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REVIEW

Efficacy, safety and tolerability of combination therapy with timolol and dorzolamide in glaucoma and ocular hypertension

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Abstract: Combination pharmacotherapy has simplified and improved glaucoma medication regimens. This update focuses on the previous and recent studies on efficacy and tolerability profile of dorzolamide–timolol in adult ocular hypertension and open angle glaucoma patients. Dorzolamide–timolol has been shown to be efficacious and well tolerated in clinical trials and the adverse effects reflect those of the individual components.

Keywords: glaucoma, ocular hypertension, dorzolamide, timolol

Introduction

Glaucoma is a worldwide epidemiological challenge affecting approximately 4% of the global population.[1–7] Research shows that by 2010, an estimated 60.5 million people globally will be living with either angle closure glaucoma (ACG) or primary open angle glaucoma (POAG).[8] Elevated intraocular pressure is the most important modifiable risk factor for glaucoma and hence lowering of IOP is the goal of glaucoma therapy.[9,10] Pharmacotherapy remains the chief management modality for the patients of glaucoma and ocular hypertension.[9] Topical antiglaucoma medications act either by decreasing aqueous production (beta adrenergic antagonists, carbonic anhydrase inhibitors [CAI]) or increasing aqueous outflow (prostaglandin derivatives, cholinergic agonists) or both (alpha-2 adrenergic agonists).[9] Treatment is started with monotherapy but in cases where monotherapy fails to attain the target IOP, other drugs are added.[9,10] Factors that influence the choice of an agent are efficacy, safety profile, ease of administration and cost.[11,12] Fixed drug combinations can help to avoid complex dosing schedules of multi drug glaucoma therapy and thus improve compliance.[12,13] Several fixed combinations of commonly used IOP-lowering medications have been developed and are available in various markets worldwide. Most fixed combinations contain timolol, as it can be dosed either once or twice daily and can be combined with prostaglandin analogs, adrenergic agonists, and CAIs.[13] Cosopt® (Merck & Co., Inc.,Whitehouse Station, NJ, USA), a commonly available combination drug that consists of dorzolamide hydrochloride 2% and timolol maleate 0.5% was first commercially introduced in 1998. Each milliliter of Cosopt consists of 22.26 mg dorzolamide hydrochloride and 6.83 mg timolol maleate with 0.0075% benzalkanoium chloride as preservative.[14] This update focuses on the previous and recent studies on efficacy and tolerability profile of dorzolamide–timolol in adult ocular hypertension and open angle glaucoma patients.

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Mode of action, pharmacodynamic and pharmacokinetic profile

The pharmacodynamic properties of timolol and dorzolamide have been extensively reviewed elsewhere.[15–17] As there is no direct pharmacodynamic interaction between the two drugs, a brief overview of the pharmacodynamic and pharmacokinetic profile of each drug is presented here.

Timolol is a non-selective β-blocker (β1 and β2) which has little or no local anesthetic, membrane stabilizing or sympathomimetic properties.[16] Timolol lowers IOP by inhibiting aqueous humor production[18–20] and it has been suggested that timolol down-regulates adenylate cyclase by inhibiting β2-adrenoceptor sites at the ciliary process.[21] Dorzolamide is a highly selective inhibitor of CA-II, an isoenzyme present on the ciliary process in the eye.[15] Inhibition of CA-II slows local bicarbonate production, decreases sodium and fluid transport and, consequently, decreases aqueous humor production and lowers IOP.[17] Because their mechanisms of action differ, they have an additive effect when administered together.[22]

Approximately 80% of the volume of topically administered eye drops is absorbed systemically within 15 to 30 seconds of instillation.[23] Chronic administration of dorzolamide leads to its accumulation in erythrocytes. Hepatic metabolism of dorzolamide produces N-desthyl metabolite which also binds to red blood cells but inhibits carbonic anhydrase I more than carbonic anhydrase II.[24] Approximately 24% to 32% of systemically absorbed dorzolamide is bound to plasma proteins.[25]

Urine is the major route of excretion for both parent and metabolite drug.[26] There is a rapid decline of dorzolamide from red blood cells, on discontinuation of the medication. This is followed by a gradual decline due to an elimination phase half-life of approximately 4 months.[27] However, in patients with glaucoma treated with dorzolamide 2% 3 times daily, plasma concentrations after 12 months were similar to those after 6 months (≈20 μmol/L).[28] Because of its renal elimination, dorzolamide eyedrops are not recommended in patients with severe renal impairment. Topical dorzolamide has not been studied in patients with hepatic dysfunction, but should be used with caution as the drug undergoes hepatic metabolism.

Not much has been published on the pharmacokinetic characteristics of fixed combination of dorzolamide and timolol, accordingly the characteristics of individual components are being discussed.

Topical dorzolamide is absorbed through nasopharyngeal mucosa into systemic circulation.[15] Biollaz et al have shown that plasma concentration of dorzolamide remained below level of detection after instillation of single or multiple doses of dorzolamide 2 or 3% in healthy volunteers.[29] Dorzolamide undergoes slow metabolism by cytochrome P450 (CYP) 2B1/2, CYP2E1 and CYP3A2.[30]

CAIs have been reported to improve ocular blood flow profile by causing ocular vasodilation through metabolic acidosis via elevated carbon dioxide levels.[31] Topically administered dorzolamide–timolol has been shown to improve some markers of ocular blood flow in small studies (n = 15–30) in patients with POAG.[32–35] Retinal arteriovenous time passage time from superior temporal artery to the corresponding vein was significantly shorter following 1 month of double masked treatment with dorzolamide–timolol twice daily (1.76 s) than with timolol 0.5% twice daily (2.13 s) (P = 0.01).[35] The fixed combination did not alter choroidal perfusion or retrobulbar hemodynamics relative to timolol 0.5% baseline in this randomized crossover comparison (n = 15).[35] However, this finding contrasts with that of a crossover comparison of latanoprost 0.005% in which 1 month of non-blind treatment with dorzolamide–timolol significantly (P = 0.003) increased pulsatile ocular blood flow by 2.05 ÂμL/s relative to the timolol 0.5% baseline.[32] Dorzolamide–timolol also significantly improved retrobulbar hemodynamic parameters relative to baseline in another randomized cross over comparative study with latanoprost.[34] The fixed combination increased end diastolic velocity and decreased the resistance index in both the ophthalmic artery and short posterior ciliary artery. Improvements in ocular blood flow markers following treatment with dorzolamide 2%/timolol 0.5% generally exceeded those observed with latanoprost 0.005% once daily in 2 cross over randomized studies.[32,34]

