

Class Update: Ophthalmic Glaucoma Agents

Month/Year of Review: January 2015

PDL Class: Ophthalmic Glaucoma Agents

Literature Search End Date: July 2014

Date of Last Review: August 2012

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Current Preferred Drugs	Current Non-preferred Drugs
<i>Beta-receptor Antagonists</i>	
Betaxolol Carteolol Timolol (Timoptic) Timolol/dorzolamide (Cosopt)	Betaxolol (Betopic S) Levobunolol (Betagan) Metipranolol Timolol (Betimol; Istalol; Timoptic Ocudose; Timoptic XE)
<i>Acetylcholinesterase Inhibitors, Miotic Agents</i>	
Pilocarpine (Isopto Carpine; Pilocar)	Acetylcholine (Miochol-E) Carbachol (Isopto Carbachol; Miostat) Echothiophate (Phospholine Iodide)
<i>Alpha-2 Agonists</i>	
Brimonidine (Alphagan, Alphagan P)	Apraclonidine (Iopidine) Brimonidine/timolol (Combigan) Brimonidine/brinzolamide (Simbrinza)
<i>Carbonic Anhydrase Inhibitors</i>	
Brinzolamide (Azopt) Dorzolamide/timolol (Cosopt)	Brinzolamide/brimonidine (Simbrinza) Dorzolamide (Trusopt)
<i>Prostaglandins</i>	
Latanoprost (Xalatan) Travoprost (Travatan, Travatan Z)	Bimatoprost (Lumigan) Tafluprost (Zioptan) Unoprostone (Rescula)

Research Questions:

- Is there any new comparative evidence of meaningful difference in effectiveness for different drug classes of ophthalmic medications used to treat glaucoma?
- Is there any new comparative evidence of meaningful difference in harms for different drug classes of ophthalmic medications used to treat glaucoma?
- Is there any evidence that brinzolamide/brimonidine fixed-combination or unoprostone are safer or more effective than other ophthalmic glaucoma agents?
- Are there subgroups of patients in which brinzolamide/brimonidine or unoprostone are safer or more effective than other available ophthalmic treatments for glaucoma?

Previous Recommendations:

- No changes to current preferred drug list (PDL) status are necessary based on continued lack of clinical evidence for differences in efficacy/effectiveness or harms between drugs within each class.
- Continue to include a medication from each pharmacologic category on the PDL, including miotics, sympathomimetics, beta blockers, carbonic anhydrase inhibitors, and prostaglandin analogues.

Current Conclusions:

- There is insufficient evidence to determine if there are any meaningful differences in efficacy/effectiveness or harms for the different drug classes of ophthalmic medications used to treat glaucoma.
- There is insufficient evidence to determine if there is any difference in efficacy/effectiveness or safety with brinzolamide/brimonidine fixed-combination compared to the individual components of the drug together. However, there is moderate quality evidence brinzolamide/brimonidine as a fixed-combination is more effective than the individual components alone.^{1,2}
- There is moderate quality evidence that unoprostone is less effective than latanoprost or timolol at lowering intra-ocular pressure.³⁻⁸
- There is insufficient evidence that unoprostone is safer than other ophthalmic prostaglandins.^{3,4,6-8}

Current Recommendations:

- Maintain brinzolamide/brimonidine fixed-combination product and unoprstone as non-preferred.
- Continue to include a medication from each category including miotics, alpha-adrenergic agonists, beta-blockers, carbonic anhydrase inhibitors, and prostaglandin analogues on the PDL.
- Evaluate comparative costs in the executive session.

Background:

Glaucoma is a group of eye diseases traditionally characterized by elevated intraocular pressure (IOP).⁹ Lowering intraocular pressure (IOP) reduces the risk of glaucomatous progression of visual field loss and optic disc changes and is therefore the primary goal of therapy.¹⁰ Topical medications work either by increasing aqueous outflow (prostaglandins, alpha adrenergic agonists, acetylcholinesterase inhibitors/miotic agents) or by decreasing aqueous production (alpha adrenergic agonists, beta-blockers, carbonic anhydrase inhibitors).⁹

Methods:

An Ovid MEDLINE search was conducted using all available ophthalmic glaucoma agents and limited to randomized controlled trials, systematic reviews, English language, and studies conducted in humans since the last review was performed. The Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were searched for high quality systematic reviews. The FDA website was searched for new drugs, indications, and safety alerts, and the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines. After review of the citations from Medline and manual searches, two systematic reviews, three head-to-head trials and two new drug formulations were included.

New Systematic Reviews:

Quranta, et al.¹¹ conducted a systematic review and meta-analysis on the IOP-lowering effect of prostaglandin analogs (PGAs) administered in combination with beta-blockers in patients with glaucoma or ocular hypertension. The efficacy endpoint was the mean difference (MeD) in reduction of IOP from baseline. Tolerability was assessed by evaluating the incidence of hyperemia. The review included 18 trials using PGAs and timolol as monotherapy (MT) or in fixed combinations (FC) or unfixed combinations (UC). There were a total of 23 comparisons of FC vs. MT, and 5 comparisons of FC vs. UC. The FCs were less efficacious than UCs (0.69 mm Hg, 95% CI: 0.29 to 1.08 mm Hg). In comparison with timolol MT, the latanoprost/timolol FC led to a greater IOP reduction (-2.74 mm Hg, 95% CI: -3.24 to -2.23 mm Hg) than the bimatoprost/timolol FC (-1.49 mm Hg, 95% CI: -1.86 to -1.12 mm Hg) or the travoprost/timolol FC (-1.93 mm Hg, 95% CI: -2.98 to -0.88 mm Hg). The FCs led to a lower hyperemia risk than UCs [relative risk (RR): 0.70, 95% CI: 0.43 to 1.14] and PGA MT (RR: 0.61, 95% CI: 0.53 to 0.70). The authors concluded FCs are more efficacious than their individual components, but less efficacious than their respective UCs. There was a lower risk of hyperemia associated with FCs compared to UCs and their respective PGA MTs.

