eye Database, First Annual Report Malaysia published in 2007 showed that the most common type of glaucoma among registered patients is POAG, accounting for 55% of total glaucoma cases [12]. Glaucoma remains the leading cause of irreversible blindness worldwide with over 8.4 million people having bilateral blindness [13] and in the year 2010, it was estimated that one out of 15 people was blind from glaucoma [14].

Ocular hypertension

Elevated IOP was a diagnostic criterion for POAG before the new definition based on funduscopic findings associated with reproducible visual function defects

was introduced. Although not all patients with increased IOP develop POAG, it has been recognized as the most important risk factor for the disease and control of IOP remains the main focus of treatment in POAG. Patients without glaucomatous signs and symptoms but having IOP above 21 mmHg are diagnosed to have ocular hypertension (OHT) and ocular hypertensive patients have a 17.5% cumulative risk of conversion to glaucoma in 5-year [15]. The findings of the studies such as OHTS and EMGT suggested that elevated IOP is a significant predictive factor for the development and progression of POAG [6]–[8]. EMGT study also revealed that a reduction by 1 mmHg in IOP from baseline leads to 10% decrease in the risk of glaucoma progression, whereby 1 mmHg increment leads to 11% increase in the risk of glaucoma progression [8]. IOP lowering therapy reduces the conversion rate from OHT to POAG with a predicted 5-year conversion rate of 14% and 26.9% in the treated and untreated group, respectively [15]. Despite the strong association between OHT and glaucoma, there is a subset of POAG patients that has glaucomatous neuropathy in the absence of ocular hypertension known as 'normal-tension glaucoma'. Management of this condition is similar to the treatment of other chronic glaucoma, which is to lower the IOP enough to prevent progression to visual loss.

Mechanism of IOP elevation

Since IOP elevation is the main risk factor for glaucomatous development and progression, all currently available antiglaucoma drugs act by reducing IOP. The mechanisms that regulate IOP primarily work to maintain the correct equilibrium between the AH production and drainage. Overproduction or reduced outflow of AH may tilt the balance, cause aqueous accumulation and produce IOP elevation. IOP is determined by three major factors: the rate of AH formation, the rate of aqueous outflow at the drainage pathway and the episcleral venous pressure. The mechanisms affecting these internal factors can be classified into pre-trabecular, trabecular and post trabecular. However, there is little evidence to show overproduction of AH or pre-trabecular factors can lead to elevated IOP.

a) Trabecular

The main mechanism of elevated IOP is the increased resistance to AH outflow at the TM. Under normal conditions, the heterogeneity of the trabecular cells including the endothelial cells lining the Schlemm's canal contribute to the resistance to aqueous outflow and allow for adequate drainage by maintaining the right balance of porosity and resistance. Increased deposition of ECM within the TM blocks the patency of the conventional outflow pathway and produces outflow resistance, hence ocular hypertension. An imbalance between the rate of synthesis and breakdown of ECM within the outflow pathway leads to accumulation and subsequently, blockage of AH drainage pathways.

The specific properties of TM allow it to function as a filter for draining AH. It allows unidirectional flow of AH and is sensitive to pressure changes. The cells in TM also carry out their own 'self-cleaning' by phagocytosing ECM debris to keep the 'filter' patent [16], [17]. The abnormal phagocytic activity of these cells causes deposition of debris as they are not readily phagocytosed, or the bulk of debris outdoes the ability of the cells to phagocytose, thus blocking the 'filter'. In glaucoma, ECM deposition and accumulation occur within the layers of TM rendering overload to phagocytic activity of trabecular cells and increased resistance to AH outflow. The kinetics of phagocytic activity of human trabecular meshwork cells (HTMCs) has been demonstrated by incubation of HTMCs with fluorescein-labelled polystyrene beads [18], which the beads simulated the debris deposited at the TM. Some of the HTMCs engorged with the ingested beads were observed to undergo necrosis, suggesting detrimental effect of excessive phagocytic activity. In addition to necrosis, apoptosis has also been implicated as the mechanism of cell death in TM. Apoptotic TM cells or their morphological features were seen more frequently in specimens from open-angle glaucoma patients than ACG patients [19].

b) Post Trabecular

After leaving the anterior chamber via the trabecular pathway into the Schlemm's canal, AH drains into the systemic circulation via the episcleral vein. Episcleral venous pressure (EVP) is another important factor in regulating AH dynamics. A rise in EVP could lead to an increase in IOP since the pressure poses resistance to the entry of AH into the systemic circulation. EVP elevation is significantly correlated with IOP in both POAG (IOP >21 mmHg) and normal-tension glaucoma (IOP < 21 mmHg) with relatively higher IOP/EVP ratio in normotensive glaucoma (normal IOP, raised EVP) [20].

EVP elevation can be caused by diseases such as venous obstruction (superior vena cava syndrome), arterio-venous shunts (AV-shunt), Sturge-Weber syndrome (arterio-venous malformation) and orbital tumours causing congestion of the blood vessels. Foroozan et al., (2003) reported a case whereby a patient with the idiopathic dilated episcleral vein (IDEV) had unilateral visual field defect and bilateral IOP elevation [21]. This is also supported by other case reports of dilated episcleral vein without identifiable cause and association with OAG [22].

Medical Management of Glaucoma

An increase in IOP has been accepted as the main risk factor for the development and progression of glaucomatous neuropathy. As with other diseases, modification of risk factors is important to prevent the subsequent outcome of the disease progression. The management of glaucoma can be divided into medical or surgical treatment. Medical treatment could be divided further according to the mode of administration of the drug: topical or systemic. Surgical treatment of patients with glaucoma also aims to lower the IOP by enhancing the outflow facility (drainage) or reducing the amount of AH which includes laser trabeculoplasty, trabeculectomy and cyclophotocoagulation that ablates the ciliary body.