A recent study has shown dorzolamide 2%/timolol 0.5% fixed combination increased blood flow significantly at the neuroretinal rim showing a combination of hypotensive and hemodynamic effects.[36] Twenty-eight patients with early-moderate glaucomatous damage treated with beta-blockers (>6 months) with IOP values ranging from 18 to 22 mmHg at trough participated in this trial. After a 4-week washout period, patients were randomized in two groups: group I started with dorzolamide 2% monotherapy and group II with timolol 0.5% monotherapy for 4 weeks. After this period, both groups switched to dorzolamide 2%/timolol 0.5% fixed combination for 4 weeks. IOP, ocular diastolic perfusion pressure (ODPP), heart rate, and Scanning Laser Doppler Flowmetry measurements at the peripapillary retina and neuroretinal rim were taken at T0 (enrolment), T1 (wash out), T2 (monotherapy), and T3 (dorzolamide–timolol). Between T1 and T3, IOP decreased significantly in group I (–21.40%)

($P < 0.001$) and in group II (–21.25%) ($P < 0.001$). At the same time intervals, blood flow increased significantly at rim level for group I (+30.03%) ($P < 0.05$) and also when all patients were considered (rim +17.99%) ($P < 0.05$). Between T1 and T3, there was a significant increase of ODPP in group I (+7.24%) ($P < 0.01$) and in group II (+6.08%) ($P < 0.05$) and when all patients were considered (+8.43%) ($P < 0.01$).[36]

The improvement in ocular blood flow parameters with the fixed combination appears to reflect the activity of the dorzolamide 2% component. When included as a comparator, timolol 0.5% had no significant effect on ocular blood flow markers in these studies.[31,37,38] However these improved ocular blood flow parameters were not accompanied by any enhancement in visual function.[35,37]

Dosage and administration

Dorzolamide 2%/timolol 0.5% is indicated for the treatment of raised IOP in patients with ocular hypertension, open-angle glaucoma, pseudoexfoliative glaucoma or other secondary open-angle glaucomas when concomitant therapy is appropriate. It may be used alongwith prostaglandin analogs when IOP control is not possible with a single medication. It can also be used when prostaglandin analogs cannot be used such as, if patient has a history of herpetic keratitis or is concerned about side effects like iris heterochromia and periocular pigmentation.

Dorzolamide/timolol should be used with caution in those with hepatic insufficiency and is not recommended in patients with severe renal impairment (creatinine clearance <1.8 L/h [<30 mL/min]). It is contraindicated in Europe in patients with hyperchloremic acidosis. Dorzolamide/timolol is contraindicated in patients with a history of bronchial asthma, severe obstructive pulmonary disease, cardiac failure, sinus bradycardia, atrioventricular block or cardiogenic shock. Finally, the formulation should not be used in patients with known hypersensitivity to either of the components (eg, sensitivity to sulfonamides).

Therapeutic efficacy

The fixed combination dorzolamide–timolol has been compared with monotherapy dorzolamide 2%,[39,40] timolol 0.5%,[39,40] latanoprost 0.005%,[41–48] bimatoprost 0.03%,[49,50] travoprost 0.004%,[47,48,51] unoprostone 0.15%[52] and with concomitant therapy with dorzolamide 2% and timolol 0.5%,[53,54] brimonidine 0.2% plus either timolol 0.5%[55–58] or latanoprost 0.005%[59] and pilocarpine 2% with timolol 0.5%.[60,61] Recently, it has also been compared with fixed combination latanoprost 0.005%/timolol 0.5%,[62–64] brinzolamide 1%/timolol 0.5%[65,66] and travoprost 0.004%/timolol 0.5%[67] in randomized clinical trials carried out at various centers across the world. Another recent study reports the additive effect of dorzolamide 2%/timolol 0.5% fixed combination in patients under monotherapy with latanoprost.[68]

Adults with POAG or ocular hypertension who did not have any contraindications for the study medications were enrolled in these trials. Based on the available demographic details, the mean or the median age of trial participants ranged from 58.5 to 66.5 years. The subjects were recruited if they had a baseline morning trough and/or morning peak IOP of ≥ 20 mmHg, after completing a 2- to 6-week run in period on timolol 0.5% twice daily or a washout period of 3 to 28 days (depending on drug class).

In most studies the primary efficacy endpoint was the mean change in IOP from time-matched baseline values, the mean change in diurnal IOP from baseline or the between group difference in the mean reduction in daytime diurnal IOP from baseline.

Versus concomitant or monotherapy

The efficacy of dorzolamide 2%/timolol 0.5% compared with mono or concomitant therapy with the same drugs has been evaluated in 4 major clinical studies involving a total of 1129 patients with glaucoma[39,40,53,54] (Table 1). All studies were multicenter, randomized, parallel and double-blind with active controls. Many patients enrolled in these trials were previously using one or the other antiglaucoma medications.[39,40,54] To establish a comparable baseline, patients underwent a 2-[53,54] or 3-week[40] run-in period on timolol 0.5% twice daily, or a washout period of 3 to 21 days depending on the medication.[39] Where dorzolamide 2%/timolol 0.5% was compared with timolol 0.5% or dorzolamide 2% monotherapy, the hypothesis tested was that there was 95% confidence that mean IOP in the combined therapy group differed from that in the monotherapy groups by ≥6%[40] or 8%.[39] Only 1 trial reported p values for treatment comparisons.[40] The controlled study period was 90 days in all trials, with a 9-month open-label extension in 1 trial.[54] The age at entry was 21 to 85 years in 3 trials[40,53,54] and ≥21 years in 1 trial.[39] The IOP at baseline in the worst eye was required to be ≥22 mmHg in 3 of the studies[40,53,54] and ≥24 mmHg in 1 study.[39] In all studies change in IOP was the primary end-point and was measured at trough (0 hours) and peak (2 hours) in relation to the morning dose of medication 14, 30, 60 and 90 days after

Table 1 FCDT vs monotherapy or concomitant therapy with dorzolamide and/or timolol

