Review Article

Pharmaceutical treatment of primary open angle glaucoma

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ABSTRACT

Background: Glaucoma is a progressive, irreversible optic neuropathy that results in serious vision loss and blindness. This review aimed to summarize key concepts of primary open angle glaucoma (POAG) pharmaceutical treatment trials over the last decade.

Methods: We searched PubMed/MEDLINE and clinicaltrials.gov from January 1, 2010, to August 31, 2020, using the key words "POAG" and "Ocular topical therapeutics". This search yielded 77 and 120 papers, respectively.

Results: Thirty-three records were compatible with our inclusion criteria. Pharmaceutical treatment is a common intervention in POAG for lowering IOP. Prostaglandin (PG) analogues are most commonly recommended as initial medical therapy, which are administrated either as a monotherapy or in combination with other IOP-lowering classes of medications. Alternative therapies, such as β-blockers, α-2 adrenergic receptor agonists, and topical carbonic anhydrase inhibitors, have been used in combination or as a monotherapy. Rho-kinase inhibitors, such as netarsudil 0.02%, AR-13324 0.02%, and ripasudil are new IOP-lowering medications. Despite IOP reduction, there is a significant number of patients with POAG that may experience disease progression, and the risk of blindness over the long term is considerable.

Conclusions: Clinical trials have indicated that pharmaceutical treatment of POAG is effective and safe. In addition, the new novel Rho-kinase inhibitors have shown significant IOP reduction. The new fixed combinations have also yielded significant reductions in IOP. POAG is a cause of irreversible vision loss, if not diagnosed and treated early. The condition is likely to progress in a significant number of patients, with a considerable risk of blindness in the long-term.

KEY WORDS

primary open angle glaucoma, POAG, intervention study, randomized clinical trials, RCTs, drug therapies, pharmaceutical treatment, medical therapy, prostaglandin analogues, beta adrenergic blockers, α-2 adrenergic receptor agonist, carbonic anhydrase inhibitor, Rho-kinase inhibitor

INTRODUCTION

Glaucoma is the second leading cause of blindness worldwide. Primary open-angle glaucoma (OAG) is the most prevalent type of glaucoma in almost all countries. Primary OAG is a progressive optic neuropathy that causes retinal ganglion cell axon loss and visual field deterioration. Usually, glaucoma progresses gradually over the course of years, and the progression of vision loss can be delayed with treatment [1, 2]. A longitudinal cohort study found that the prevalence rate of primary OAG in patients aged ≥ 50 years was 2.79% [3]. In a randomized cohort study, the definite glaucoma prevalence was 1.1% in patients aged 45-49 years at the time

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of clinical examination [4].

Elevated intraocular pressure (IOP) [5, 6] and older age [7-9] are the most important risk factors for the development and progression of primary OAG, of which only IOP is a modifiable factor [10]. Other risk factors include a family history of glaucoma [8, 11, 12], African American ancestry [13, 14], systemic disease [15], thinner corneas [16], myopia [17], and steroid use [18]. Since IOP is the only modifiable risk factor, management of primary OAG has focused on decreasing IOP, which can delay disease progression, decrease the visual field (VF) loss rate, and protect against visual function loss and vision loss [19].

This review aimed to include current evidence on the primary OAG pharmaceutical treatment. The key concepts of the primary OAG trials performed over the last decade were identified and summarized.

METHODS

A literature search was conducted using PubMed/MEDLINE and clinicaltrials.gov from January 1, 2010, to August 31, 2020, using the keywords "POAG" and "ocular topical therapeutics." The keyword "completed" was added to the keyword list for the clinicaltrials.gov search. No language limitation was applied. The search of these databases identified 77 and 120 potentially relevant reports, respectively. The full-text review of these papers yielded 33 papers considered to be compatible with our inclusion criteria.

