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
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            | 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. |
|                        | Betaxolol          |                                                                                      |                                                                                        |
| Prostaglandin analogues| Latanoprost        | 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 |
|                        | Bimatoprost        |                                                                                      |                                                                                        |
|                        | Travoprost         |                                                                                      |                                                                                        |
| α-2 adrenergic stimulant| Brimonidine        | Stimulation of α-2 receptor causing: a) Reduction of AH production; b) Increase AH outflow at the non-conventional pathway | Local: Conjunctival hyperaemia, blepharitis                                                                                       |
|                        | Apraclonidine      |                                                                                      | Systemic: Hypotension, fatigue, dry mouth.                                                                                         |
| Carbonic anhydrase inhibitor| Dorzolamide        | Inhibition of carbonic anhydrase enzyme reducing AH production                      | Local: Stinging, blurred vision, burning, periorbital dermatitis, conjunctival hyperaemia. Systemic: Altered taste, renal stones, hypersensitivity. |
|                        | (Topical) Acetazolamide (Systemic) |                                                                                   |                                                                                        |
| 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          | 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 |
|                        | Netarsudil         |                                                                                      |                                                                                        |

**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.
which is selective to β₁-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, iridal 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 adrenoceptors 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 adenyly 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-adrenergic receptor 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$_2$O $\rightarrow$ 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.

Muscarnic 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.

| 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%      | Taptiqon®         |
| 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 efficacious as a new option 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.

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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.

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