Authors	Time point	Treatment	N	Baseline IOP (SD) (mmHg)	Treatment IOP (SD) (mmHg)	Change (SD)	% change (SD)
Boyle et al[40]	Month 3 trough	FCDT	114	27.8 (5.0)	20.1 (4.5)	–7.7 (4.2)	–27.4 (13.1)
		Dorzolamide	109	28.1 (4.7)	23.5 (4.2)	–4.6 (4.3)	–15.5 (13.5)
		Timolol	111	27.9 (4.6)	21.5 (4.0)	–6.4 (4.1)	–22.2 (12.5)
	Month 3 peak	FCDT	112	27.1 (4.3)	18.1 (3.8)	–9.0 (4.3)	–32.7 (12.9)
		Dorzolamide	109	27.3 (3.8)	21.8 (4.3)	–5.4 (3.6)	–19.8 (12.6)
		Timolol	110	27.3 (4.4)	21.0 (4.7)	–6.3 (4.7)	–22.6 (15.6)
Clineschmidt et al[39]	Month 3 trough	FCDT	102	25.5 (3.4)	22.7 (3.9)	–2.8 (3.4)	–10.6 (12.5)
		Dorzolamide	51	25.5 (3.8)	24.2 (5.1)	–1.4 (4.3)	–4.9 (16.7)
		Timolol	98	25.2 (3.1)	23.6 (4.3)	–1.7 (3.1)	–6.7 (11.9)
	Month 3 peak	FCDT	103	25.0 (3.9)	20.7 (4.5)	–4.4 (3.3)	–17.3 (12.9)
		Dorzolamide	51	24.7 (3.3)	22.7 (3.8)	–2.0 (4.1)	–7.4 (15.8)
		Timolol	95	24.3 (2.6)	22.8 (4.6)	–1.6 (3.7)	–6.6 (15.3)
Hutzelmann et al[53]	Month 3	FCDT	151	25.6 (3.1)	21.4 (4.1)	–4.2 (3.3)	–16.3 (12.5)
	Trough	D + T	148	25.3 (3.2)	21.1 (3.7)	–4.2 (3.1)	–16.3 (11.5)
		FCDT	151	24.7 (3.2)	19.4 (3.7)	–5.4 (3.1)	–21.6 (12.3)
	Month 3 peak	D + T	148	24.5 (3.2)	19.1 (3.5)	–5.4 (3.3)	–21.8 (11.9)
Strohmaier et al[54]	Month 3	FCDT	120	26.1 (3.0)	22.5 (4.1)	–3.6 (3.0)	–13.8 (11.1)
	Trough	D + T	121	26.1 (3.8)	22.0 (4.4)	–4.1 (3.7)	–15.5 (13.8)
		FCDT	119	25.1 (3.3)	20.1 (3.8)	–5.0 (3.5)	–19.7 (12.9)
	Month 3 peak	D + T	120	25.0 (3.7)	20.2 (4.2)	–4.9 (3.8)	–19.1 (14.4)
		FCDT	116	23.7 (3.9)	20.0 (3.9)	–3.7 (3.4)	–14.9 (13.2)

Abbreviations: FCDT, fixed combination dorzolamide–timolol; D, dorzolamide; T, timolol.

initiation of therapy. In 1 study, an additional measurement was made at 8 hours.[53] The concentrations of the individual drugs in both the combined and monotherapy formulations were dorzolamide 2% and timolol 0.5%. In all studies the primary efficacy analyses were based on the last observation carried forward approach, although secondary analyses were performed using other methods in 3 studies.[39,40,53] The studies that compared combined and concomitant therapy were designed to determine equivalence and this was assessed by calculating the 90%[54] or 95%[53] confidence interval for the hypothesis that the mean IOP of each of the 2 treatment groups differed by ≤1.5 mmHg.

Versus prostaglandin analogs

Versus latanoprost 0.005%

Dorzolamide 2%/timolol 0.5% was comparable to latanoprost 0.005% once daily in two double masked comparisons that followed a washout period[41] (Table 2). The mean reduction of daytime diurnal IOP between the groups from baseline at 3 months was within ±1.5 mmHg study 1: –0.04 mmHg [95% CI: –0.85, 0.77] in favor of dorzolamide 2%/timolol 0.5%; study 2: –0.57 mmHg [95% CI: 1.31, 0.16] in favor of dorzolamide 2%/timolol 0.5%.

Additional post hoc analyses of pooled data from these trials showed dorzolamide 2%/timolol 0.5% and latanoprost 0.005% were similar with respect to percentages of patients achieving target levels of IOP reduction.[69]

Versus bimatoprost 0.03%

Dorzolamide 2%/timolol 0.5% twice daily lowered IOP less consistently than did bimatoprost 0.03% once daily in a double-masked, parallel-group comparison following a run-in period on timolol 0.5% twice daily.[49] Mean reductions in IOP from baseline at morning trough and peak were greater with bimatoprost 0.03% at all time points, with the exception of the morning peak time point at 3 months.[49] Dorzolamide 2%/timolol 0.5%

Table 2 FCDT vs other prostaglandin analogs

Authors	Time point	Treatment	Mean baseline IOP (SD) (mmHg)	Mean treatment IOP (SD) (mmHg)	*P*-value
Orzalesi et al[45]	Month 1	FCDT	22.6 (2.7)	16.9 (1.4)	
		Latanoprost	22.6 (2.7)	16.7 (0.6)	>0.05
Fechtner et al[69]	Month 3 (study 1)	FCDT	26.1	18.9	
		Latanoprost	25.6	18.4	>0.05
	Month 3 (study 2)	FCDT	25.3	17.4	
		Latanoprost	24.7	17.5	>0.05
Konstas et al[44]	Week 6	FCDT	25.8 (1.4)	15.3 (2.0)	
		Latanoprost	25.8 (1.4)	15.9 (2.3)	0.05
Konstas et al[44] (pseudoexfoliation patients)	Month 2	FCDT	31.2 (6.5)	18.1 (3.0)	
		Latanoprost	31.2 (6.5)	18.9 (4.1)	0.21
Susanna et al[42]	Month 2	FCDT	23.6 (3.3)	17.2 (3.1)	
		Latanoprost	23.5 (2.8)	16.6 (3.0)	>0.05
Day et al[50]	Month 2	FCDT	24.8 (2.4)	18.1 (2.8)	
		Bimatoprost	24.8 (2.4)	17.4 (2.9)	0.35
Ozturk et al[46]	Month 6	FCDT	24.1 (2.1)	17.6 (2.9)	
		Bimatoprost	23.7 (2.0)	17.5 (2.3)	0.48
Coleman[49]	Month 3 (0800 h)	FCDT	24.8 (2.5)	19.8	
		Bimatoprost	25.0 (2.5)	18.2	<0.001

Abbreviation: FCDT, fixed combination dorzolamide–timolol.