RESULTS

Table 1 summarizes the characteristics and key findings of the 33 included studies, which were clinical trials and prospective studies. The most frequently used medications for IOP control were prostaglandin (PG) analogues, β-blockers, carbonic anhydrase inhibitors (CAIs), and α-2 adrenergic agonists. PG analogues were the most widely used treatment. Table 2 summarizes the mechanisms of action of each IOP-lowering medication.

PG analogues were prescribed either alone or in combination with β-blockers, CAIs, and α-2 adrenergic agonists. In newly diagnosed, treatment-naive OAG or ocular hypertension (OHT) patients, topical PG analogues, including bimatoprost, latanoprost, and travoprost, were effective at lowering IOP. Although bimatoprost was initially the most effective, no significant difference in efficacy among the different PG analogues was found after 6 months [20]. A prospective, multicenter observational cohort study of 1221 normal, suspected glaucoma, and definite glaucoma subjects revealed the impact of IOP reduction after administration of latanoprost 0.005% in reducing VF deterioration in newly diagnosed OAG [21]. In another randomized controlled trial (RCT) on newly diagnosed, treatment-naive OAG or OHT patients, patients who did not respond to 1 month of latanoprost were switched to another topical PG (bimatoprost or travoprost) which had no additive benefit [22]. A significant IOP-lowering effect of once-daily travoprost was reported in a clinical trial of patients with OAG or OHT [23]. Once-daily administration of benzalkonium chloride (BAK)-preserved travoprost 0.004% was an effective IOP-lowering treatment in patients with newly diagnosed primary OAG [24]. Once-daily administration of bimatoprost 0.03% or travoprost 0.004% achieved effective IOP reduction in patients with primary OAG or OHT. However, the effect of bimatoprost on the mean IOP was more but not significant [25]. Preservative-free (PF) latanoprost had better tolerability and a comparable IOP-lowering effect as compared to BAK–latanoprost in patients with glaucoma or OHT [26].

In addition to the above trials on PG analogues per se, a few other studies compared their efficacy against different classes of IOP-lowering eye drops. Among adult subjects with unilateral or bilateral OAG or OHT, latanoprostene bunod (LBN) 0.024% every evening had a greater IOP-lowering effect than timolol 0.5% twice daily during the daytime, over 3 months of treatment. This study verified the efficacy and safety of LBN [27]. LBN administered at 8 PM had a greater IOP reduction and ocular perfusion pressure increase during the night hours than timolol 0.5% twice daily in patients with OHT or early primary OAG [28]. The mean 24-hour IOP-lowering effect of bimatoprost 0.01% and timolol 0.5% were comparable, but bimatoprost 0.01% was more effective than timolol 0.5% during the nocturnal period [29].

The efficacy and safety of either preserved or PF fixed combination (FC) of PG analogues with timolol were also investigated. The efficacy of a PF latanoprost/timolol FC was equivalent to that of BAK-preserved latanoprost/timolol FC. This treatment was well-tolerated in patients with OAG or OHT who were previously treated with the preserved formulation, and the overall safety profile was similar [30]. The IOP-lowering effect of a PF tafluprost 0.0015%/timolol 0.5% FC was greater than that of both tafluprost (0.0015%) and timolol (0.5%) monotherapies [31]. The once-daily administration of a FC of latanoprost/timolol further reduced IOP compared with twice daily 0.50% timolol monotherapy in patients with primary OAG [32].

The IOP-lowering effect of a PF tafluprost/timolol FC was comparable to that of a preserved latanoprost/timolol FC. A tafluprost/timolol FC improved superficial punctate keratopathy scores [33]. Moreover, a PF tafluprost/timolol FC reduced IOP in primary OAG and OHT patients [34]. The IOP-lowering effect of a FC of bimatoprost/timolol in Chinese patients with OAG or OHT was comparable with concurrent dosing with the single components [35]. Once-daily administration of a FC of bimatoprost 0.03%/timolol maleate 0.5% had greater IOP-lowering efficacy than the triple combination of dorzolamide 2%, brimonidine 0.2%, and timolol maleate 0.5%, although both treatment types were well-tolerated [36].