In glaucoma, the mainstay of therapy to lower IOP is the use of pharmacological agents particularly the topically applied drugs. Topical antiglaucoma drugs act by reducing the production and/or enhancing the drainage. There are six main classes of antiglaucoma drugs currently in clinical use. They include β-blockers, prostaglandin analogues, α-adrenergic agonists, carbonic anhydrase inhibitors, muscarinic receptor agonists and rho-kinase inhibitors. The currently available antiglaucoma drug classes, their generic names, mechanism of action and adverse drug reactions are summarised in Table 1.

Table 1 Summary of currently available antiglaucoma agents.

Antiglaucoma classes	Generic Name	Mechanism of Action	Adverse Drug Reaction
β-blockers	Timolol Betaxolol	β-adrenergic blocking leading to: a) Reduction of AH production; b) Increase AH outflow through reduced outflow resistance	Local: Superficial punctate keratitis. corneal anaesthesia, burning, stinging, dry eyes. Systemic: Bronchospasm, hypotension, bradycardia.
Prostaglandin analogues	Latanoprost Bimatoprost Travoprost	Stimulation of prostaglandin F2α leading to enhanced AH outflow via uveoscleral pathway	Local: Permanent iris and eyelashes pigmentation, cystoid macular oedema, uveitis. Systemic: Conjunctival congestion, hypertension
α-2 adrenergic stimulant	Brimonidine Apraclonidine	Stimulation of α-2 receptor causing: a) Reduction of AH production; b) Increase AH outflow at the non-conventional pathway	Local: Conjunctival hyperaemia, blepharitis Systemic: Hypotension, fatigue, dry mouth.
Carbonic anhydrase inhibitor	Dorzolamide (Topical) Acetazolamide (Systemic)	Inhibition of carbonic anhydrase enzyme reducing AH production	Local: Stinging, blurred vision, burning, periorbital dermatitis, conjunctival hyperaemia. Systemic: Altered taste, renal stones, hypersensitivity.
Muscarinic receptor agonist	Pilocarpine	Stimulation of muscarinic receptors in the iris ciliary muscle leading to enhanced aqueous outflow	Local: Miosis, frontal headache, accommodative spasm, blurred vision. Systemic: Excessive cholinergic stimulation such as lacrimation, sweating, diarrhoea.
Rho Kinase Inhibitor	Ripasudil Netarsudil	Inhibition of Rho Kinase causing: a) enhanced conventional AH outflow; b) reducing AH production; c) reduction of episcleral venous pressure.	Local: Hyperaemia, corneal deposition, conjunctival haemorrhage Systemic: constipation, headache, nausea

β-Blockers

The β-adrenergic receptor blockers were one of the most commonly used class of drugs in clinical practice as the first line treatment for glaucoma. Timolol maleate is an example of a non-selective β-adrenoceptor antagonist and is clinically used as a topical agent to control IOP. Topical formulation of timolol is available in two doses; 0.25% and 0.5%. The solution is instilled twice daily. A single dose application of 0.5% timolol in human provides significant IOP reduction for 7 hours with maximum IOP reduction at 2 hours post-instillation [23]. Betaxolol is another β-receptor blocker

7

which is selective to β_1-receptor and available in similar doses with timolol. Although betaxolol exhibited lesser magnitude of IOP reduction when compared to timolol [24] it produced less bronchospasm in asthmatic patients [25]. Topical beta-blockers can be used as the first-line treatment in pregnant women with glaucoma [26].

a) Mechanism of action

The exact mechanism of action of timolol is still unclear despite its use for a long time. It has been suggested that β-adrenergic receptor blockers have a dual mechanism of action. Firstly, they reduce AH production and secondly, enhance the drainage from the anterior segment. β-adrenergic antagonists block the β-adrenergic receptors resulting in the reduction of intracellular second messenger, cAMP. Elevation of cAMP in the ciliary epithelial cells was suggested to increase chloride ion (Cl^-) efflux, which attracts water and increases AH production. These effects are blocked by β-blockers [27]. Timolol was shown previously not to have any effect on AH outflow facility [28], however, later study showed it was able to reduce the resistance at the trabeculo-uveoscleral pathway [29] suggesting that IOP lowering effect of β-blockers involves multiple mechanisms. Nevertheless, the exact mechanism behind the enhancement of the outflow facility is still under investigation.

b) Adverse effects

The side effects of timolol occur both locally and systemically. Some common local adverse effects include superficial punctate keratitis and reduced corneal sensitivity/ corneal anaesthesia. Timolol can also be absorbed into systemic circulation through conjunctiva leading to systemic adverse reactions due to β-adrenergic receptor blockade. Patients with chronic pulmonary disease such as asthma or chronic bronchitis should use timolol with caution since β-blockers can initiate or exacerbate bronchospasm [30]. According to Malaysia Clinical Practice Guidelines on the treatment of glaucoma, the use of β-blockers is contraindicated in patients with asthma, chronic obstructive pulmonary disease and heart problems such as heart block, heart failure and bradycardia [26]. Other systemic adverse reactions from topical β-blockers include cardiovascular effects such as bradycardia and heart failure.

Prostaglandin Analogues

Prostaglandins are important mediators of several physiological functions in the body and are found in most tissues and organs. There are a few types of prostaglandins that act on different prostaglandin receptor and produce responses depending on the site of the receptor. Prostaglandin F2α (FP) receptors were found to be widely distributed within the eye especially in cornea, iridial epithelium, ciliary muscle and ciliary processes [31]. Latanoprost is a prostaglandin analogue that stimulates FP receptors in the eye and is used in the treatment of glaucoma. The drug is available in 0.005% formulation and is given once daily owing to its prolonged ocular hypotensive effects. Other prostaglandin analogues include bimatoprost and travoprost which oculohypotensive effects may last for more than 24 hours [32], [33].

a) Mechanism of action

During the 1990s, the use of prostaglandin analogue such as latanoprost increased and the use of beta-blockers reduced. Its IOP lowering effect is attributed to the enhancement of the non-pressure dependent outflow or the uveoscleral outflow. The action of latanoprost is suggested to be mediated by direct stimulation of the FP receptors and this was supported by the observation that latanoprost administration in homozygous FP knockout mice did not produce a significant IOP lowering effect [34].