Chang, et al.¹² performed a systematic review and meta-analysis to evaluate the IOP-lowering effect of the commonly used FCs containing 0.5% timolol. Forty-one randomized clinical trials of patients with primary open angle glaucoma (POAG) or ocular hypertension (OHT) were conducted. The primary efficacy endpoints were the absolute and relative values of mean diurnal IOP reduction, and the highest and lowest IOP reduction on the diurnal IOP curve. The relative reductions for mean diurnal IOP were 34.9% for travoprost/timolol, 34.3% for bimatoprost/timolol, 33.9% for latanoprost/timolol, 32.7% for brinzolamide/timolol, 29.9% for dorzolamide/timolol, and 28.1% for brimonidine/timolol. For the highest IOP decrease, relative reductions ranged from 31.3% for dorzolamide/timolol to 35.5% for travoprost/timolol; for the lowest IOP decrease, those varied from 25.9% for dorzolamide/timolol to 33.1% for bimatoprost/timolol. Both latanoprost/timolol and travoprost/timolol were more effective in lowering mean diurnal IOP than brimonidine/timolol (WMD: 5.9 and 7.0) and dorzolamide/timolol (WMD: 3.8 and 3.3). The analysis concluded that the six commonly used FC drugs containing timolol can effectively lower IOP in patients with POAG and OHT, and both latanoprost/timolol and travapost/timolol might achieve greater IOP-lowering effects.

New Guidelines:

None identified.

New FDA Safety Alerts:

None identified.

New Drugs:

None identified.

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New Formulations or Indications:

In April 2013, the FDA approved a fixed combination ophthalmic suspension product of brinzolamide 1%/brimonidine 0.2% (Simbrinza®) to lower the IOP in patients with open angle glaucoma or ocular hypertension.¹³ Approval was based on two published randomized clinical trials.^{1,2} Both trials were Phase 3, factorial-design, double-masked studies comparing brinzolamide 1%/brimonidine 0.2% fixed combination (BBFC) to each of the two components individually. The primary end point of IOP was measured at four time points during one day at baseline, one day at Week 2, one day at Week 6, and one day at Month 3. Study C-10-033² enrolled 660 patients at 68 sites and Study C-10-039¹ enrolled 690 patients at 64 sites in the U.S. The results of study C-10-033 showed at 3 months, the mean IOP of the BBFC group was statistically significantly lower than that of either the brinzolamide group (ranging from -1.1 to -3.4 mmHg) or the brimonidine group (ranging from -1.5 to -2.8 mmHg) across all time four points at each of the three visits.² Study C-10-039 also found similar results, with mean IOP in the BBFC group significantly lower than that of either the brinzolamide group or the brimonidine group alone ($P \leq 0.005$) across all time points.² Common adverse reactions reported in these studies were essentially analogous to adverse reactions previously reported with one or the other ingredient when used in treatment of IOP. Most common adverse reactions occurring in approximately 3 to 5% of patients included blurred vision, eye irritation, dysgeusia (bad taste), and dry mouth.

Unoprostone (Rescular®) was approved by the FDA to lower IOP in patients with open angle glaucoma or ocular hypertension in 2000¹⁴; however, it was not marketed until 2013. Since its approval, there have been several randomized comparative studies investigating its efficacy and safety as adjunctive therapy. Information on these trials are summarized in **Table 1** and abstracts are available in **Appendix 1**.^{3-8,15,16,17} Studies that directly compared latanoprost and unoprostone showed statistically significant IOP reduction favoring latanoprost^{4,7,8}. Similar results was also observed in two small randomized crossover studies.^{3,6} When unoprostone was compared with the two beta-blockers timolol or betaxolol, each drug produced a clinically and statistically ($P < .001$) significant reduction from baseline in 12-hour diurnal IOP at month 6. Unoprostone was clinically equivalent to betaxolol (0.53 mmHg [95% CI: - 0.03, 1.09 mmHg]) but did not have as great an IOP-lowering effect as timolol (adjusted mean of 1.57 mmHg (95% CI: 1.00, 2.13)).⁵ Two studies investigated the efficacy of unoprostone as adjunctive therapy to timolol compared with brimonidine as adjunctive therapy to timolol¹⁵ or dorzolamide as a FC with timolol¹⁷; each treatment produced additive IOP reduction, but showed no statistical difference between treatments.

Table 1: Studies of Unoprstone 0.15% Ophthalmic Solution Applied Twice Daily.

Study	Comparison	Population	Primary Outcome	Results
Aung, et al. ³ 2002 RCT	Latanoprost 0.005% at HS added to unoprostone (n= 15) vs. unoprsterone added to latanoprost 0.005% at HS (n=17).	POAG or OH	Reduction in IOP when both medications were used compared with when one medication used	IOP decreased by 1.9 (± 0.6) mmHg ($p = 0.012$) when latanoprost was added to patients already treated with unoprostone. However, unoprostone added to patients already treated with latanoprost, IOP increased +0.4 (± 0.5) mm Hg ($p = 0.42$).
Gianpani, et al. ⁴ 2001 RCT, DB, PG	Latanoprost 0.005% at HS with AM placebo (n= 54) vs. unoprostone (n= 54).	POAG or OH	Mean change of IOP between baseline and at the end of 8 weeks treatment	Latanoprost reduced IOP by 6.7 mmHg (28%) and unoprostone reduced IOP by 3.3 mmHg (14%), a significant difference of 3.4 mmHg (95% CI, -4.7 to -2.1; $p < 0.001$). Incidences of AEs were low and comparable between groups.
Nordmann,	Unoprostone (n= 278)	POAG or OH	Mean IOP change	Each drug produced a clinically and statistically ($P < .001$) significant