An additive IOP-lowering effect of topical brimonidine added to topical PG was seen in patients with primary OAG or OHT, but this effect was less than that of topical timolol as monotherapy [37]. Patients with glaucoma with symptoms or signs of ocular surface disease, who were treated with BAK-preserved latanoprost, were switched to PF tafluprost therapy and a triple PF treatment (tafluprost and dorzolamide/timolol FC). These patients had significantly lower mean, peak, and fluctuation of 24-hour IOP following treatment with PF-tafluprost, and enhanced ocular surface parameters and tolerability. On the other hand, the triple PF treatment yielded a more significant 24-hour IOP control than latanoprost baseline therapy [38].

The IOP-lowering outcome of PF timolol 0.1% gel in treatment-naive patients with primary OAG or OHT was effective. Furthermore, this treatment reduced ocular signs and symptoms in patients who were intolerant to preserved eye drops [39]. The IOP-lowering effect of both PF and preserved brimonidine tartrate in patients with OAG or OHT was comparable. Formulations of brimonidine tartrate showed no significant differences in pain, stinging, and blurred vision after instillation. However, at the first instillation, the PF formulation produced a significantly greater burning sensation than the preserved formulation [40].

No significant differences were found in IOP, retrobulbar blood flow velocities, and ocular perfusion pressure between brimonidine/timolol and dorzolamide/timolol FCs after 1 month of treatment in patients with primary OAG [41]. A topical FC of brinzolamide 1% and brimonidine 0.2% was safe and effective in lowering IOP in a 3-month period in patients with OHT or OAG, and reduced IOP significantly more than either brinzolamide 1% or brimonidine 0.2% monotherapy [42]. Azarga (a FC of brinzolamide 1%/timolol 0.5% suspension) had better tolerability than Cosopt (a FC of dorzolamide 2%/timolol 0.5% solution) in patients with primary OAG [43]. Administration of topical CAIs either as monotherapy or in combination with other IOP-lowering medications resulted in a significantly greater difference in IOP measured by dynamic contour tonometry (DCT) and Goldmann applanation tonometry (GAT). The diagnosis type (OAG or OHT) and the number of IOP-lowering medications had no significant influence on the difference in IOP as measured using the two instruments [13]. Dorzolamide/timolol and brinzolamide/timolol FCs effectively decreased IOP, which was a lower target IOP with dorzolamide/timolol than with brinzolamide/timolol, in patients with primary OAG or normal tension glaucoma [44].

Rho-kinase inhibitors, such as netarsudil 0.02% (which has been used since 2018), AR-13324 0.02%, and ripasudil were recently shown to have IOP-lowering effects. Netarsudil 0.02% once-daily was non-inferior to timolol. A clinically and statistically significant IOP-lowering effect of netarsudil 0.02% once-daily has been reported [45]. AR-13324 0.02% (a small molecule inhibitor of Rho-kinase) was not as efficient as latanoprost in patients with OAG or OHT, with unmedicated IOPs of 22-35 mmHg [46]. Ripasudil reduced IOP for at least 7 h following instillation in patients with primary OAG or OHT [47]. Topical administration of ripasudil 0.4% alone or in combination with PG analogues or β-blockers over 1 year had sustained IOP-lowering effects and acceptable safety profiles in patients with OAG (primary OAG and exfoliation glaucoma) or OHT [48]. A once-daily FC of netarsudil/latanoprost had a significant IOP-lowering effect, which was superior to that of netarsudil and latanoprost monotherapy, in patients with OAG or OHT [49]. Once-daily netarsudil had a comparable IOP-lowering effect as compared to twice-daily timolol, with similar frequencies of adverse effects and a similar tolerability profile in adults with bilateral OAG or OHT [50]. Finally, MGV354 0.1% (soluble guanylate cyclase) showed no statistically significant IOP-lowering effect as compared to vehicle-treated patients in subjects with OHT or glaucoma [51].