Studies have been carried out to determine the potential molecular mechanism behind the effect of latanoprost on modulation of AH dynamics. Since FP receptors are found in ciliary muscle cells, in vitro studies using human ciliary smooth muscle cells showed that stimulation of FP receptors by latanoprost increases the release of MMPs [35], [36]. Extracellular spaces between the ciliary muscles are part of the uveoscleral pathway. ECM was found to occupy these spaces and its degradation by an increased level of MMPs reduces the uveoscleral outflow resistance.

b) Adverse effects

The common side effects of latanoprost and other prostaglandin analogues are not serious but rather cosmetic. Patients can experience pigmentation of the iris and changes in eyelashes including darkening and thickening, which could be permanent. It is important to warn patients regarding this effect especially in patients receiving topical latanoprost unilaterally. Other local side effects include periocular skin pigmentation, conjunctival hyperaemia, blurred vision, stinging and burning, and deepening of upper eyelid sulcus [37], [38]. Rajan et al., (2003) reported a few case studies on patients aged more than 65 years experiencing chest tightness after starting latanoprost eye drop for the treatment of glaucoma [39]. Since prostaglandin F2α is a known vasoconstrictor, systemic adverse effects are possible in vulnerable aged patients [40], [41]. It was recently reported that latanoprost eye drop causes cutaneous blistering rash of eyelids, the neck and dorsum of hands, which resolved with cessation of treatment [42]. A meta-analysis by Tang et al., observed that latanoprost was better tolerated compared to travoprost or bimatoprost [43]. Conjunctival hyperaemia occurs more frequently with bimatoprost and travoprost whereas more patients experienced growth of lashes compared to latanoprost.

α-2 Adrenergic Receptor Agonists

α-adrenergic receptors are divided into two subtypes; α-1 and α-2 adrenoceptors. These receptors are widely distributed in the eye. Ocular α-1 adrenoreceptors are responsible for eyelid retraction, pupillary dilation and ocular vasoconstriction. Stimulation of α-2 receptors produces oculohypotensive effect and possibly neuroprotection and is used in the treatment of chronic glaucoma. Apraclonidine and brimonidine tartrate are topical formulations relatively selective towards α-2 receptors and have been used as antiglaucoma medication with the latter being more selective to α-2 receptors. Brimonidine is available in a single concentration of 0.2%, produced peak ocular hypotensive effect at two hours post-instillation [44] and it is applied on a twice-daily basis. There are two concentrations of apraclonidine available, 0.5% and 1%

with the higher dose is indicated to prevent perioperative increase in IOP.

a) Mechanism of action

Brimonidine induced ocular hypotensive effect in humans has been demonstrated to be contributed by a dual mechanism of action: 1) an increase in uveoscleral outflow and 2) a reduction in AH production [45]. Stimulation of α-2 adrenergic receptors located in the ciliary epithelium influences the level of cAMP, an effect similarly produced by β-adrenoceptor blockers. Brimonidine stimulates α-2 adrenoceptor in the ciliary epithelium, inhibiting adenylyl cyclase and cAMP production. Reduction in cAMP causes reduction of Cl⁻ efflux thus preventing the movement of water to form AH. Hence, lowering the AH production and consequently IOP.

Toris et al. demonstrated that brimonidine produces IOP lowering in human hypertensive eyes by increasing uveoscleral drainage [45]. Although they did not study the mechanism behind enhanced uveoscleral drainage by brimonidine, it was suggested that the brimonidine acts on α-2 adrenoceptors located on the ciliary muscle and improves the aqueous outflow facility through non-conventional pathway. Ooi et al. demonstrated presence of α-2 adrenergic receptors on ciliary body smooth muscle cells in culture [46]. Treatment with brimonidine caused an increase in pro-MMP-9 but not the cleaved or active MMP-9. The study failed to relate the increase in ECM turnover in ciliary muscle with the increased uveoscleral outflow by brimonidine. Furthermore, the effect of brimonidine on human uveoscleral outflow was not considered acute since it took approximately 1-week before the change in outflow facility was observed [45].

b) Adverse effects

The most common adverse effects associated with brimonidine are dry mouth and allergy such as allergic conjunctivitis. A study showed that topical brimonidine significantly reduces systolic and diastolic blood pressure, however, no clinical symptoms accompany the blood pressure reduction [47]. The systemic side effects could be attributed to systemic α-adrenoceptor stimulation.

Carbonic Anhydrase Inhibitors

Carbonic anhydrase is an enzyme found in abundance in various tissues and it is an essential catalyst for the formation of AH. Blocking the enzyme leads to a reduction in AH production, hence lowering IOP. Dorzolamide, a sulfonamide derivative, was the first topical carbonic anhydrase inhibitor used for the treatment of glaucoma and ocular hypertension. The drug is available in a 2% formulation and the agent is applied three times per day. Peak IOP reduction occurs at 2 hours post-instillation [48]. Another topical carbonic anhydrase inhibitor is brinzolamide.