provided a less stable reduction in IOP over the whole day, as evidenced significantly lower mean IOP values in bimatoprost 0.03% recipients at the 0-, 8- and 12-hour post-dose time points at 3 months ($P \leq 0.038$).[49] The percentage of recipients reaching target IOPs of 17 to 20 mmHg was similar between the dorzolamide 2%/timolol 0.5% and bimatoprost 0.03% treatment groups based on measurements at 0-, 2- and 12-hour post-dose time points at 3 months; however, a significantly ($P < 0.008$) greater percentage of bimatoprost 0.03% recipients reached the lower target pressures ≤13 mmHg (0% vs 8%), ≤14 mmHg (2% vs 17%), ≤15 mmHg (9% vs 24%) and ≤16 mmHg (14% vs 31%).[49]

A relevant concern with this study is whether the selection of patients who are inadequately controlled on timolol 0.5% twice daily provides a valid basis on which to judge the relative merits of a timolol-containing therapy versus bimatoprost 0.03%.[49] Moreover, the study authors did not conduct a reverse therapeutic trial and hence did not know the number of trial participants who were non-responders to timolol.[49] Contrasting with the results of this trial, reductions in day time diurnal IOP (0800–1600 hours) and IOP at 2 of the 3 measured timepoints (morning peak and 8 hours post-dose) were not significantly different with dorzolamide 2%/timolol 0.5% twice daily vs. bimatoprost 0.03% once daily in a small (n = 35), double-masked, cross-over, 3-center, 8-week study that followed an initial washout period.[50]

Versus travoprost 0.004%

The IOP-lowering effect of dorzolamide 2%/timolol 0.5% twice daily was greater than that of travoprost 0.004% once daily in one[48] of two small (n = 50[45] and 56[48]), single-blind, parallel-group, single-center studies that followed a washout period. After 6 months of treatment, the reduction in mean diurnal IOP (average of measurements made at 0800, 1000 and 1600 hours) from baseline with dorzolamide 2%/timolol 0.5% was superior to that with travoprost 0.004% (11.5 vs 9.3 mmHg; $P < 0.05$).[48] The IOP-lowering effect of dorzolamide 2%/timolol 0.5% was also greater than that of another comparator, latanoprost 0.005% once daily (reduction in mean diurnal IOP from baseline, 8.2 mmHg; $P < 0.05$ vs dorzolamide/timolol); the IOP-lowering effect of the two prostaglandin analogs was similar. Of note, this study exclusively enrolled patients with pseudoexfoliation glaucoma. Dorzolamide 2%/timolol 0.5% was, however, less effective than travoprost 0.004%[47,51] in the other single dose blind, parallel-group, single-center comparison,[51] and less effective than both travoprost 0.004% and latanoprost 0.005%

Table 3 A, B FCDT versus other combination antiglaucoma drugs

A

Authors	Time point	Treatment	Mean baseline IOP (SD) (mmHg)	Mean treatment IOP (SD) (mmHg)	Treatment difference	*P*-value
Arcieri et al[58]	Month 1	FCDT	22.9 (1.6)	15.4 (2.1)	0.4	0.43
		FCBT	22.9 (1.6)	15.0 (2.1)		
Konstas et al[63]	Month 2	FCDT	20.2 (1.9)	17.0 (2.0)	0.27	0.36
		FCLT	20.1 (2.0)	17.3 (2.2)		
Shin et al[62]	Month 3	FCDT	27.5 (3.1)	19.1 (3.3)	0.6	0.005
		FCLT	27.9 (3.6)	18.5 (2.9)		
Kalzuny et al[61]	Week 6 trough	FCDT	23.4 (2.3)	18.0 (2.2)	0.6	0.22
		FCPT		17.4 (2.0)		
	Diurnal curve	FCDT	22.3 (3.7)	18.1 (2.2)	1.4	0.0007
		FCPT		16.7 (1.9)		
Day et al[52]	Week 6 trough	FCDT	24.3 (3.0)	20.1 (4.5)		0.55
		T + U		20.1 (4.5)		
	Diurnal curve	FCDT	23.4 (3.2)	19.8 (4.1)		0.63
		T + U		19.8 (4.1)		
Teus et al[67]	Week 6	FCDT	26.1 (0.18)	17.7 (0.25)		0.002
		Tr + T	26 (0.18)	16.6 (0.26)	1.1	

B

Zabriskie and Netland[59]	Month 3 (study 1)	FCDT	6.5	25.3		
		B + L	9.0	33.9		0.044
	Month 3 (study 2)	FCDT	6.6	26.3		
		B + L	9.1	33.4		0.047

Abbreviations: FCDT, fixed combination dorzolamide–timolol; FCBT, fixed combination brimonidine–timolol; FCPT, fixed combination pilocarpine; timolol; FCLT, fixed combination latanoprost–timolol; T + U, timolol + unoprostone; Tr + T, travoprost + timolol; B + L, brimonidine + latanoprost.

in a small (n = 38), single-blind, cross-over, single-center comparison that followed a run-in period on timolol 0.5% twice daily.[47] In the parallel-group comparison,[51] the reductions in mean diurnal IOP (average of measurements made at 0800, 1200, 1600 and 2000 hours) from baseline were significantly less with dorzolamide 2%/timolol 0.5% than with travoprost 0.004% after both 3 (23.1% vs 32.7%; $P < 0.01$) and 6 (21.7% vs 30.7%; $P < 0.01$) weeks of treatment. Similarly, in the cross-over comparison,[47] the decrease in mean diurnal IOP (average of measurements made at 8 am, 10 am and 4 pm) from baseline following 3 months of treatment with dorzolamide 2%/timolol 0.5% (14.3%; $P < 0.0001$ vs baseline) was significantly less than that with travoprost 0.004% (18.4%; $P < 0.0001$ vs baseline and dorzolamide 2%/timolol 0.5%) and latanoprost 0.005% (22.1%; $P < 0.0001$ vs baseline and dorzolamide 2%/timolol 0.5%).[47] Again, the IOP-lowering effect of the two prostaglandin analogs was similar.

Versus unoprostone 0.15% and timolol 0.5%

Day et al conducted a prospective multicenter, randomized, double-masked, crossover comparison study and found a similar efficacy and safety between dorzolamide 2%/timolol 0.5% and concomitant use of unoprostone 0.15%and timolol maleate 0.5% (n = 32).[52] After a 4-week run in period on timolol 0.5% twice daily, the patients received one treatment for 6 weeks and then crossed over to the opposite treatment. The authors found comparable IOP reduction for all the time points, for the diurnal curve or in the extended reduction from baseline[52] (Table 3).