DISCUSSION

The pathophysiology of primary OAG pertaining to retinal ganglion cell loss is linked to the IOP level. The IOP is dependent on the equilibrium between the aqueous humor of the ciliary body and its drainage by two individual pathways: the trabecular meshwork (conventional) and the uveoscleral (non-conventional) outflow pathways. Primary OAG patients have increased resistance to aqueous outflow through the trabecular meshwork [62].

Table 1. Characteristics of included studies in this review and summary of their main concepts

First author	Study design	Main Findings
Faridi et al., 2010 [20]	Prospective single-masked comparative RCT	Bimatoprost, latanoprost, and travoprost had effective IOP-lowering outcomes, but bimatoprost was the most effective in the initial phase. However, after 6 months of treatment, the difference in the efficacy of the three topical PG analogues was not statistically significant.
Ge et al., 2010 [23]	Open-label, non-comparative clinical trial	A significant IOP-lowering effect of once-daily travoprost in patients with OAG or OHT was found.
Macky et al., 2010 [25]	Hospital-based, prospective RCT	Once-daily administration of bimatoprost 0.03% or travoprost 0.004% achieved effective IOP reduction in patients with primary OAG or OHT. However, bimatoprost provided a greater, although non-significant mean IOP-lowering effect as compared to baseline.
Pacella et al., 2010 [32]	Prospective study	Once-daily administration of a FC of latanoprost/timolol could further reduce IOP than twice daily 0.50% timolol, in patients with primary OAG.
Araie et al., 2012 [37]	Phase III clinical trial	An additive IOP-lowering effect of topical brimonidine in addition to topical PG in patients with primary OAG or OHT was found; this treatment was less effective than topical timolol as monotherapy.
Nebbioso et al., 2012 [43]	Prospective, single-masked study	Better tolerability of Azarga (a FC of brinzolamide 1%/timolol 0.5% suspension) than Cosopt (a FC of dorzolamide 2%/timolol 0.5% solution) was seen in patients with primary OAG.
Siesky et al., 2012 [41]	Prospective, randomized, double-blind, crossover study	The differences in IOP, retrobulbar blood flow velocities, and ocular perfusion pressure between brimonidine/timolol and dorzolamide/timolol were not significant after 1-month treatment in patients with primary OAG.
Katz et al., 2013 [42]	Phase III, double-masked, parallel-group, multicenter RCT	Topical administration of a FC of brinzolamide 1%/brimonidine 0.2% was safe and effective in IOP reduction over 3 months in patients with OHT or OAG, with a significant greater IOP-reduction than with brinzolamide 1% or brimonidine 0.2% monotherapy.
Lascaratos et al., 2013 [21]	Randomized, double-masked, placebo-controlled, multicenter treatment trial	IOP-lowering with latanoprost 0.005% reduced visual field deterioration of newly diagnosed OAG. The early stage of the glaucoma and relatively low baseline IOP indicated markedly sensitive case findings in patients with previously untreated OAG.
Tomic et al., 2013 [24]	Prospective study	Once-daily administration of BAK-preserved travoprost 0.004% was an effective IOP-lowering treatment in patients with newly diagnosed primary OAG.
Tzamalis et al., 2013 [13]	A randomized cross-sectional study	Significant greater difference in IOP measured by DCT and GAT was detected after treatment with topical CAIs, either as monotherapy or in combination with other IOP-lowering medications. Patient diagnosis (OAG or OHT) and the number of IOP-lowering medications had no significant influence on this difference.
Bacharach et al., 2014 [46]	Double-masked, dose-response RCT	AR-13324 0.02% (a small molecule inhibitor of Rho-kinase) had a less marked IOP-lowering effect than latanoprost in patients with OAG or OHT, with unmedicated IOPs of 22-35 mmHg.
Garcia-Lopez et al., 2014 [36]	Phase IV, 6-month, investigator-masked, prospective, crossover multicenter RCT	Once-daily bimatoprost/timolol could have a greater IOP-lowering efficacy than the triple FC of dorzolamide 2%, brimonidine 0.2%, and timolol maleate 0.5% (dorz/brim/tim; Krytantek). Both treatment types were well-tolerated.
Ling et al., 2014 [35]	Multicenter, double-masked, parallel controlled RCT	The IOP-lowering effect of a FC of bimatoprost 0.03%/timolol maleate 0.5% was seen in Chinese patients with OAG or OHT and was comparable with concurrent dosing with the single components.
Pfeiffer et al., 2014 [31]	Phase III, stratified, double-masked, multicenter RCT	The IOP-lowering effect of a PF tafluprost 0.0015%/timolol 0.5% FC was better than that of tafluprost 0.0015% or timolol 0.5% monotherapy.
Tanihara et al., 2015 [47]	Prospective, open-label, three-period, Latin-square crossover multicenter RCT	Ripasudil reduced IOP within 7 hours after instillation in patients with primary OAG or OHT.
Oddone et al., 2015 [29]	Prospective, double-masked, crossover RCT	The mean 24-hour IOP-lowering effect of bimatoprost 0.01% and timolol 0.5% are comparable, but bimatoprost 0.01% was more effective than timolol 0.5% during the night hours.
Galose et al., 2016 [44]	Prospective, controlled, RCT	Dorzolamide/timolol and brinzolamide/timolol provided effective IOP reduction. The reduction was greater and lower target pressures were achieved with dorzolamide/timolol than with brinzolamide/timolol in patients with primary OAG or normal tension glaucoma.
Liu et al., 2016 [28]	Prospective, open-label crossover RCT	LBN eye drop instillation at 8 PM yielded a greater IOP reduction and ocular perfusion pressure increase than timolol 0.5% twice daily during the night hours in patients with OHT or early primary OAG.
Tanihara et al., 2016 [48]	Prospective, open-label clinical trial	Topical administration of ripasudil 0.4% alone or paired with PG analogues or β-blockers over 1 year had a sustained IOP-lowering effect and an acceptable safety profile in patients with OAG (primary OAG and exfoliation glaucoma) or OHT.
Weinreb et al., 2016 [28]	Phase III, double-masked, parallel-group multicenter RCT	LBN eye drop instillation every evening yielded a greater IOP-lowering effect than timolol 0.5% twice daily, in the daytime, in adults with OAG or OHT over a 3-month period of treatment. Efficacy and safety of LBN was also reported.
Konstas et al., 2017[38]	Prospective, observer-masked, crossover, comparison, RCT	Patients with glaucoma and concurrent symptoms or signs of ocular surface disease on BAK-preserved latanoprost were switched to PF tafluprost therapy or a triple PF regimen (tafluprost and dorzolamide/timolol FC). A significantly lower mean, peak, and fluctuation of 24-hour IOP was seen after treatment with PF-tafluprost, along with enhancement of ocular surface parameters and tolerability. The triple PF medication produced a significantly greater 24-hour IOP control than seen with the latanoprost baseline treatment.