a) Mechanism of action

Carbonic anhydrase enzyme is important in catalysing a reversible reaction of carbon dioxide (CO_2) hydration: $CO_2 + H_2O \rightarrow HCO_3^- + H^+$. This occurs in the ciliary epithelium and other body tissues. Bicarbonate and hydrogen ions pass from the ciliary epithelium into the posterior chamber and the movement attracts fluids; therefore, AH is produced. Dorzolamide inhibits the enzyme and prevents AH formation. Additionally, dorzolamide may also reduce the AH production by affecting the active transport system of the ciliary epithelium. It is known that active transport contributes to AH production and this process requires energy, which is supplied by hydrolysis of adenosine triphosphate (ATP) to adenosine diphosphate (ADP). $Na^+K^+ATPase$ is the enzyme responsible for the hydrolysis and is found on both the pigmented and non-pigmented ciliary epithelium. The $Na^+K^+ATPase$ enzymatic function can be altered by many factors including pH change and administration of acetazolamide, a systemic carbonic anhydrase inhibitor [49]. The alteration in ciliary epithelial tissue pH has not been associated with topical dorzolamide.

b) Adverse effects

Topical dorzolamide is associated with a few local adverse reactions, whereas its systemic counterpart, acetazolamide, produces systemic adverse reactions. Dorzolamide produces local side effects such as stinging, tearing and blurred vision. Periorbital dermatitis has also been reported to be associated with topical dorzolamide and stopping the eye drops resulted in complete resolution of the skin manifestation [50]. This is possibly due to the sulphonamide group in dorzolamide, which is commonly associated with hypersensitivity reactions.

Muscarinic Receptor Agonist

Pilocarpine is one of the well-known cholinergic agents used in the treatment of glaucoma. Although it is still being used in practice, its use is mainly for short term usually in pre-laser patients with ACG and use in long-term treatment is currently limited due to adverse effects. Cholinergic stimulants are the oldest antiglaucoma agent and pilocarpine was used as a glaucoma remedy in the late 19th century [51]. The topical formulation is available in doses ranging from 0.5 to 4% with rapid onset of action starting from 30 minutes post-administration. The effect lasts for 3 to 5 hours, thus topical pilocarpine requires at least 4 times daily administration, rendering compliance issue for its use.

a) Mechanism of action

Pilocarpine stimulates muscarinic receptors in the sphincter muscle of iris and ciliary body. The ciliary muscle has tendons that connect it to the Bárány (1966) studied the effect of pilocarpine on aqueous outflow resistance in primate and he suggested that contraction of ciliary muscle pulled the scleral spur thus opening the trabecular lamellae [51]. This was further supported by Grierson et al., who studied the effect of pilocarpine on the morphology of human outflow apparatus [52]. They demonstrated that in pilocarpine treated eyes, the scleral spur was pulled posteriorly and the spaces between corneoscleral trabeculae broaden. Widening of spaces assists the outflow of AH causing the lowering of IOP.

b) Adverse effects

Ocular adverse effects from topical pilocarpine are not uncommon. Miosis, due to contraction of iris sphincter, causes a reduction in visual acuity. Accommodative spasm due to ciliary muscle contraction leads to myopia thus increasing the risk of retinal detachment. Since pilocarpine stimulates the cholinergic system, it can induce systemic parasympathetic effects such as

bronchospasm, salivation, diarrhoea, sweating and bradycardia [53].

Rho Kinase Inhibitors

Almost two decades after the introduction of prostaglandin analogues, α-2 adrenergic and topical carbonic anhydrase, no new class of antiglaucoma agent was discovered until the breakthrough finding of rho kinase (ROCK) inhibitors were established in the market. This new novel therapy includes ripasudil (K-115) and netarsudil (AR-13503) have been approved and progressed to a few phases of clinical studies [54]. Topical ripasudil with formulation of 0.4% is applied twice-daily to treat glaucoma and ocular hypertension and was reported to produce maximum IOP reduction by -4.5 mmHg at two hours post-instillation [55], [56]. A single dose of netarsudil 0.02% topically has been proven to have similar efficacy in IOP lowering with latanoprost and timolol [57]–[59].

a) Mechanism of action

Rho kinase is a serine/threonine protein kinase that regulates fundamental cell behaviours including cell contraction, adhesion, proliferation and apoptosis via Rho/ROCK pathway. Compared to other glaucoma medications, ROCK inhibitors are different because they target the TM (conventional pathway) to reduce IOP. Since they are still quite new as glaucoma agents, there are still clinical trials in progress and the exact mechanism of action is uncertain. Most studies however, concluded that these agents have increased the conventional outflow pathway, reduced AH production and decrease EPV.

ROCK inhibitors increased the trabecular outflow pathway by terminating Rho/ROCK signalling that leads to relaxation of TM cells and reorganization of extracellular matrix (ECM) [60], [61]. A study using rabbits and monkeys treated with ripasudil by Kaneko et al (2016) reported that there were changes in the morphology along with disruption of actin bundles in TM cells and deconstruction of focal adhesion in Schlemm's canal (SC) cells [62]. Hence, this mechanism reduced the resistance in TM and increase the permeability of SC. Netarsudil has an additional effect which is inhibition of norepinephrine transporter

(NET) that leads to the reduction of the AH production. The exact mechanism is unknown but this interaction seems to block the uptake of norepinephrine and increase adrenergic transmission, believed to have similar action with brimonidine [63]. As ROCK inhibitors lead to vasodilation and NET inhibitors play role in vasoconstriction, the decrease EVP effect from netarsudil is likely to be part of the NET inhibitory response [64]. A further study using ROCK inhibitors need to be done to determine either ROCK inhibitor itself can reduce the EVP.

b) Adverse effects

There were mild and reversible local adverse effects reported with the use of ROCK inhibitors. Conjunctival hyperemia or eye redness is the most common effect resulting from the vasodilation of blood vessels in both drugs [59]. In ripasudil treatment, it was reported that patients may have allergic reactions and inflammation such as blepharitis, allergic conjunctivitis and punctate keratitis with further analysis showing that patients having a past history of allergy with other glaucoma medications are more likely to get blepharitis [65]. Corneal verticillata (corneal deposits) and conjunctival haemorrhage were commonly observed with netarsudil application [58]. Clinically significant systemic adverse drug reactions were not observed with netarsudil application however, drug-related systemic adverse reactions were experienced by patients during ripasudil treatment. These adverse effects include constipation, headache and nausea, and their incidences were rare and generally not severe.