Versus latanoprost 0.005%/timolol 0.5%

The reduction in daytime diurnal IOP (0800–1600 hours[62] or 0800–2000 hours[63]) with dorzolamide 2%/timolol 0.5% twice daily vs latanoprost 0.005%/timolol 0.5% once daily significantly favored the latter in a large

(n = 253), single-blind, parallel-group trial preceded by a washout period.[62] However, the between-group difference after 3 months' treatment (primary endpoint) was only 1.0 mmHg (95% CI 0.4, 1.69; $P = 0.005$) and the clinical relevance of this small difference is questionable.[62] Daytime diurnal IOP was not significantly different following treatment with these two fixed combinations in a small (n = 33) double-masked, cross-over comparison that followed a run-in period on timolol 0.5% twice daily.[63] For other endpoints in these studies, mean reductions in IOP were significantly less with dorzolamide 2%/timolol 0.5% than with latanoprost 0.005%/timolol 0.5% at morning trough (8.1 vs 9.6 mmHg; $P = 0.007$) and the 8-hour post-dose timepoint (8.3 vs 9.5 mmHg; $P = 0.014$) after 3 months' treatment in the larger trial,[62] but not at the corresponding timepoints after 2 months' treatment in the smaller trial.[63] Conversely, mean IOP values favored dorzolamide 2%/timolol 0.5% over latanoprost 0.005%/timolol 0.5% at morning peak (17.3 vs 17.8 mmHg; $P = 0.04$) and the 4-hour post dose timepoint (16.7 vs 17.5 mmHg; $P = 0.03$) after 2 months' treatment in the smaller comparison,[63] but not at the 4-hour post-dose timepoint after 3 months' treatment in the larger comparison (18.6 vs. 18.5 mmHg).[62] In the larger trial,[62] consistently fewer dorzolamide 2%/timolol 0.5% than latanoprost 0.005%/timolol 0.5% recipients achieved specific reductions (range ≥5% to ≥40%) in daytime diurnal IOP at 3 months; these between group differences were statistically significant for the ≥15% (92% vs 99%; $P < 0.05$), ≥20% (80% vs 92%; $P \leq 0.01$), ≥25% (66% vs 81%; $P \leq 0.01$) and ≥30% (50% vs 67%; $P \leq 0.01$) reduction levels (values estimated from a graph) (Table 3).

Versus brimonidine 0.2%/timolol 0.5%

Nixon et al presented a pooled data analysis of 2 randomized, investigator-masked, 3-month, parallel-group studies with identical protocols (10 sites) (n = 180). Patients received topical brimonidine 0.2%/timolol 0.5% twice daily or dorzolamide 2%/timolol 0.5% twice daily as monotherapy (n = 101) or as adjunctive therapy to a prostaglandin analog (latanoprost, bimatoprost, or travoprost) (n = 79). At month 3, the mean (SD) reduction from baseline IOP for patients on fixed-combination monotherapy was 7.7 (4.2) mmHg (32.3%) with brimonidine 0.2%/timolol 0.5% vs 6.7 (5.0) mmHg (26.1%) with dorzolamide 2%/timolol 0.5% ($P < 0.040$).The mean reduction from prostaglandin analog-treated baseline IOP for patients on fixed-combination adjunctive therapy was 6.9 (4.8) mmHg (29.3%) with brimonidine 0.2%/timolol 0.5% vs 5.2 (3.7) mmHg (23.5%) with dorzolamide 2%/timolol 0.5% ($P = 0.213$).[57]

According to preliminary results from a small (n = 30), single-blind trial of cross-over, multicenter design and 3 month duration, the mean reduction in morning peak IOP from baseline at 3 months was 3.0 mmHg in the dorzolamide 2%/timolol 0.5% group versus 6.8 mmHg in the brimonidine 0.2%/timolol 0.5% group ($P = 0.02$).[58]

Versus brinzolamide 1%/timolol 0.5%

In a 1-year, multicenter, randomized, double masked, active-controlled, parallel-group trial of brinzolamide 0.1%/timolol 0.5% and dorzolamide 2%/timolol 0.5% with 437 patients, 220 were dosed brinzolamide 0.1%/timolol 0.5% and 217 received dorzolamide 2%/timolol 0.5%. IOP assessments were taken at 0800 and 1000 hours at week 2 and months 3 and 9, and at 0800, 1000, and 1600 hours at months 6 and 12.[65] Brinzolamide 0.1%/timolol 0.5% produced IOP-lowering efficacy comparable to dorzolamide 2%/timolol 0.5%, with the upper 95% confidence limits for the differences between groups within +1.5 mmHg at all assessment times, including the month 6 primary efficacy time points, establishing noninferiority. The IOP reductions ranged from 7.2 to 9.2 mmHg for brinzolamide 0.1%/timolol 0.5% and from 7.4 to 8.9 mmHg for dorzolamide 2%/timolol 0.5%.

Versus travoprost 0.004%/timolol 0.5%

In a multicenter, double-masked, randomized clinical trial, 319 patients received either travoprost 0.004%/timolol 0.5% once daily in the morning (n = 157) or dorzolamide 2%/timolol 0.5% twice daily (n = 162).[67] IOP was assessed morning and evening at 2 and 6 weeks. Mean pooled diurnal IOP was significantly lower in the travoprost 0.004%/timolol 0.5% group (16.5 mmHg ± 0.23) than in the dorzolamide 2%/timolol 0.5% group (17.3 mmHg ± 0.23; $P = 0.011$). Moreover, travoprost 0.004%/timolol 0.5% combination produced superior mean IOP reductions from baseline of 35.3% to 38.5%, while the dorzolamide 2%/timolol 0.5% combination produced mean IOP reductions from baseline of 32.5% to 34.5%.