Lazreg et al., 2018 [39]	Phase IV, open-label, non-controlled, multicenter RCT	PF timolol 0.1% gel was effective in lowering IOP in treatment-naive patients with primary OAG or OHT. Furthermore, it reduced ocular signs and symptoms in patients who were intolerant to preserved eye drops.
Serle et al., 2018 [45]	Two large double-masked, noninferiority RCTs	Once-daily netarsudil 0.02% was non-inferior to timolol. A clinically and statistically significant IOP-lowering effect of once-daily netarsudil 0.02% was reported.
Stacy et al., 2018 [51]	Phase I and II, double-masked, randomized, and vehicle-controlled, study	MGV354 0.1% (soluble guanylate cyclase) had no significant IOP-lowering effect as compared to vehicle in patients with OHT or glaucoma.
Suzuki et al., 2019 [33]	Prospective, open-label RCT	The IOP-lowering effect of a preserved tafluprost/timolol FC was comparable with that of a preserved latanoprost/timolol FC. Tafluprost/timolol revealed an improvement in superficial punctate keratopathy scores.
Aptel et al., 2019 [30]	Phase II, parallel-group, investigator-masked RCT	A PF latanoprost/timolol FC showed equivalent efficacy as compared with a BAK-preserved latanoprost/timolol FC. It was well-tolerated in patients with OAG or OHT who were previously treated with the preserved formulation, and the overall safety profile was similar.
Blondeau et al., 2019 [22]	A prospective randomized switch design study	Switching latanoprost to another topical PG (bimatoprost or travoprost) had no additive benefit for patients who were non-responders to the initial1-month latanoprost treatment.
Misiuk-Hojlo et al., 2019 [26]	Prospective, longitudinal, open-label, multicenter trial	PF latanoprost had better tolerability and a comparable IOP-lowering effect as compared to BAK–latanoprost in patients with glaucoma or OHT.
Asrani et al., 2020 [49]	Pooled data of two phase III, double-masked, multicenter, active controlled, parallel-group RCTs	A once-daily FC of netarsudil/latanoprost had a significant IOP-lowering effect, which was superior to netarsudil and latanoprost monotherapy in patients with OAG or OHT.
Duru et al., 2020 [40]	RCT	The IOP-lowering effect of both PF and preserved brimonidine in patients with OAG or OHT was comparable.
Karlova et al., 2020 [34]	Prospective multicenter European RCT	A PF tafluprost/timolol FC reduced IOP in primary OAG and OHT.
Singh et al., 2020 [50]	Pooled data of the ROCKET-1 to -4 randomized, phase III trials	Once-daily netarsudil had a comparable IOP-lowering effect against twice-daily timolol, with similar frequencies of adverse effects and a similar tolerability profile in adults with bilateral OAG or OHT.