Combination treatment

It is not uncommon that the use of a single antiglaucoma agent is not able to achieve the desired IOP reduction and the use of multiple agents can lead to compliance issues. Hence, combined medication can be an alternative for patients needing to use more than one type of antiglaucoma medication. Using one eyedrop bottle containing drug combinations is not only convenient but can decrease the exposure of patients to preservatives and further reduces preservatives-induced adverse drug reactions. Given many types of antiglaucoma medications are currently available, the

development of a fixed drug combination (FDC) is a treatment strategy to benefit the management of patients with glaucoma needing multiple agents to achieve target IOP. FDC can also enhance the ocular hypotensive effect to achieve improved IOP compared to corresponding monotherapies. FDC benefits include reduction of instillation frequency, less exposure to preservatives and increased compliance [66]. Inadequate adherence to prescribed therapy can contribute to the progression of glaucoma [67].

Most currently available FDCs contain β-blockers with other classes of antiglaucoma such as prostaglandin analogues, carbonic anhydrase inhibitors and α-2 agonists. Dorzolamide/timolol (dorzolamide 2% and timolol 0.5%) was the first antiglaucoma FDC commercialised in the US and Europe under the commercial name Cosopt® (Merck & Co Inc., Whitehouse Station, NJ, USA) in 1998. It was licensed to use in patients with OAG and OHT who failed to achieve target IOP with timolol monotherapy. Cosopt® is now formulated as preservative-free formulation and study comparing formulations with or without preservatives showed similar tolerability to treatment, with adverse effects such as ocular stinging and bitter taste less frequently observed in the preservative-free group compared to with preservatives [68]. Among the

FDCs that contains timolol, the combination of timolol and prostaglandin analogue produced the most IOP lowering between -33.9 to 34.9% [69]. Apart from dual FDC, there are also triple FDC which includes bimatoprost / brimonidine / timolol and dorzolamide / brimonidine / timolol combinations. Both of the triple FDC showed no serious adverse events and they were reported to be as safe as and well tolerated as bimatoprost/timolol FC and dorzolamide/timolol FC [66]. Soon after the development of netarsudil, Aerie Pharmaceuticals Inc (Durham, NC, USA) developed an FDC combining netarsudil and latanoprost and has recently been tested in two Phase III clinical trials, MERCURY-1 and MERCURY-2 [70]–[72]. The most commonly reported adverse event was conjunctival hyperaemia and the FDC otherwise has negligible treatment-related serious local or systemic adverse drug reactions.

The major limitation for FDC is the dosing awareness of the concomitant medication. Some patients may require less or more content of one drug, hence it is important that a clinician considers all available evidence and try to achieve an optimal balance between the efficacy, tolerability and adherence of patients to FDC. The list of currently available FDCs is summarised in Table 2.

Table 2 Available fixed-dose combinations of antiglaucoma drugs.

Available Combination	Dose	Commercial Name
Latanoprost/timolol	0.005%:0.5%	Xalacom®
Travoprost/timolol	0.004%:0.5%	DuoTrav®
Bimatoprost/timolol	0.03%:0.5%	Ganfort®
Tafluprost/timolol	0.0015%:0.5%	Taptiqom®
Dorzolamide/timolol	2%:0.5%	Cosopt®
Brinzolamide/timolol	1%:0.5%	Azarga®
Brimonidine/timolol	0.2%:0.5%	Combigan®
Brinzolamide/brimonidine	1%:0.2%	Simbrinza®
Bimatoprost/brimonidine/timolol	0.01%:0.15%:0.5%	Triplenex®
Dorzolamide/brimonidine/timolol	2%:0.2%:0.5%	Krytantek Ofteno®
Netarsudil/latanoprost	0.02%:0.005%	Rocklatan®

CONCLUSION

This review highlights the medical management of glaucoma including the use of drug combinations. Prostaglandin analogues are currently the drug of choice for first line treatment in many parts of the world as it has good efficacy, prolonged oculohypotensive activity and minimal systemic adverse drug reactions. Beta-blockers can still be considered to be used as first-line medication, however, its use in patients with respiratory illnesses such as asthma and cardiac problems such as heart block is contraindicated. Other drugs such as brimonidine and dorzolamide are efficacious as adjunctive therapy, whereas pilocarpine is no longer preferred as long-term treatment option of POAG. The recently approved antiglaucoma medication such as ripasudil and netarsudil are new in the market and not widely used as yet, however, their effects are noninferior to the established antiglaucoma agents and they have good tolerability with minimal adverse effects. In patients needing more than one antiglaucoma drugs for IOP control, fixed drug combination should be considered in order to reduce frequency of applications of multiple drugs and improve compliance.

Conflict of Interest

Authors declare none.

Authors Contribution

Norhafiza Razali and Amy Suzana Abu Bakar prepared the main body of the manuscript with contribution of two of the subtopics from Mohammed Daniel Shafiq Hassan. Renu Agarwal was responsible for the overall flow of this manuscript. Norhafiza Razali is the principal investigator of one of the grants and Renu Agarwal are both co-investigators for both research grants, they also coordinated the study and supervise the students.

REFERENCES

1. Resnikoff S, Pascolini D, Etya'Ale D, Kocur I, Pararajasegaram R, Pokharel GP, Mariotti SP. Global data on visual impairment in the year 2002. Bulletin of the world health organization. 2004;82:844-51.