Versus timolol 0.5% and pilocarpine 2%

Dorzolamide 2%/timolol 0.5% was as effective as timolol 0.5% plus pilocarpine 2% in patients with glaucoma or ocular hypertension and was the preferred formulation. The dorzolamide/timolol has been compared with concomitant pilocarpine and timolol therapy in 2 trials (published as a single report).[60] Two randomized trials with identical drug

administration and assessment protocols were performed; 1 in the US and 1 internationally (5 countries). Patients ≥18 years with baseline IOP of ≥ 22 mmHg after a 3-week run-in with timolol 0.5% twice daily were assigned to receive dorzolamide 2%/timolol 0.5% twice daily or timolol (0.5%) twice daily plus pilocarpine (2.0%) 4 times daily for 14 days. After a 7-day wash-out period, patients crossed over to receive the alternative therapy for a further 14 days. There were 97 patients in the US study and 93 in the international trial. The primary endpoints were patient preference and impact on daily life, and were assessed by a questionnaire administered by study physicians. IOP was also measured at baseline and on days 15, 22 and 36 at 2 and 4 hours after drug administration; only the IOP values from day 36 were published. After the 36-day study period there were no significant differences in IOP between the 2 treatment groups in either study.[50] In the US study, the peak (2-hour) IOP in the dorzolamide/timolol group dropped from 23.7 mmHg at baseline to 19.8 mmHg at 36 days, and the corresponding values for the timolol plus pilocarpine concomitant therapy group were 23.5 mmHg at baseline and 20.1 mmHg at 36 days. In the international study, baseline peak IOP in the dorzolamide 2%/timolol 0.5% group was 24.4 mmHg dropping to 19.1 mmHg after 36 days, while peak IOP in the concomitant therapy group was 24.4 mmHg at baseline and 18.7 mmHg at the end of the trial. In both studies, patients preferred dorzolamide/timolol combination to concomitant therapy with timolol and pilocarpine by a ratio of approximately 4:1. The primary reason for this preference was the reduced frequency and severity of adverse effects although patients also reported that the combination therapy interfered less with daily life. Compliance was also improved and patients reported missing fewer doses with the twice daily combined therapy.

Kalzuny et al conducted a 6 week trial to compare the efficacy and safety of dorzolamide 2%/timolol 0.5% with fixed combination pilocarpine timolol, each given twice daily, in patients with POAG or ocular hypertensive patients. They found that both combinations were equally efficacious in IOP reduction[61] (Table 3).

Safety and tolerability

Tolerability of a drug has been identified as a barrier to compliance.[70] The adverse event profile of dorzolamide 2%/timolol 0.5% mirrors that of the individual components and consists primarily of ocular and local adverse events. The most common adverse events associated with dorzolamide (Trusopt®; Merck & Co., Inc., Whitehouse Station, NJ, USA) are ++ burning, stinging, and discomfort, and taste perversion (Trusopt® prescribing information, Merck & Co., Inc., 2005; http://www.merck.com/product/usa/pi_circulars/t/trusopt/trusopt_pi.pdf); a similar safety profile is observed with the dorzolamide 2%/timolol 0.5% fixed combination (Cosopt®) (Cosopt® prescribing information, Merck & Co., Inc., 2006; http://www.merck.com/product/usa/pi_circulars/c/cosopt.html).

Dorzolamide 2%/timolol 0.5% twice daily was generally well tolerated in large (n = 177–492) trials of 3 to 6 months duration which evaluated this fixed combination in relation to the individual components, given either as monotherapy or concomitantly, or against other ocular hypotensive agents.[39–43,49,53–56,62] Between 33% and 77% of patients receiving dorzolamide 2%/timolol 0.5% in these studies reported adverse events (regardless of cause);[39–45,53,54,65] 10% to 68% reported drug-related adverse events.[42,43,53–56,67] Transient and mild to moderate burning and/or stinging[39–41,45,49,53–56] of the eye (5%–41%) was the most commonly reported ocular adverse event in majority of the trials. Dysgeusia[39–41,49,53–56] (2%–38%) was the most common local adverse effect.

Recently, timolol 0.5% and brinzolamide 1% (Azopt®; Alcon Laboratories, Inc., Ft. Worth, TX, USA) have been formulated in a fixed combination (Azarga™; Alcon Laboratories, Inc., Ft. Worth, TX, USA). The most common side effects with brinzolamide 1% are blurred vision and taste perversion; fewer than 5% of patients report ocular discomfort associated with brinzolamide use in clinical trials (Azopt® prescribing in formation, Alcon Laboratories, Inc. 2003; http://ecatalog.alcon.com/pi/Azopt_us_en.pdf). In a prospective, double-masked, randomized, active-controlled, crossover, multicenter study, 127 patients received 1 drop of brinzolamide 1%/timolol 0.5% and dorzolamide 2%/timolol 0.5% in both eyes on consecutive days in random order. Ocular discomfort was rated 1 minute after instillation of each medication, and preference was noted on Day 2. Of the 106 subjects who expressed a drug preference, 79.2% preferred brinzolamide 1%/timolol 0.5% ($P < 0.0001$). Ocular discomfort scores were significantly higher with dorzolamide 2%/timolol 0.5% than brinzolamide 1%/timolol 0.5% (2.9 vs 1.4, respectively; $P < 0.0001$). Significantly more patients reported ocular pain and discomfort after dorzolamide 2%/timolol 0.5% instillation and transient blurred vision after brinzolamide 1%/timolol 0.5% instillation.[66] Manni et al observed a similar overall safety profile between the two groups, but brinzolamide 1%/timolol 0.5% showed significantly less ocular irritation (2.7% vs 10.6%; $P = 0.0009$) than dorzolamide 2%/timolol 0.5%.[65]

Teus et al have shown statistically significant difference in the amount of conjunctival hyperemia in travoprost 0.004%/timolol 0.5% group compared to dorzolamide 2%/timolol 0.5%, but it does not present any untoward safety issues.[67]

Long-term tolerability data are limited, although fixed combination was generally well tolerated for up to 1 year in a non-blind extension of one study.[54]

Conclusions

Efficacy and safety studies published till date show that dorzolamide with timolol is more efficacious than the individual components, and as effective as the components used concomitantly in controlled settings. Dorzolamide–timolol also has efficacy comparable to latanoprost 0.004%, pilocarpine 2%/timolol 0.5%, brinzolamide 0.1%/timolol 0.5% and unoprostone 0.15%/timolol 0.5% KLC. Dorzolamide-timolol is slightly more efficacious than latanoprost 0.005%/timolol 0.05% and brimonidine 0.2%/timolol 0.5%. In conclusion, dorzolamide–timolol combination has a good efficacy, safety and tolerability profile and hence an increased patient compliance.

Disclosures

The authors declare no conflicts of interest.