Abbreviations: BAK, benzalkonium chloride; CAIs, Carbonic Anhydrase Inhibitors; DCT, dynamic contour tonometry; FC, fixed combination; GAT, Goldmann applanation tonometry; IOP, Intraocular pressure; LBN, latanoprostene bunod ophthalmic solution 0.024; mmHg, millimeters of mercury; OAG, open angle glaucoma; OHT, ocular hypertension; PG, prostaglandins; PM, afternoon; PF, preservative-free; ROCKET-1, Rho Kinase Elevated IOP Treatment Trial 1; RCT, Randomized Controlled Trial.

Table 2. Summary of mechanism of action of intraocular pressure (IOP)-lowering medications

Drug Class	Mechanism of action
ROCK inhibitor* and norepinephrine transporter inhibitor	The netarsudil IOP-lowering effect was accomplished via three effects on aqueous humor dynamics, including a trabecular-outflow facility increase, and aqueous humor production decrease, as well as an episcleral venous pressure decrease [52, 53].
PG analogues	Increases uveoscleral outflow. One plausible mechanism may involve induction of metalloproteinases in the ciliary body, and breakdown of the extracellular matrix, with subsequent reduction in outflow resistance through the uveoscleral pathway (traditional PG analogues: bimatoprost, latanoprost, and travoprost) [28, 54-57].
Beta-adrenergic agonists	Aqueous humor production is apparently activated by a β receptor-mediated cyclic adenosine monophosphate (AMP) /protein kinase A (PKA) pathway. β blockers blunt adrenergic activation of this pathway. An additional hypothesis is that ocular blood flow is reduced by β blockers, which subsequently leads to reduction in the ultrafiltration that controls aqueous production [58, 59].
Alpha-adrenergic agonists	Reduce IOP by reducing aqueous humor production, and by enhancing both conventional and uveoscleral outflow [60].
Carbonic anhydrase Inhibitors	Reduce bicarbonate ion formation and fluid transport, and consequently, the IOP [30].

Note: * ROCK inhibitor and norepinephrine transporter inhibitor [61], example netarsudil (AR-13324).