2. Tham YC, Li X, Wong TY, Quigley HA, Aung T, Cheng CY. Global prevalence of glaucoma and projections of glaucoma burden through 2040: a systematic review and meta-analysis. Ophthalmology. 2014;121(11):2081-90.

3. Casson RJ, Chidlow G, Wood JP, Crowston JG, Goldberg I. Definition of glaucoma: clinical and experimental concepts. Clinical & experimental ophthalmology. 2012;40(4):341-9.

4. Foster PJ, Buhrmann R, Quigley HA, Johnson GJ. The definition and classification of glaucoma in prevalence surveys. British journal of ophthalmology. 2002;86(2):238-42.

5. Kapetanakis VV, Chan MP, Foster PJ, Cook DG, Owen CG, Rudnicka AR. Global variations and time trends in the prevalence of primary open angle glaucoma (POAG): a systematic review and meta-analysis. British Journal of Ophthalmology. 2016;100(1):86-93.

6. Gordon MO, Beiser JA, Brandt JD, Heuer DK, Higginbotham EJ, Johnson CA, Keltner JL, Miller JP, Parrish RK, Wilson MR, Kass MA. The Ocular Hypertension Treatment Study: baseline factors that predict the onset of primary open-angle glaucoma. Archives of ophthalmology. 2002;120(6):714-20.

7. Kass MA, Heuer DK, Higginbotham EJ, Johnson CA, Keltner JL, Miller JP, Parrish RK, Wilson MR, Gordon MO. The Ocular Hypertension Treatment Study: a randomized trial determines that topical ocular hypotensive medication delays or prevents the onset of primary open-angle glaucoma. Archives of ophthalmology. 2002;120(6):701-13.

8. Leske MC, Heijl A, Hussein M, Bengtsson B, Hyman L, Komaroff E. Factors for glaucoma progression and the effect of treatment: the early manifest glaucoma trial. Archives of ophthalmology. 2003;121(1):48-56.

9. Rohen JW. Why is Intraocular Pressure Elevated in Chronic Simple Glaucoma?: Anatomical Considerations.Ophthalmology. 1983;90(7):758-65.

10. Cho HK, Kee C. Population-based glaucoma prevalence studies in Asians. Survey of ophthalmology. 2014;59(4):434-47.

11. Zainal M, Ismail SM, Ropilah AR, Elias H, Arumugam G, Alias D, Fathilah J, Lim TO, Ding LM, Goh PP. Prevalence of blindness and low vision in Malaysian population: results from the National Eye Survey 1996. British journal of ophthalmology. 2002;86(9):951-6.

12. Goh PP, Hussein E, Mustari Z, Ismail M. The First Annual Report of the National Eye Database, *National Eye Database Malaysia*. 2008:1–140.

13. Quigley HA, Broman AT. The number of people with glaucoma worldwide in 2010 and 2020. British journal of ophthalmology. 2006;90(3):262-7.

14. Bourne RR, Taylor HR, Flaxman SR, Keeffe J, Leasher J, Naidoo K, Pesudovs K, White RA, Wong TY, Resnikoff S, Jonas JB. Number of people blind or visually impaired by glaucoma worldwide and in world regions 1990–2010: a meta-analysis. PloS one. 2016;11(10):e0162229.

15. Kelly SR, Khawaja AP, Bryan SR, Azuara-Blanco A, Sparrow JM, Crabb DP. Progression from ocular hypertension to visual field loss in the English hospital eye service. British Journal of Ophthalmology. 2020;104(10):1406-11.

16. Stamer WD, Acott TS. Current understanding of conventional outflow dysfunction in glaucoma. Current opinion in ophthalmology. 2012;23(2):135-43.

17. Stamer WD, Clark AF. The many faces of the trabecular meshwork cell. Experimental eye research. 2017;158:112-23.

18. Shirato S, Murphy CG, Bloom E, Franse-Carman L, Maglio MT, Polansky JR, Alvarado JA. Kinetics of phagocytosis in trabecular meshwork cells. Flow cytometry and morphometry. Investigative ophthalmology & visual science. 1989;30(12):2499-511.

19. Baleriola J, García-Feijoo J, Martínez-de-la-Casa JM, Fernández-Cruz A, De la Rosa EJ, Fernández-Durango R. Apoptosis in the trabecular meshwork of glaucomatous patients. Molecular vision. 2008;14:1513-16.

20. Selbach JM, Posielek K, Steuhl KP, Kremmer S. Episcleral venous pressure in untreated primary open-angle and normal-tension glaucoma. Ophthalmologica. 2005;219(6):357-61.

21. Foroozan, R., Buono, L.M., Savino, P.J. and Sergott, R.C., 2003. Idiopathic dilated episcleral veins and increased intraocular pressure. British journal of ophthalmology, 87(5):652-654.

22. D. J. Rhee, M. Gupta, M. B. Moncavage, M. L. Moster, and M. R. Moster, *Idiopathic elevated episcleral venous pressure and open-angle glaucoma.*, vol. 93, no. 2. 2009, pp. 231–234.

23. Katz IM, Hubbard WA, Getson AJ, Gould AL. Intraocular pressure decrease in normal volunteers following timolol ophthalmic solution. Investigative ophthalmology & visual science. 1976;15(6):489-92.

24. Allen RC, Hertzmark E, Walker AM, Epstein DL. A double-masked comparison of betaxolol vs timolol in the treatment of open-angle glaucoma. American journal of ophthalmology. 1986;101(5):535-41.

25. Dunn TL, Gerber MJ, Shen AS, Fernandez E, Iseman MD, Cherniack RM. The effect of topical ophthalmic instillation of timolol and betaxolol on lung function in asthmatic subjects. American Review of Respiratory Disease. 1986 Feb;133(2):264-8.