et al. ⁵ 2002 RCT, MC, DB	vs. timolol 0.5% BID (n= 138) vs. betaxolol 0.5% BID (n= 140)		between baseline and at the end of 6 months treatment for each drug and comparison between drugs at the end of 6 months treatment	reduction from baseline in 12-hour diurnal IOP at month 6 (-4.3 mmHg for unoprostone; -5.8 mmHg for timolol; -4.9 mmHg for betaxolol). Differences in adjusted treatment means between unoprostone and timolol and unoprostone and betaxolol were 1.57 mmHg (95% CI: 1.00, 2.13) and 0.53 mmHg (95% CI: - 0.03, 1.09), respectively. Unoprostone was clinically equivalent to betaxolol but did not have as great an IOP-lowering effect as timolol.
Aung, et al. ⁶ 2001 RCT, DB, CO	Latanoprost 0.005% at HS for 4 weeks (n= 30) vs. unoprostone twice daily for 4 weeks (n= 30).	POAG or OH	Mean reduction in IOP between two treatments	The difference of 1.9 mmHg between treatments was statistically significant in favor of latanoprost (p =0.003) after 4 weeks. Unadjusted analysis of responders using the percent decrease in IOP showed that the proportion of responders in the latanoprost-treated group was greater than in the unoprostone-treated group.
Sharpe, et al. ¹⁵ 2005 MC, DB, CO	Brimonidine 0.2% TID vs. unoprostone both added to timolol 0.5% BID (n=33)	POAG or OH	Comparison of IOP measured at 0800, 1000, 1600, 1800, and 2000 hours at baseline and at the end of 6 weeks treatment	No significant difference between treatment groups at any time point for the diurnal curve, or in the reduction from baseline (P>0.05). Both treatments failed to statistically reduce the IOP from baseline at 1800 hours. There was no difference between treatment groups regarding unsolicited ocular and systemic AEs, but patients admitted to more dryness (P=0.02) and burning upon instillation (P<0.0001) with unoprostone.
Sponsel, et al. ⁷ 2002 RCT	Unoprostone in one eye and latanoprost 0.005% in other eye at HS with placebo in AM (n=25)	POAG or OH	Mean reduction in IOP between two treatments at end of 28 days measured in the morning and afternoon.	Latanoprost decreased IOP by 2.6 mmHg (14%) in the AM to 16.2 ±0.6 mmHg among eyes treated with latanoprost (P < .0001), and decreased by -1.6 mm Hg (8%), among eyes treated with unoprostone, to a level of 17.9 ±0.7 mmHg (P < .02). Difference in mean IOP after 1 week of therapy was statistically significant (P < .001). Similarly, the PM IOP showed statistically significant difference between two drugs (p = 0.04) favoring latanoprost.
Jampel, et al. ⁸ 2002 RCT, PG, MC	Latanoprost 0.005% at HS with morning placebo (n= 84) vs. unoprostone (n= 81).	POAG or OH	Mean reduction in IOP between baseline and at the end of 8 weeks treatment measured at 0800, 1000, and 1600 hours	The change in the mean ±SD of the IOPs measured at 8:00 AM, noon, and 4:00 PM was -7.2 ±3.2 mmHg (28%) for latanoprost (25.3 ±2.8 mmHg at baseline to 18.2 ±2.8 mm Hg at 8 weeks) and -3.9 ±2.6 mmHg (15%) for unoprostone (25.5 ±3.3 mmHg at baseline to 21.6 ±4.0 mmHg (P ≤0.01). No SAEs related to either medication were reported.
Hommer, et al. ¹⁶ 2003 MC, RCT, DB,	Unoprostone (n = 50), brimonidine 0.2% BID (n= 48) or dorzolamide 2% BID	POAG or OH	Mean change from baseline to week 12 in 8-hour diurnal IOP	At week 12, each adjunctive therapy produced statistically significant (p<0.001) reductions from timolol treated baseline in the mean 8-hour diurnal IOP (-2.7 mmHg for unoprostone; -2.8 mmHg for brimonidine; -3.1 mmHg for dorzolamide). The extent of IOP

PG	(n= 48) as adjunctive therapy to timolol 0.5% BID for 12 weeks.			reduction did not differ significantly between unoprostone and either brimonidine (p = 0.154) or dorzolamide (p = 0.101). Burning/ stinging were the most commonly reported AEs.
Day, et al. ¹⁷ 2003 MC, RCT, CO, DB	Timolol 0.5%/dorzolamide 2% fixed combination vs. timolol 0.5% and unoprostone for 6 weeks (n=13)	POAG or OH	IOP measured at 0800, 1000, 1600, 1800, and 2000 hours at baseline and at the end of 6 weeks	No significant difference for the diurnal curve (p = 0.63), or in the extended IOP reduction from baseline (p>0.05) between treatment groups at any time point at 6 weeks. No SAEs reported.

Key: AE = adverse event; AM = morning; BID = twice daily; CI = confidence interval; CO = cross-over; DB = double blind; HS = bedtime; IOP = intraocular pressure; MC = multi-center; OH = ocular hypertension; PC = placebo control; PG= parallel group; PM = afternoon; POAG = primary open-angle glaucoma; RCT = Randomized controlled trial; SAE = serious adverse events.

New Trials:

A total of 105 citations were identified from initial literature search. After screening, 3 head-to-head randomized trials were included (**Appendix 1**). These trials are briefly described in **Table 2**.

Table 2: Potential Relevant New Clinical Trials.

Study	Comparison	Population	Primary Outcome	Results
Shoji, et al. ¹⁸ 2013 MC, SB, CO, RCT	Travoprost/timolol (TTFC) 0.004%/0.5% daily vs. latanoprost/timolol (LTFC) 0.005%/0.5% daily	Normal-tension glaucoma	Reduction of IOP from baseline	Mean reduction in IOP at 12 weeks was significantly greater in the TTFC group than in the LTFC group (-2.4 ±2.3 mmHg vs. -1.1 ±2.3 mmHg; P = 0.021).
Delval, et al. ¹⁹ 2013 RCT, DB	Unpreserved timolol 0.1% gel daily vs. preserved latanoprost 0.005% daily	OH	20% reduction at Day 84 of the sum of the scores of the eight ocular symptoms and the six objective signs, as well as satisfactory IOP reduction.	At day 84, 91.5% of patients were responders to the primary composite outcome with timolol vs. 48.6% with latanoprost (P<0.001). Response was driven by symptom relief with the unpreserved product. IOP was not statistically different between the two groups at day 28 or day 84.
Day, et al. ²⁰ 2013 MC, DB, PG, NI, RCT	Bimatoprost 0.03% PF twicw daily vs. bimatoprost 0.03% (Lumigan) twice daily.	POAG or OH	Non-inferiority evaluated as change from baseline in IOP in worst eye in the per-protocol population at week 12.	Bimatoprost PF is noninferior to bimatoprost (Lumigan) as both treatments showed similar decreases in mean average eye IOP at all follow-up time points (p<0.001).

Key: CI = confidence interval; CO = cross-over; DB = double blind; IOP = intraocular pressure; LTFC = latanoprost-timolol fixed combination; MC = multi-center; NI = non-inferiority; PF = preservative free; PG = parallel group; SB = single-blinded; RCT = randomized controlled trial; TTFC = travoprost-timolol fixed combination.

References:

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Appendix 1: Abstract of RCTs and Systematic Reviews

1. Whitson J, Realini, Nguyen, McMenemy, Goode. Six-month results from a Phase III randomized trial of fixed-combination brinzolamide 1% + brimonidine 0.2% versus brinzolamide or brimonidine monotherapy in glaucoma or ocular hypertension. *Clinical Ophthalmology*. 2013;1053.

Abstract

Background: The objective of this study was to examine the safety and intraocular pressure (IOP)-lowering efficacy of a fixed combination of brinzolamide 1% + brimonidine 0.2% (BBFC) after six months of treatment in patients with open-angle glaucoma or ocular hypertension.