Currently, IOP is the single modifiable risk factor in the management of glaucoma. The goal of therapy is to prevent or delay glaucoma progression by reducing IOP, regardless of the initial IOP level [9, 63]. Pharmaceutical treatment is a common intervention in primary OAG for IOP reduction. The first line of therapy for primary OAG in published guidelines is topical eye drops [64, 65]. Therefore, we concentrated only on pharmaceutical treatment rather than surgical procedures or laser intervention.

PG analogues

PG analogues are more widely used to reduce IOP than other classes [1, 64, 65]. Compared to placebo, bimatoprost, latanoprost, and travoprost are among the most efficacious drugs for decreasing IOP in 3 months, although the variations within the class were small and probably not clinically significant [19]. PG analogues have increasingly replaced β-adrenergic receptor antagonists as first-line medical therapy because of their once-daily dosing, low occurrence of systemic side effects, and potent IOP-lowering effect. While PG analogues are the most commonly recommended first-line medications, both PG analogues and β-blockers are considered as first-line medications to lower IOP [1, 64, 65]. Examples of PG analogues (PGF2α analogues) available as eye drops are latanoprost, travoprost, bimatoprost, tafluprost, and unoprostone. Unoprostone and tafluprost are available for prescription in Japan. Generic latanoprost has been demonstrated to be no less, and probably more effective than its branded counterparts, in avoiding the need for additional treatment modalities [66]. Patients who were non-responsive to latanoprost did not benefit from switching to other topical PG analogues [22].

PF latanoprost has at least the same IOP-reducing effectiveness as BAK-preserved latanoprost, with a higher tolerability profile. This could result in better treatment control and improved quality of life [26]. Once-daily administration of travoprost reduced IOP [23]. BAK-preserved travoprost 0.004% disrupted the tear film stability in the long-term, despite having a significant IOP-lowering effect [24]. Bimatoprost, latanoprost, and travoprost were effective at lowering IOP, with comparable long-term results [20].

Beta-adrenergic antagonists

Nonselective β-blockers that bind to both β1 and β2 receptors include timolol, levobunolol, metipranolol, and carteolol [58]. The β1-selective antagonist betaxolol is available for ophthalmic use, but is less effective. PF timolol 0.1% gel effectively reduced IOP in treatment-naive patients [39].

Alpha-adrenergic agonists

If the use of PG analogues or β-receptor antagonists is contraindicated, other agents, such as α-2 adrenergic receptor agonists or topical CAIs, can be administered as first-line treatment. Examples of α-adrenergic agonists are brimonidine tartrate ophthalmic solution 0.1% or 0.15 % (Alphagan-P), brimonidine tartrate ophthalmic solution 0.2%, and apraclonidine HCL 0.5% or 1 % (Idopidine). PF brimonidine tartrate and preserved brimonidine % 0.15 preparations decreased IOP at a similar rate [40].

Carbonic anhydrase inhibitors

Examples of CAIs are dorzolamide and brinzolamide. A FC of PF latanoprost/timolol T2347 showed similar efficacy to that of BAK-preserved latanoprost/timolol [30]. In comparison, a triple PF tafluprost with PF dorzolamide/timolol FC resulted in a significant improvement in 24-hour IOP control as compared to the latanoprost baseline treatment [38]. Administration of CAIs either as monotherapy or in combination with other IOP-lowering medications resulted in a statistically significant difference in IOP measured by DCT and GAT [13].

Rho-kinase inhibitors

Treatment with netarsudil 0.02% ophthalmic solution (a Rho-kinase inhibitor) was effective and well-tolerated once-daily in patients with OHT and OAG [45, 50]. The administration of 0.4% ripasudil, another Rho-kinase inhibitor, for 52 weeks resulted in a decrease in IOP and an acceptable safety profile in patients with OAG or OHT, whether treated as monotherapy or additive therapy [48].