26. Ministry of Health Malaysia, "CPG management of glaucoma (Second Edition)," 2017.

27. Chen S, Inoue R, Inomata H, Ito Y. Role of cyclic AMP-induced Cl conductance in aqueous humour formation by the dog ciliary epithelium. British journal of pharmacology. 1994;112(4):1137-45.

28. Vareilles P, Lotti VJ. Effect of timolol on aqueous humor dynamics in the rabbit. Ophthalmic Research. 1981;13(2):72-9.

29. Searles RV, Shikher V, Balaban CD, Severs WB. Timolol effects on aqueous humor dynamics in eyes of anesthetized rats. Journal of

Pharmacology and Experimental Therapeutics. 1999;288(2):838-42.

30. Schoene RB, Martin TR, Charan NB, French CL. Timolol-lnduced Bronchospasm in Asthmatic Bronchitis. JAMA. 1981;245(14):1460-1.

31. Ocklind A, Lake S, Wentzel P, Nistér M, Stjernschantz J. Localization of the prostaglandin F2 alpha receptor messenger RNA and protein in the cynomolgus monkey eye. Investigative ophthalmology & visual science. 1996;37(5):716-26.

32. Konstas AG, Mikropoulos D, Kaltsos K, Jenkins JN, Stewart WC. 24-hour intraocular pressure control obtained with evening-versus morning-dosed travoprost in primary open-angle glaucoma. Ophthalmology. 2006 Mar 1;113(3):446-50.

33. Walters TR, DuBiner HB, Carpenter SP, Khan B, VanDenburgh AM. 24-Hour IOP control with once-daily bimatoprost, timolol gel-forming solution, or latanoprost: a 1-month, randomized, comparative clinical trial. Survey of ophthalmology. 2004;49(2):S26-35.

34. Crowston JG, Lindsey JD, Aihara M, Weinreb RN. Effect of latanoprost on intraocular pressure in mice lacking the prostaglandin FP receptor. Investigative ophthalmology & visual science. 2004;45(10):3555-9.

35. Weinreb RN, Kashiwagi K, Kashiwagi F, Tsukahara S, Lindsey JD. Prostaglandins increase matrix metalloproteinase release from human ciliary smooth muscle cells. Investigative ophthalmology & visual science. 1997 Dec 1;38(13):2772-80.

36. Wang NL, Lu QJ, Li JH, Ling WA. Prostaglandin induces the expression of matrix metalloproteinase-1 in ciliary melanocytes. Chinese medical journal. 2008;121(13):1173-6.

37. Inoue K, Shiokawa M, Wakakura M, Tomita G. Deepening of the upper eyelid sulcus caused by 5 types of prostaglandin analogs. Journal of glaucoma. 2013;22(8):626-31.

38. Alm A, Grierson I, Shields MB. Side effects associated with prostaglandin analog therapy. Survey of ophthalmology. 2008;53(6):S93-105.

39. Rajan MS, Syam P, Liu C. Systemic side effects of topical latanoprost. Eye. 2003;17(3):442-4.

40. Brogiolo G, Flammer J, Haefliger IO. Latanoprost is a vasoconstrictor in isolated porcine ciliary arteries. Klinische Monatsblätter für Augenheilkunde. 2001;218(05):373-5.

41. Mitra M, Chang B, James T. Exacerbation of angina associated with latanoprost. Bmj. 2001;323(7316):783.

42. Yip IYM, Raj A. Severe cutaneous reaction to latanoprost eye drops. Journal of ophthalmic & vision research. 2018;13(3):348.

43. Tang W, Zhang F, Liu K, Duan X. Efficacy and safety of prostaglandin analogues in primary open-angle glaucoma or ocular hypertension patients: A meta-analysis. Medicine. 2019;98(30).

44. Burke J, Schwartz M. Preclinical evaluation of brimonidine. Survey of ophthalmology. 1996;41(Suppl 1):S9-18.

45. Toris CB, Gleason ML, Camras CB, Yablonski ME. Effects of brimonidine on aqueous humor dynamics in human eyes. Archives of Ophthalmology. 1995;113(12):1514-7.

46. Ooi YH, Oh DJ, Rhee DJ. Analysis of α2-adrenergic receptors and effect of brimonidine on matrix metalloproteinases and their inhibitors in human ciliary body. Investigative ophthalmology & visual science. 2009;50(9):4237-43.

47. Quaranta L, Gandolfo F, Turano R, Rovida F, Pizzolante T, Musig A, Gandolfo E. Effects of topical hypotensive drugs on circadian IOP, blood pressure, and calculated diastolic ocular perfusion pressure in patients with glaucoma. Investigative ophthalmology & visual science. 2006;47(7):2917-23.

48. Lippa EA, Carlson LE, Ehinger B, Eriksson LO, Finnström K, Holmin C, Nilsson SE, Nyman K, Raitta C, Ringvold A, Tarkkanen A. Dose response and duration of action of dorzolamide, a topical carbonic anhydrase inhibitor. Archives of ophthalmology. 1992 Apr 1;110(4):495-9.

49. Maren TH. The rates of movement of Na+, Cl-, and HCO-3 from plasma to posterior chamber: effect of acetazolamide and relation to the treatment of glaucoma. Investigative

Ophthalmology & Visual Science. 1976;15(5):356-64.

50. Delaney YM, Salmon JF, Mossa F, Gee B, Beehne K, Powell S. Periorbital dermatitis as a side effect of topical dorzolamide. British journal of ophthalmology. 2002;86(4):378-80.

51. Barany EH. The mode of action of miotics on outflow resistance. A study of pilocarpine in the vervet monkey Cercopithecus ethiops. Transactions of the ophthalmological societies of the United Kingdom. 1966;86:539-78.

52. Grierson I, Lee WR, Abraham SH. Effects of pilocarpine on the morphology of the human outflow apparatus. British Journal of Ophthalmology. 1978;62(5):302-13.