Methods: This was a randomized, multicenter, double-masked, three-month, three-arm contribution-of-elements study with a three-month safety extension. Patients were randomly assigned 1:1:1 to treatment with BBFC, brinzolamide 1%, or brimonidine 0.2% after a washout period. Patients dosed their study medications three times daily at 8 am, 3 pm, and 10 pm for six months. Patients returned for visits at two weeks, six weeks, three months, and six months. IOP measurements were used to assess efficacy. Safety assessments were adverse events, corrected distance visual acuity, slit-lamp biomicroscopy, pachymetry, perimetry, fundus parameters, and cardiac parameters.

Results: A total of 690 patients were randomized. Six-month mean IOP values were similar to those at three months, when the mean IOP in patients treated with BBFC was significantly lower than that of either monotherapy group. A total of 175 patients experienced at least one treatment-related adverse event (BBFC, 33.0%; brinzolamide, 18.8%; brimonidine, 24.7%), eight of which were severe, and five resulted in discontinuation. Seventy-seven patients discontinued participation due to treatment-related adverse events (BBFC, 17.2%; brinzolamide, 2.1%; brimonidine, 14.5%). There were 21 serious adverse events (n = 7 in each group), none of which was related to treatment. Resting mean pulse and blood pressure with BBFC were similar to those with brimonidine, demonstrating modest, clinically insignificant decreases. No new or increased risks were identified with use of BBFC relative to either monotherapy.

Conclusions: This study showed that, after six months of treatment, the safety profile of BBFC was similar to that of its individual components and its IOP-lowering activity was similar to its efficacy at three months, when it was superior to both brinzolamide 1% alone and brimonidine 0.2% alone.

2. Katz G, DuBiner H, Samples J, Vold S, Sall K. Three-month randomized trial of fixed-combination brinzolamide, 1%, and brimonidine, 0.2%. *JAMA Ophthalmol*. 2013;131(6):724-730.

Abstract

Importance: This study evaluates the contribution of the individual components of an investigational non- β -antagonist fixed combination of brinzolamide, 1%, and brimonidine, 0.2%. This study and its sister study provide the first randomized data showing the intraocular pressure (IOP)-lowering activity and the toxicity profile of this novel topical antihypertensive fixed combination.

Objective: To compare IOP-lowering efficacy of fixed-combination brinzolamide, 1%, and brimonidine, 0.2%, with that of its components in patients with open-angle glaucoma or ocular hypertension.

Design: In this phase 3, double-masked, parallel-group, multicenter study, eligible patients were randomized 1:1:1 to treatment with fixed-combination brinzolamide, 1%, and brimonidine, 0.2%; brinzolamide, 1%; or brimonidine, 0.2%, 3 times daily for 3 months.

Setting: Sixty-six academic and private practice study sites throughout the United States.

Participants: A total of 660 adults with a clinical diagnosis of open-angle glaucoma or ocular hypertension from a referred sample were enrolled. Thirty-four patients discontinued participation due to treatment-related nonserious adverse events.

Intervention: Topical administration of study medication (fixed-combination brinzolamide, 1%, and brimonidine, 0.2%; brinzolamide, 1%; or brimonidine, 0.2%) 1 drop 3 times daily for 3 months.

Main outcomes and measures: Mean IOP at the 3-month visit at all time points (8 AM, 10 AM, 3 PM, and 5 PM).

Results: A total of 660 patients were enrolled. Baseline mean IOP values were similar among treatment groups at all 4 time points. At 3 months, the mean IOP of the brinzolamide-brimonidine group (16.3-19.8 mm Hg) was significantly lower than that of either the brinzolamide group (19.3-20.9 mm Hg; $P \leq .002$) or the brimonidine group (17.9-22.5 mm Hg; $P < .001$) across all time points. One of 10 serious adverse events (chest pain, brinzolamide group) was judged as treatment related. A total of 129 patients experienced at least 1 treatment-related adverse effect (brinzolamide-brimonidine, 22.9%; brinzolamide, 18.6%; and brimonidine, 17.3%; $P = .31$), most of which were ocular.

Conclusions and relevance: This registrational study provides evidence that the fixed combination of brinzolamide, 1%, and brimonidine, 0.2%, can safely and effectively lower IOP in patients with open-angle glaucoma or ocular hypertension, showing significantly superior IOP-lowering activity compared with either brinzolamide or brimonidine monotherapy while providing a safety profile consistent with that of its individual components.

3. Aung T, Chew PTK, Oen FTS, et al. Additive effect of unoprostone and latanoprost in patients with elevated intraocular pressure. *Br J Ophthalmol* 2002;86(1):75-79.

Abstract

Aims: To assess the additive effect of unoprostone and latanoprost in patients with primary open angle glaucoma (POAG) or ocular hypertension (OHT) **METHODS:** 32 patients with POAG or OHT were randomised to receive either latanoprost once daily or unoprostone twice daily for 4 weeks. After 4 weeks, all patients received both latanoprost and unoprostone for another 4 weeks. The IOP was measured at 9 am and 5 pm on the baseline, day 28, and day 56 visits, and at 9 am on day 14 and day 42 visits. The medications were given to the patients in an open label fashion. The observer was masked to the treatment given. The mean of the measurements was calculated. Safety parameters were also recorded. The additive effect of the medications was assessed by the reduction in intraocular pressure (IOP) when both medications were used, compared with when one medication was used.

Results: 28 patients completed both treatment periods and had IOP data available for evaluation. After 1 month of treatment, latanoprost significantly reduced IOP (mean by 6.1 (SEM 0.8) mm Hg ($p < 0.001$) and unoprostone by 4.9 (1.0) mm Hg ($p < 0.001$) from the baseline of 24.4 (0.6) mm Hg and 24.4 (1.1) mm Hg respectively ($p = 0.18$). When latanoprost once daily was given to patients treated with unoprostone, there was additional IOP lowering of 1.9 (0.6) mm Hg ($p = 0.012$). However, adding unoprostone to those being treated with latanoprost produced an IOP change of +0.4 (0.5) mm Hg ($p = 0.42$). Ocular symptoms and findings were mild and equally distributed between treatment groups, and after combined therapy. Hyperaemia and ocular irritation were the most frequently reported events. Over a third of patients experienced ocular irritation with the combination of medications.

Conclusions: Latanoprost once daily causes additional IOP lowering in eyes which were being treated with unoprostone twice a day. However, there was no additional IOP lowering when unoprostone was added to eyes which were being treated with latanoprost. Both drugs were well tolerated together with few ocular adverse events.