Fixed combination products

All four classes of pharmaceuticals can be applied as additive second- or third-line treatments. The β-receptor antagonist timolol has been paired with CAIs, such as dorzolamide in a single medication. In addition, timolol was combined with the α-2 adrenergic agonist brimonidine. Furthermore, a brinzolamide/brimonidine combination has recently been introduced, and a latanoprost/timolol combination is also widely available. These combinations minimize the number of drops required and enhance patient compliance. A once-daily FC of netarsudil/latanoprost had a significant IOP-lowering effect, which was superior to that of netarsudil and latanoprost monotherapy in patients with OAG or OHT [49]. The PF tafluprost/timolol FC decreased IOP when administered in combination, as compared to as monotherapy [31, 33, 35]. In addition, another study showed that PF tafluprost/timolol yielded the greatest decrease in IOP at week 4, and that this was sustained throughout the 6-month study duration [34]. The IOP-lowering effect of bimatoprost and timolol was comparable

at 24 hours [29]. Once-daily bimatoprost/timolol may have better IOP-lowering efficacy than dorzolamide/bimatoprost/timolol [36]. Topical brimonidine has an additive IOP-lowering effect when added to topical PG analogues, but its IOP-lowering effect was lower than that of topical timolol monotherapy [37]. Brinzolamide 1% plus timolol 0.5% suspension is more tolerable than dorzolamide 2% plus timolol 0.5% [43]. A once-daily latanoprost/timolol combination reduced IOP and retained IOP control over the 24-month observation period [32].

LBN 0.024% demonstrated greater IOP-lowering effects than timolol 0.5% twice daily, during daytime, over 3 months of treatment [28]. LBN (administered at 8 PM) induced more IOP reduction and increased ocular perfusion pressure during the nocturnal period more than timolol (administered at 8 AM and 8 PM) [28]. After 1 month of treatment, brimonidine/timolol and dorzolamide/timolol resulted in well-controlled IOP in OAG patients, with a significant difference in the IOP [41]. The IOP-lowering effect of MGV354 0.1%, which is a soluble guanylate cyclase, was not significant [51].

In primary OAG patients, an FC of brinzolamide 1%/brimonidine 0.2% was a safe and effective IOP-lowering therapy and provided a significantly greater IOP-lowering activity as compared to either brinzolamide or brimonidine monotherapy [42]. Both FCs of brinzolamide/timolol and of dorzolamide/timolol provided effective IOP reduction, although patients treated with dorzolamide/timolol were more likely to achieve lower target pressures than those treated with brinzolamide/timolol [44]. Both bimatoprost and travoprost effectively decreased IOP, but bimatoprost provided a larger, although statistically non-significant, reduction in mean IOP from baseline [25]. In treatment-naive patients with IOPs of 22-35 mmHg, netarsudil (AR-13324) 0.02%, was not as effective as latanoprost [46].

There is a very strong correlation between the baseline, untreated IOP level and the amount of IOP reduction, and there appears to be a lower threshold of about 15 mmHg where treatment did not yield any IOP reduction. The importance of the disclosure of the baseline IOP level in addition to the IOP-lowering effect of drugs has been acknowledged [63].

A strength of this review is that it focused on primary OAG pharmaceutical interventions. In addition, the mechanism of action of each drug class was summarized, and new interventions, such as netarsudil and ripasudil, which are inhibitors of Rho-kinase, were discussed. Additionally, it provided an update on the latest FC interventions that have been studied in clinical trials. The limitation of this review is that it did not include a discussion of any laser or surgical procedures. Future studies focusing on both the safety and efficacy of available drug classes, besides the effects of their FC eye drops on compliance and adherence of patients with glaucoma, could provide a more comprehensive and practical overview of the outcomes of pharmaceutical treatment of glaucoma.

CONCLUSIONS

This review highlighted that new medications yield a significant decrease in IOP in patients with primary OAG. Primary OAG is a cause of irreversible vision loss. If it is not diagnosed and treated early, the condition is likely to progress in many patients, and the long-term risk of blindness is considerable. This review highlights that the novel Rho-kinase inhibitors have shown significant IOP reduction and that new FCs markedly reduce IOP.

ETHICAL DECLARATIONS

Ethical approval: This study was a review and no ethical approval was required.
Conflict of interests: None.

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