53. Lee DA, Higginbotham EJ. Glaucoma and its treatment: a review. American journal of health-system pharmacy. 2005;62(7):691-9.

54. Bali J, Bali O. Latest Update in Glaucoma: The first approvals for Rho Kinase inhibitors. The Official Scientific Journal of Delhi Ophthalmological Society. 2020;30(4):71-4.

55. Tanihara H, Inoue T, Yamamoto T, Kuwayama Y, Abe H, Fukushima A, Suganami H, Araie M, K-115 Clinical Study Group, Uchino M, Iwasaki M. One-year clinical evaluation of 0.4% ripasudil (K-115) in patients with open-angle glaucoma and ocular hypertension. Acta ophthalmologica. 2016;94(1):e26-34.

56. Kusuhara S, Nakamura M. Ripasudil Hydrochloride Hydrate in the Treatment of Glaucoma: Safety, Efficacy, and Patient Selection. Clinical Ophthalmology (Auckland, NZ). 2020;14:1229-36.

57. Bacharach J, Dubiner HB, Levy B, Kopczynski CC, Novack GD, AR-13324-CS202 Study Group. Double-masked, randomized, dose–response study of AR-13324 versus latanoprost in patients with elevated intraocular pressure. Ophthalmology. 2015;122(2):302-7.

58. Kahook MY, Serle JB, Mah FS, Kim T, Raizman MB, Heah T, Ramirez-Davis N, Kopczynski CC, Usner DW, Novack GD, ROCKET-2 Study Group. Long-term safety and ocular hypotensive efficacy evaluation of netarsudil ophthalmic solution: Rho Kinase Elevated IOP Treatment Trial (ROCKET-2). American journal of ophthalmology. 2019;200:130-7.

59. Khouri AS, Serle JB, Bacharach J, Usner DW, Lewis RA, Braswell P, Kopczynski CC, Heah T, Benza R, Boyle IV JW, Butler M. Once-daily netarsudil versus twice-daily timolol in patients with elevated intraocular pressure: the randomized phase 3 ROCKET-4 study. American journal of ophthalmology. 2019;204:97-104.

60. Honjo M, Tanihara H. Impact of the clinical use of ROCK inhibitor on the pathogenesis and treatment of glaucoma. Japanese journal of ophthalmology. 2018;62(2):109-26.

61. Kusuhara S, Nakamura M. Ripasudil Hydrochloride Hydrate in the Treatment of Glaucoma: Safety, Efficacy, and Patient Selection. Clinical Ophthalmology (Auckland, NZ). 2020;14:1229-36.

62. Kaneko Y, Ohta M, Inoue T, Mizuno K, Isobe T, Tanabe S, Tanihara H. Effects of K-115 (Ripasudil), a novel ROCK inhibitor, on trabecular meshwork and Schlemm's canal endothelial cells. Scientific reports. 2016;6(1):1-9.

63. Wang RF, Williamson JE, Kopczynski C, Serle JB. Effect of 0.04% AR-13324, a ROCK, and norepinephrine transporter inhibitor, on aqueous humor dynamics in normotensive monkey eyes. Journal of glaucoma. 2015;24(1):51-4.

64. Kiel JW, Kopczynski CC. Effect of AR-13324 on episcleral venous pressure in Dutch belted rabbits. Journal of Ocular Pharmacology and Therapeutics. 2015;31(3):146-51.

65. Saito H, Kagami S, Mishima K, Mataki N, Fukushima A, Araie M. Long-term side effects including blepharitis leading to discontinuation of ripasudil. Journal of glaucoma. 2019 Apr 1;28(4):289-93.

66. Konstas AG, Schmetterer L, Costa VP, Holló G, Katsanos A, Denis P, Quaranta L, Irkec M, Castejón MA, Teus MA, Robin AL. Current and emerging fixed combination therapies in glaucoma: a safety and tolerability review. Expert Opinion on Drug Safety. 2020;19(11):1445-60.

16

67. Susanna R, De Moraes CG, Cioffi GA, Ritch R. Why do people (still) go blind from glaucoma?. Translational vision science & technology. 2015;4(2):1.

68. Shedden A, Adamsons IA, Getson AJ, Laurence JK, Lines CR, Hewitt DJ, Ho TW. Comparison of the efficacy and tolerability of preservative-free and preservative-containing formulations of the dorzolamide/timolol fixed combination (COSOPT™) in patients with elevated intraocular pressure in a randomized clinical trial. Graefe's Archive for Clinical and Experimental Ophthalmology. 2010;248(12):1757-64.

69. Cheng JW, Cheng SW, Gao LD, Lu GC, Wei RL. Intraocular pressure-lowering effects of commonly used fixed-combination drugs with timolol: a systematic review and meta-analysis. PLoS One. 2012;7(9):e45079.

70. Walters TR, Ahmed II, Lewis RA, Usner DW, Lopez J, Kopczynski CC, Heah T, MERCURY-2 Study Group. Once-daily netarsudil/latanoprost fixed-dose combination for elevated intraocular pressure in the randomized phase 3 MERCURY-2 study. Ophthalmology Glaucoma. 2019;2(5):280-9.

71. Asrani S, Robin AL, Serle JB, Lewis RA, Usner DW, Kopczynski CC, Heah T, Ackerman SL, Alpern LM, Bashford K, Bluestein EC. Netarsudil/latanoprost fixed-dose combination for elevated intraocular pressure: three-month data from a randomized phase 3 trial. American journal of ophthalmology. 2019;207:248-57.

72. Asrani S, Bacharach J, Holland E, McKee H, Sheng H, Lewis RA, Kopczynski CC, Heah T. Fixed-dose combination of netarsudil and latanoprost in ocular hypertension and open-angle glaucoma: pooled efficacy/safety analysis of phase 3 MERCURY-1 and-2. Advances in therapy. 2020:1-12.