4. Susanna R, Giampani J, Borges AS, Vessani RM, Jordao ML. A double-masked, randomized clinical trial comparing latanoprost with unoprostone in patients with open-angle glaucoma or ocular hypertension. *Ophthalmology* 2001;108(2):259-263.

Abstract

Purpose: To compare the intraocular pressure (IOP) reducing effect and safety of latanoprost 0.005% once daily with unoprostone 0.12% twice daily in patients with primary open-angle glaucoma (POAG) or ocular hypertension (OH).

Design: An 8-week, double-masked, randomized, parallel-group, single-center clinical trial.

Participants: A total of 108 patients with POAG or OH were enrolled.

Interventions: After completing a wash-out of ocular hypotensive medications, patients were randomized to receive either latanoprost once daily in the evening plus placebo once daily in the morning, or unoprostone twice daily (morning and evening).

Main Outcomes: IOP was measured at 10:00 AM and at 5:00 PM at baseline and at week 8, and before 12:00 noon at week 2. Ocular and systemic safety assessments were performed.

Results: From an overall baseline of 24.1 mmHg, latanoprost reduced IOP by 6.7 mmHg (28%) and unoprostone reduced IOP by 3.3 mmHg (14%). The difference between the groups of 3.4 mmHg was significant ($P < 0.001$, analysis of covariance; 95% confidence interval [CI]: -4.7 to -2.1) in favor of latanoprost. A $\geq 30\%$ reduction in mean IOP from baseline was achieved by 44% of latanoprost-treated patients compared with 8% of unoprostone-treated patients. The incidence of adverse events was low and comparable between the groups.

Conclusions: Latanoprost administered once daily was significantly more effective in reducing IOP compared with unoprostone administered twice daily in patients with POAG and OH.

5. Nordmann J-P, Mertz B, Yannoulis NC, et al. A double-masked randomized comparison of the efficacy and safety of unoprostone with timolol and betaxolol in patients with primary open-angle glaucoma including pseudoexfoliation glaucoma or ocular hypertension. 6 month data. *Am. J. Ophthalmol.* 2002;133(1):1-10.

Abstract

Purpose: A long-term comparison of the ocular hypotensive efficacy and safety of unoprostone isopropyl 0.15% twice daily with that of timolol maleate 0.5% twice daily and betaxolol HCl 0.5% twice daily.

Design: This was a randomized, multicenter, double-masked, active-controlled 24-month clinical trial involving 27 centers in Europe and Israel.

Methods: The study population was composed of patients with primary open-angle glaucoma (including pseudoexfoliation) or ocular hypertension. After washout of antiglaucoma medications, intraocular pressure (IOP) was measured at 0, + 2, + 8, and + 12 hours. Patients were randomized in a 2:1:1 ratio to unoprostone, timolol, or betaxolol. Patients returned for examinations at 2 and 6 weeks and 3 and 6 months.

Results: 556 patients were randomized. Each drug produced a clinically and statistically ($P < .001$) significant reduction from baseline in 12-hour diurnal IOP at month 6 (- 4.3 mm Hg, unoprostone; - 5.8 mm Hg, timolol; - 4.9 mm Hg, betaxolol). Differences in adjusted treatment means between unoprostone and timolol and unoprostone and betaxolol were 1.57 mm Hg (95% CI: 1.00, 2.13) and 0.53 mm Hg (95% CI: - 0.03, 1.09), respectively. Unoprostone was clinically equivalent to betaxolol but did not have as great an IOP-lowering effect as timolol. Discontinued for inadequate control of IOP were 7%, 1%, and 4% of the patients for unoprostone, timolol, and betaxolol, respectively. There were no changes of note in visual acuity, pupil size, cup-to-disk ratio, visual fields, or iris color. Changes in heart rate and blood pressure were small, with no clinically significant differences between groups.

Conclusions: Unoprostone provided a clinically significant IOP-lowering effect equivalent to betaxolol but not to timolol. The side effect profile of unoprostone appears to be comparable to other established IOP-lowering agents.

6. Aung T, Chew PT, Yip CC, et al. A randomized double-masked crossover study comparing latanoprost 0.005% with unoprostone 0.12% in patients with primary open-angle glaucoma and ocular hypertension. *Am. J. Ophthalmol.* 2001;131(5):636-642.

Abstract

Purpose: To compare the intraocular pressure)-lowering effect and side effects of latanoprost 0.005% once daily with unoprostone 0.12% twice daily.

Methods: Sixty patients with primary open-angle glaucoma or ocular hypertension were randomized to receive either latanoprost once daily in the evening and placebo once daily in the morning, or unoprostone twice daily in the morning and evening. The study was double masked and followed a crossover design with two treatment periods of 1 month separated by a 3-week washout period. The intraocular pressure was measured at 9 AM and 5 PM on the baseline and day 28 visits, and at 9 AM on day 2 and day 14 visits of each treatment period. The 9 AM measurement was taken 2 hours and 13 hours after the last drop of unoprostone and latanoprost, and the 5 PM measurement was at 10 and 21 hours, respectively. The mean of the measurements was calculated. Safety parameters were also recorded.

Results: Fifty-six patients completed both treatment periods and had intraocular pressure data available for evaluation. After 1 month of treatment, latanoprost significantly reduced intraocular pressure (mean $\pm$ SEM) by 6.1 $\pm$ 0.5 mm Hg ($P < .001$) and unoprostone by 4.2 $\pm$ 0.4 mm Hg ($P < .001$) adjusted from an overall baseline of 22.3 $\pm$ 0.5 mm Hg and 23.2 $\pm$ 0.4 mm Hg, respectively. The difference of 1.9 mm Hg between treatments was statistically significant in favor of latanoprost [$P = .003$, analysis of covariance (ANCOVA)]. Unadjusted analysis of responders using the percentage decrease in intraocular pressure showed that the proportion of responders in the latanoprost-treated group was greater than in the unoprostone-treated group. Adverse ocular symptoms and findings were mild in both treatment groups. Eye redness and ocular irritation were the most frequently reported events.

Conclusions: Latanoprost once daily was significantly more effective in reducing intraocular pressure compared with unoprostone twice daily after 1 month of treatment in patients with primary open-angle glaucoma and ocular hypertension. Both drugs were well tolerated with few ocular adverse events.

7. Sharpe ED, Henry CJ, Mundorf TK, et al. Brimonidine 0.2% vs unoprostone 0.15% both added to timolol maleate 0.5% given twice daily to patients with primary open-angle glaucoma or ocular hypertension. *Eye (Lond)* 2005;19(1):35-40.