References

1. Vijaya L, George R, Paul PG, et al. Prevalence of open-angle glaucoma in a rural South India population. *Invest Ophthalmol Vis Sci*. 2005;46:4461–4467.
2. Iwase A, Suzuki Y, Araie M, et al; Tajimi Study Group, Japan Glaucoma Society. The Prevalence of Primary Open-Angle Glaucoma in Japanese: The Tajimi Study. *Ophthalmology*. 2004;111:1641–1648.
3. Leske CM. Open-angle glaucoma – an epidemiologic overview. *Ophthalmic Epidemiol*. 2007;14:166–172.
4. Sakata K, Sakata LM, Sakata VM, et al. Prevalence of glaucoma in a South Brazilian population: Projeto Glaucoma. *Invest Ophthalmol Vis Sci*. 2007;48:4974–4979.
5. The Eye Diseases Prevalence Research Group. Causes and prevalence of visual impairment among adults in the United States. *Arch Ophthalmol*. 2004;122:477–485.
6. Astrom S, Stenlund H, Linden C. Incidence and prevalence of pseudoexfoliations and open-angle glaucoma in northern Sweden: Results after 21 years of follow-up. *Acta Opthalmol Scand*. 2007;85:832–837.
7. Anton A, Andrada MT, Mujica V, Calle MA, Portela J, Mayo A. Prevalence of primary open-angle glaucoma in a spanish population: The Segovia Study. *J Glaucoma*. 2004;13:371–376.
8. Quigley H, Broman AT. The number of people with glaucoma worldwide in 2010 and 2020. *Br J Ophthalmol*. 2006;90:262–267.
9. Schwartz K, Budenz D. Current management of glaucoma. *Curr Opin Ophthalmol*. 2004;15:119–126.
10. The Royal College of Ophthalmologists. Guidelines for the management of open angle glaucoma and ocular hypertension. http://www.rcophth.ac.uk. Accessed Dec 10, 2009.
11. Marquis RE, Whitson JT. Management of glaucoma: focus on pharmacological therapy. *Drugs Aging*. 2005;22:1–21.
12. Hoyng PFJ, van Beek LM. Pharmacological therapy for glaucoma: a review. *Drugs*. 2000;59:411–434.
13. Higginbotham EJ, Hansen J, Davis EJ, Walt JG, Guckian A. Glaucoma medication persistence with a fixed combination versus multiple bottles. *Curr Med Res Opin*. 2009;25:2543–2547.
14. Yeh J, Kravitz D, Francis B. Rational use of the fixed combination of dorzolamide – timolol in the management of raised intraocular pressure and glaucoma. *Clin Ophthalmol*. 2008;2:389–399.
15. Balfour JA, Wilde MI. Dorzolamide: a review of its pharmacology and therapeutic potential in the management of glaucoma and ocular hypertension. *Drugs Aging*. 1997;10:384–403.
16. Heel RC, Brogden RN, Speight TM, et al. Timolol: a review of its therapeutic efficacy in the topical treatment of glaucoma. *Drugs*. 1979;17:38–55.
17. Sugrue MF. Pharmacological and ocular hypotensive properties of topical carbonic anhydrase inhibitors. *Prog Retinal Eye Res*. 2000;19:87–112.
18. Coakes RL, Brubaker RF. The mechanism of timolol in lowering intraocular pressure in the normal eye. *Arch Ophthalmol*. 1978;96:2045–2048.
19. Sonntag JR, Brindley GO, Shields MB. Effect of timolol therapy on outflow facility. *Invest Ophthalmol Vis Sci*. 1978;17:293–296.
20. Zimmerman TJ, Harbin R, Pett M, et al. Timolol and facility of outflow. *Invest Ophthalmol Vis Sci*. 1977;16:623–624.
21. Phylactos AC. Timolol inhibits adenylate cyclase activity in the iris-ciliary body and trabecular meshwork of the eye and blocks activation of the enzyme by salbutamol. *Acta Ophthalmol (Copenh)*. 1986;64:613–622.
22. Ormrod D, McClellan K. Topical dorzolamide 2%/timolol 0.5%: a review of its use in the treatment of open-angle glaucoma. *Drugs Aging*. 2000;17:477–496.
23. Shell JW. Pharmacokinetics of topically applied ophthalmic drugs. *Surv Ophthalmol*. 1982;26:207–218.
24. Hasegawa T, Hara K, Hata S. Binding of dorzolamide and its metabolite, N-deethylated dorzolamide, to human erythrocytes in vitro. *Drug Metab Dispos*. 1994;22:377–382.
25. Wong BK, Bruhin PJ, Barrish A, et al. Nonlinear dorzolamide pharmacokinetics in rats: concentration-dependent erythrocyte distribution and drug-metabolite displacement interaction. *Drug Metab Dispos*. 1996;24:659–663.
26. Maren TH, Conroy CW, Wynns GC, et al. Ocular absorption, blood levels, and excretion of dorzolamide, a topically active carbonic anhydrase inhibitor. *J Ocul Pharmacol Ther*. 1997;13:23–30.
27. Wilkerson M, Cyrlin M, Lippa EA, et al. Four-week safety and efficacy study of dorzolamide, a novel, active topical carbonic anhydrase inhibitor. *Arch Ophthalmol*. 1993;111:1343–1350.
28. Strahlman E, Tipping R, Vogel R. A six-week dose-response study of the ocular hypotensive effect of dorzolamide with a one-year extension. Dorzolamide Dose-Response Study Group *Am J Ophthalmol*. 1996;122:183–194. Erratum: *Am J Ophthalmol*. 1996;122:928.
29. Biollaz J, Munafo A, Buclin T, et al. Whole-blood pharmacokinetics and metabolic effects of the topical carbonic anhydrase inhibitor dorzolamide. *Eur J Clin Pharmacol*. 1995;47:453–460.
30. Martens-Lobenhoffer J, Banditt P. Clinical pharmacokinetics of dorzolamide. *Clin Pharmacokinet*. 2002;41:197–205.
31. Siesky B, Harris A, Brizendine E, et al. Literature review and meta-analysis of topical carbonic anhydrase inhibitors and ocular blood flow. *Surv Ophthalmol*. 2009;54:33–46.
32. Januleviciene I, Harris A, Kagemann L, et al. A comparison of the effects of dorzolamide/timolol fixed combination versus latanoprost on intraocular pressure and pulsatile ocular blood flow in primary open-angle glaucoma patients. *Acta Ophthalmol Scand*. 2004;82:730–737.