Abstract

Purpose: To compare the efficacy and safety of brimonidine 0.2% vs unoprostone 0.15%, both added to timolol maleate 0.5% each given twice daily.

Methods: In this prospective, multi-centred, double-masked, crossover comparison, patients were randomized to one treatment group for a 6-week treatment period, and then crossed over to the opposite treatment. Measurements were performed at 0800, 1000, 1600, 1800, and 2000 h at baseline and at the end of each treatment period.

Results: In all, 33 patients entered this trial and 29 completed. The baseline trough intraocular pressure (IOP) was 23.3+/-2.4 and the diurnal curve IOP was 22.0+/-1.3 mmHg. For the brimonidine and timolol maleate treatment group, the trough IOP was 21.6+/-3.3 and the diurnal curve IOP was 19.8+/-2.1 mmHg, while the timolol and unoprostone treatment showed a trough IOP of 20.9+/-3.8 and a diurnal curve IOP of 19.3+/-2.4 mmHg. There was no significant difference between treatment groups at any time point for the diurnal curve, or in the reduction from baseline ($P>0.05$). Both treatments failed to statistically reduce the IOP from baseline at 1800 h. There was no difference between treatment groups regarding ocular and systemic unsolicited adverse events, but patients admitted to more dryness ($P=0.02$) and burning upon instillation ($P<0.0001$) with unoprostone by survey.

Conclusion: Brimonidine 0.2% or unoprostone 0.15% added to timolol maleate 0.5% provide similar efficacy and safety throughout the daytime diurnal curve.

8. Sponsel WE, Paris G, Trigo Y, Pena M. Comparative effects of latanoprost (Xalatan) and unoprostone (Rescula) in patients with open-angle glaucoma and suspected glaucoma. *Am. J. Ophthalmol.* 2002;134(4):552-559.

Abstract

Purpose: To compare, in paired eyes of open-angle glaucoma patients and glaucoma suspects, hydrodynamic and visual changes after 1 month of topical latanoprost in one eye and unoprostone in the other.

Design: Single-center, institutional randomized clinical trial.

Methods: After completing a washout period off all topical medication, 25 adults (mean age 54 +/- SEM 2 years) with bilateral open-angle glaucoma or glaucoma suspect status underwent morning (8 to 10 AM) and afternoon (1 to 3 PM) measurements of intraocular pressure (IOP), pulsatile ocular blood flow (POBF), contrast, sensitivity, frequency doubling technology, and Humphrey 10-2 perimetry (HVFA II) in both eyes. Each then started unoprostone 0.15% (Rescula) in one randomly assigned eye and latanoprost 0.005% (Xalatan) in the other. Unoprostone was administered at 8 AM and 8 PM and latanoprost at 8 PM with placebo at 8 AM, both from masked bottles. After 28 days, differences were determined for each measured variable by two-tailed paired t test.

Results: Starting from similar baseline IOP levels, after 1 month of treatment, the mean morning IOP values differed according to the topical agent received (16.2 +/- SEM 0.6 mm Hg for latanoprost vs 17.9 +/- 0.7 mm Hg for unoprostone; $P=.001$). These morning pressures were 2.6 mm Hg lower than baseline in the eyes receiving latanoprost ($P<.0001$), and 1.6 mm Hg lower in unoprostone-treated eyes ($P=.02$). Afternoon values were 3.1 +/- SEM 0.6 lower than corresponding baseline in eyes receiving latanoprost, and 2.4 +/- SEM 0.6 mm Hg in unoprostone-treated eyes ($P<.0001$) from baseline for both medications; inter drug mean IOP difference ($P=.04$). Eyes receiving unoprostone showed a 1.7-db improvement in frequency doubling mean deviation ($P=.03$), the only significant visual function change observed. Pulsatile ocular blood flow increased 30% relative to baseline in eyes receiving latanoprost, ($P<.0001$) and 16% in eyes receiving unoprostone ($P=.05$) by the morning of day 28. That afternoon, mean POBF had increased 30% ($P<.0001$) relative to afternoon baseline values among eyes receiving latanoprost and 18% ($P=.03$) among those receiving unoprostone (interdrug change difference, $P=.05$). Humphrey perimetry and contrast sensitivity remained stable with both prostanoids.

Conclusions: Both latanoprost and unoprostone produced significant reductions in IOP and increases in POBF, with stable central and perimacular visual function. Latanoprost once daily produced IOP reduction and POBF increases nearly twofold greater than those obtained with unoprostone twice daily. These differences in IOP and POBF change between unoprostone and latanoprost were statistically significant.

9. Jampel HD, Bacharach J, Sheu W-P, et al. Randomized clinical trial of latanoprost and unoprostone in patients with elevated intraocular pressure. *Am. J. Ophthalmol.* 2002;134(6):863-871.

Abstract

Purpose: To compare the intraocular pressure (IOP)-lowering effect and safety of latanoprost 0.005% once daily with that of unoprostone 0.15% twice daily for patients with primary open-angle glaucoma or ocular hypertension.

Design: Randomized clinical trial.

Methods: In a prospective, 8-week, investigator-masked, parallel-group study conducted at numerous centers in the United States, 165 previously treated patients with IOP $\geq$ 25 mm Hg in one or both eyes after washout were randomly assigned to receive either latanoprost 0.005% once daily in the evening or unoprostone 0.15% twice daily. Observations procedures were Goldmann applanation tonometry, best-corrected visual acuity, slit lamp biomicroscopy, and ophthalmoscopy. The main outcome measure was change in the mean of the IOPs measured at 8:00 AM, 12 noon, and 4:00 PM between baseline (before treatment) and after 8 weeks of treatment.

Results: The change in the mean $\pm$ SD of the IOPs measured at 8:00 AM, 12 noon, and 4:00 PM was -7.2 ± 3.2 mm Hg (28%) for latanoprost (25.3 ± 2.8 mm Hg at baseline to 18.2 ± 2.8 mm Hg at 8 weeks) and -3.9 ± 2.6 mm Hg (15%) for unoprostone (25.5 ± 3.3 mm Hg at baseline to 21.6 ± 4.0 mm Hg; $P \leq 0.01$). No serious adverse event related to either medication was reported.

Conclusions: Over an 8-week period, latanoprost 0.005% once daily lowered IOP more than unoprostone 0.15% twice daily in patients with elevated IOP. Both agents were safe and well tolerated.

10. Hommer A, Kapik B, Shams N, Unoprostone Adjunctive Therapy Study Group. Unoprostone as adjunctive therapy to timolol: a double masked randomised study versus brimonidine and dorzolamide. *Br J Ophthalmol* 2003;87(5):592-598.

Abstract

Aims: To compare the safety and efficacy of unoprostone, brimonidine, and dorzolamide as adjunctive therapy to timolol in patients with primary open angle glaucoma or ocular hypertension.

Methods: This was a randomised, double masked, parallel group, multicentre (14) study. After using timolol maleate 0.5% monotherapy twice a day for 2 weeks, patients ($n = 146$) with an early morning intraocular pressure (IOP) between 22 and 28 mm Hg, inclusively, received unoprostone isopropyl 0.15% ($n = 50$), brimonidine tartrate 0.2% ($n = 48$), or dorzolamide hydrochloride 2.0% ($n = 48$) twice daily as adjunctive therapy to timolol maleate 0.5% for another 12 weeks. Safety was based on comprehensive ophthalmic examinations, adverse events, and vital signs. Efficacy was based on mean change from baseline in the 8 hour diurnal IOP at week 12. Baseline was defined as values obtained after 2 weeks of timolol monotherapy.

Results: Each drug was safe and well tolerated. Burning/stinging was the most common treatment emergent adverse event. No clinically relevant changes from baseline were observed for any ophthalmic examination or vital signs. At week 12, each adjunctive therapy produced statistically significant ($p < 0.001$) reductions from timolol treated baseline in the mean 8 hour diurnal IOP (-2.7 mm Hg, unoprostone; -2.8 mm Hg, brimonidine; -3.1 mm Hg, dorzolamide). The extent of IOP reduction did not differ significantly between unoprostone and either brimonidine ($p = 0.154$) or dorzolamide ($p = 0.101$).

Conclusion: Unoprostone was safe and well tolerated and provided a clinically and statistically significant additional reduction in IOP when added to stable monotherapy with timolol. Furthermore, unoprostone was not significantly different from brimonidine and dorzolamide as adjunctive therapy to timolol.

11. Day DG, Schacknow PN, Wand M, et al. Timolol 0.5%/dorzolamide 2% fixed combination vs timolol maleate 0.5% and unoprostone 0.15% given twice daily to patients with primary open-angle glaucoma or ocular hypertension. *Am. J. Ophthalmol.* 2003;135(2):138-143.

Abstract

Objective: To compare the efficacy and safety of timolol 0.5%/dorzolamide 2% fixed combination vs timolol maleate 0.5% and unoprostone 0.15% given twice daily.

Design: Prospective multicenter, randomized, double-masked, crossover comparison study.

Methods: Primary open-angle glaucoma or ocular hypertension patients were randomly assigned to one of the treatment groups for a 6-week treatment period and then crossed over to the opposite treatment. Diurnal curve testing was performed at 8:00 AM, 10:00 AM, 4:00 PM, 6:00 PM, and 8:00 PM at baseline and the end of each treatment period. The run-in medicine was timolol twice daily for 28 days.

Results: Thirty-two patients completed this trial. The baseline trough pressure was 24.3 +/- 3.0 mm Hg, and the diurnal curve was 23.4 +/- 3.2 mm Hg. For the fixed combination the treatment trough pressure was 20.8 +/- 4.1 mm Hg and the diurnal curve was 19.6 +/- 3.6 mm Hg, whereas timolol and unoprostone concomitant therapy showed a treatment trough pressure of 20.1 +/- 4.5 mm Hg and a diurnal pressure of 19.8 +/- 4.1 mm Hg. There was no significant difference between treatment groups at any time point, for the diurnal curve, or in the extended reduction from baseline. There was no difference between treatment groups regarding ocular and systemic unsolicited or solicited adverse events. Burning, stinging, and conjunctival hyperemia were the adverse events most noted. There were no serious adverse events during this trial.

Conclusions: This study suggests that both timolol/dorzolamide 2% fixed combination and concomitant timolol maleate 0.5% and unoprostone 0.15% therapy provide similar efficacy and safety throughout the daytime diurnal curve.

12. Shoji T, Sato H, Mizukawa A, et al. Hypotensive effect of latanoprost/timolol versus travoprost/timolol fixed combinations in NTG patients: a randomized, multicenter, crossover clinical trial. *Invest Ophthalmol Vis Sci.* 2013;54(9):6242-6247.

Abstract

Purpose: To compare the ocular hypotensive effect of travoprost plus timolol (TTFC) and latanoprost plus timolol fixed combinations (LTFC) in patients with normal-tension glaucoma (NTG).

Methods: A two-sequence 12-week, multicenter, prospective, randomized, single-blinded, crossover clinical trial examined 59 NTG patients. If both eyes were eligible, only one eye (chosen at random) was used for analytical purposes. After a 12-week run-in period with dorzolamide plus timolol fixed combination (DTFC), patients were randomized into one of the two crossover sequences of treatment for 12 weeks with TTFC or LTFC and were subsequently crossed over to the alternative treatment for a further 12 weeks. The primary endpoint was reduction in IOP after 12 weeks of each treatment sequence. The effect of treatment on IOP was assessed using a linear mixed model.

Results: The mean baseline IOP was 14.8 ± 3.3 mm Hg (95% confidence interval [CI], 14.1-15.3 mm Hg) for treatment with DTFC. The TTFC treatment period showed consistently lower mean IOP compared with LTFC treatment period at all measurement time points. Mean reduction in IOP at 12 weeks was significantly greater in the TTFC group than in the LTFC group (-2.4 ± 2.3 mm Hg vs. -1.1 ± 2.3 mm Hg; $P = 0.021$). No interaction between the drug and treatment sequence was detected. The effects of intraocular lens implantation and measurement time were also not significant. The tolerability profiles of both treatments were similar.

Conclusions: The additional reduction in IOP was greater with TTFC than with LTFC, and their tolerability profiles were similar.

13. Delval L, Baudouin C, Gabisson P, Alliot E, Vincent B, Diamant Study Group. Safety and efficacy of unpreserved timolol 0.1% gel in patients controlled by preserved latanoprost with signs of ocular intolerance. *J Fr Ophtalmol*. 2013;36(4):316-323.

Abstract

Purpose: To assess the safety and efficacy of unpreserved timolol 0.1% gel in ocular hypertensive (OHT) or glaucomatous patients controlled by preserved latanoprost 0.005% but with signs of ocular intolerance.

Methods: Patients initially treated with preserved latanoprost were randomized to receive once daily either one drop of unpreserved timolol gel in the morning or one drop of preserved latanoprost in the evening for 84 days. All patients attended three visits (D0, D28 and D84). A patient was considered as responder to primary criteria at Day 84 if the sum of the scores of the eight ocular symptoms and the six objective signs had decreased by at least 20% and if the effect on intra-ocular pressure (IOP) was assessed as either satisfactory or acceptable.

Results: At D84, 91.5% of patients were responders to the primary combined efficacy/safety criteria under unpreserved timolol gel treatment versus 48.6% under latanoprost treatment ($P < 0.001$). As early as D28, 85.3% of patients were responders in the unpreserved timolol gel group compared to 40.3% of patients in the preserved latanoprost group ($P < 0.001$). IOP change from baseline was not significant between treatments ($P > 0.05$) at D28 or D84. Both signs and symptoms were significantly improved ($P < 0.001$) with unpreserved timolol gel compared to preserved latanoprost.

Conclusions: Unpreserved timolol 0.1% gel maintained the efficacy of preserved latanoprost and reduced signs and symptoms of intolerance in almost all glaucomatous/OHT patients on preserved latanoprost.

14. Day DG, Walters TR, Schwartz GF, et al. Bimatoprost 0.03% preservative-free ophthalmic solution versus bimatoprost 0.03% ophthalmic solution (Lumigan) for glaucoma or ocular hypertension: a 12-week, randomised, double-masked trial. *Br J Ophthalmol*. 2013;97(8):989-993.

Abstract

Background/Aim: To evaluate efficacy and safety of bimatoprost 0.03% preservative-free (PF) ophthalmic solution versus bimatoprost 0.03% (Lumigan) ophthalmic solution for glaucoma or ocular hypertension.

Methods: In this double-masked, parallel-group study, patients were randomised to bimatoprost PF or bimatoprost for 12 weeks. The primary analysis for non-inferiority was change from baseline in worse eye intraocular pressure (IOP) in the per-protocol population at week 12. For equivalence, it was average eye IOP in the intent-to-treat population at each time point at weeks 2, 6 and 12.

Results: 597 patients were randomised (bimatoprost PF, n=302 and bimatoprost, n=295). The 95% CI upper limit for worse eye IOP change from baseline was <1.5 mm Hg at each week 12 time point, meeting prespecified non-inferiority criteria. The 95% CI upper limit for the treatment difference for average IOP was 0.69 mm Hg and the lower limit was -0.50 mm Hg at all follow-up time points (hours 0, 2 and 8 at weeks 2, 6 and 12), meeting equivalence criteria. Both treatments showed decreases in mean average eye IOP at all follow-up time points ($p < 0.001$), were safe and well tolerated.

Conclusions: Bimatoprost PF is non-inferior and equivalent to bimatoprost in its ability to reduce IOP-lowering with a safety profile similar to bimatoprost.

15. Quaranta L, Biagioli E, Riva I, et al. Prostaglandin analogs and timolol-fixed versus unfixed combinations or monotherapy for open-angle glaucoma: a systematic review and meta-analysis. *J Ocul Pharmacol Ther.* 2013;29(4):382-389.

Abstract

Purpose: To estimate the intraocular pressure (IOP)-lowering effect of prostaglandin analogs (PGAs) administered in combination with β -blockers.

Methods: We searched the Medline and Embase databases for randomized trials comparing topical therapies with PGAs and timolol administered as monotherapy (Mt), or in fixed (FC) or unfixed combinations (UC) to patients with glaucoma or ocular hypertension. The efficacy endpoint was the mean difference (MeD) in the reduction in IOP from baseline; the tolerability endpoint was the incidence of hyperemia.

Results: The 18 eligible trials involved 23 comparisons of FC versus Mt, and 5 of FC versus UC. The FCs were less efficacious than UCs (MeD: 0.69, 95% CI: 0.29 to 1.08). In comparison with timolol Mt, the latanoprost/timolol FC led to a greater IOP reduction (MeD: -2.74, 95% CI: -3.24 to -2.23) than the bimatoprost/timolol FC (MeD: -1.49, 95% CI: -1.86 to -1.12) or the travoprost/timolol FC (MeD: -1.93, 95% CI: -2.98 to -0.88). The FCs led to a lower hyperemia risk than UCs [relative risk (RR): 0.70, 95% CI: 0.43 to 1.14] and PGA Mt (RR: 0.61, 95% CI: 0.53 to 0.70).

Conclusions: FCs are more efficacious than their individual components, but less efficacious than their respective UCs. FCs lead to a lower hyperemia risk than UCs and their respective PGA Mts.

16. Cheng J-W, Cheng S-W, Gao L-D, Lu G-C, Wei R-L. Intraocular pressure-lowering effects of commonly used fixed-combination drugs with timolol: a systematic review and meta-analysis. *PLoS ONE.* 2012;7(9):e45079.

Abstract

Background: The first goal of medical therapy in glaucoma is to reduce intraocular pressure (IOP), and the fixed-combination medications are needed to achieve sufficiently low target IOP. The aim of this systematic review and meta-analysis is to evaluate IOP-lowering effect of the commonly used fixed-combination drugs containing 0.5% timolol.

Methods: Pertinent publications were identified through systematic searches. Over 85% of the patients had to be diagnosed with primary open-angle glaucoma (POAG) or ocular hypertension (OHT). Forty-one randomized clinical trials were included in the meta-analysis. The main efficacy measures were the absolute and relative values of mean diurnal IOP reduction, and the highest and lowest IOP reductions on the diurnal IOP curve. The pooled 1- to 3-month IOP-lowering effects after a medicine-free washout period was calculated by performing meta-analysis using the random effects model, and relative treatment effects among different fixed combinations were assessed using a mixed-effects meta-regression model.

Results: The relative reductions for mean diurnal IOP were 34.9% for travoprost/timolol, 34.3% for bimatoprost/timolol, 33.9% for latanoprost/timolol, 32.7% for brinzolamide/timolol, 29.9% for dorzolamide/timolol, and 28.1% for brimonidine/timolol. For the highest IOP decrease, relative reductions ranged from 31.3% for dorzolamide/timolol to 35.5% for travoprost/timolol; for the lowest IOP decrease, those varied from 25.9% for dorzolamide/timolol to 33.1% for bimatoprost/timolol. Both latanoprost/timolol and travoprost/timolol were more effective in lowering mean diurnal IOP than brimonidine/timolol (WMD: 5.9 and 7.0) and dorzolamide/timolol (WMD: 3.8 and 3.3).

Conclusions: All six commonly used fixed-combination drugs containing timolol can effectively lower IOP in patients with POAG and OHT, and both latanoprost/timolol and travoprost/timolol might achieve better IOP-lowering effects among the six fixed-combination agents.