33. Manni G, Centofanti M, Gregori D, et al. The pulsatile ocular blood flow behaviour in open angle glaucoma patients after replacing timolol therapy with timolol and dorzolamide fixed combination: preliminary study. *Acta Ophthalmol Scand*. 2002;236:55–56.
34. Martinez A, Sanchez M. A comparison of the effects of 0.005% latanoprost and fixed combination dorzolamide/timolol on retrobulbar haemodynamics in previously untreated glaucoma patients. *Curr Med Res Opin*. 2006;22:67–73.
35. Harris A, Jonescu-Cuypers CP, Kagemann L, et al. Effect of dorzolamide timolol combination versus timolol 0.5% on ocular bloodflow in patients with primary open-angle glaucoma. *Am J Ophthalmol*. 2001;132: 490–495.
36. Rolle T, Tofani F, Brogliatti B, Grignolo FM. The effects of dorzolamide 2% and dorzolamide/timolol fixed combination on retinal and optic nerve head blood flow in primary open-angle glaucoma patients. *Eye (Lond)*. 2008;22:1172–1179.
37. Fuchsjager-Mayrl G, Wally B, Rainer G, et al. Effect of dorzolamide and timolol on ocular blood flow in patients with primary open angle glaucoma and ocular hypertension. *Br J Ophthalmol*. 2005;89: 1293–1297.
38. Galassi F, Sodi A, Renieri G, et al. Effects of timolol and dorzolamide on retrobulbar hemodynamics in patients with newly diagnosed primary open-angle glaucoma. *Ophthalmologica*. 2002;216:123–128.
39. Clineschmidt CM, Williams RD, Snyder E, et al. A randomized trial in patients inadequately controlled with timolol alone comparing the dorzolamide-timolol combination to monotherapy with timolol or dorzolamide. Dorzolamide-Timolol Combination Study Group. *Ophthalmology*. 1998;105:1952–959.
40. Boyle JE, Ghosh K, Gieser DK, et al; A randomized trial comparing the dorzolamide-timolol combination given twice daily to monotherapy with timolol and dorzolamide. Dorzo lamide-Timolol Study Group. *Ophthalmology*. 1998;105:1945–1951.
41. Fechtner RD, Airaksinen PJ, Getson AJ, et al. Efficacy and tolerability of the dorzolamide 2%/timolol 0.5% combination (COSOPT) versus 0.005% (XALATAN) in the treatment of ocular hypertension or glaucoma: results from two randomized clinical trials. *Acta Ophthalmol Scand*. 2004;82:42–48.
42. Susanna R Jr, Sheu WP. Comparison of latanoprost with fixed combination dorzolamide and timolol in adult patients with elevated intraocular pressure: an eight-week, randomized, open-label, parallel-group, multicenter study in Latin America. *Clin Ther*. 2004;26:755–768.
43. Honrubia FM, Larsson LI, Spiegel D, et al. A comparison of the effects on intraocular pressure of latanoprost 0.005% and the fixed combination of dorzolamide 2% and timolol 0.5% in patients with open-angle glaucoma. *Acta Ophthalmol Scand*. 2002;80:635–641.
44. Konstas AG, Papapanos P, Tersis I, et al. Twenty-four-hour diurnal curve comparison of commercially available latanoprost 0.005% versus the timolol and dorzolamide fixed combination. *Ophthalmology*. 2003;110:1357–1360.
45. Orzalesi N, Rissetti L, Bottoli A. The effect of latanoprost, brimonidinee and a fixed combination of timolol and dorzolamide on circadian intraocular pressure in patients with glaucoma or ocular hypertension. *Arch Ophthalmol*. 2003;121:453–457.
46. Ozturk F, Ermis S, Inan U. Comparison of ocular hypotensive effects of bimatoprost and timolol-dorzolamide combination in patients with elevated intraocular pressure: a 6 month study. *Acta Ophthalmol Scand*. 2007;85:80–83.
47. Chiselita D, Antohi I, Medvichi R, et al. Comparative analysis of the efficacy and safety of latanoprost, travoprost and the fixed combination timolol-dorzolamide; a prospective, ran-domized, masked, cross-over design study. *Oftalmologia*. 2005;49:39–45.
48. Parmaksiz S, Yuksel N, Karabas VL, et al. A comparison of travoprost, latanoprost, and the fixed combination of dorzolamide and timolol in patients with pseudoexfoliation glaucoma. *Eur J Ophthalmol*. 2006;16:73–80.
49. Coleman AL, Lerner F, Bernstein P, et al. A 3-month randomized controlled trial of bimatoprost (LUMIGAN) versus combined timolol and dorzolamide (Cosopt) in patients with glaucoma or ocular hypertension. *Ophthalmology*. 2003;110:2362–2368.
50. Day DG, Sharpe ED, Beischel CJ, et al. Safety and efficacy of bimatoprost 0.03% versus timolol maleate 0.5%/dorzolamide 2% fixed combination. *Eur J Ophthalmol*. 2005;15:336–342.
51. Suzuki ERJ, Franklin LM, da Silva LJ, et al. Comparison of the efficacy and safety of travoprost with a fixed-combination of dorzolamide and timolol in patients with open-angle glaucoma or ocular hypertension. *Curr Med Res Opin*. 2006;22:1799–1805.
52. Day DG, Schacknow CJ, 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;135:138–143.
53. Hutzelmann J, Owens S, Shedden A, et al. Comparison of the safety and efficacy of the fixed combination of dorzolamide/timolol and the concomitant administration of dorzolamide and timolol: a clinical equivalence study. International Clinical Equivalence Study Group. *Br J Ophthalmol*. 1998;82:1249–1253.
54. Strohmaier K, Snyder E, DuBiner H, et al; The efficacy and safety of the dorzolamide-timolol combination versus the concomitant administration of its components. Dorzolamide-Timolol Study Group. *Ophthalmology*. 1998;105:1936–1944.
55. Sall KN, Greff LJ, Johnson-Pratt LR, et al. Dorzolamide/timolol combination versus concomitant administration of brimonidinee and timolol: six-month comparison of efficacy and tolerability. *Ophthalmology*. 2003;110:615–624.
56. Solish AM, DeLucca PT, Cassel DA, et al. Dorzolamide/timolol fixed combination versus concomitant administration of brimonidinee and timolol in patients with elevated intraocular pressure: a 3-month comparison of efficacy, tolerability, and patient-reported measures. *J Glaucoma*. 2004;13:149–157.
57. Nixon DR, Yan DB, Chartrand JP, Piemontesi RL, Simonyi S, Hollander DA. Three-month, randomized, parallel-group comparison of brimonidinee-timolol versus dorzolamide-timolol fixed-combination therapy. *Curr Med Res Opin*. 2009:251645–1653.
58. Arcieri ES, Pereira ACA, Andreo EGV, et al. Fixed combination brimonidinee-timolol (Combigan) versus fixed combination dorzolamide-timolol (Cosopt) each given twice daily to reduce intraocular pressure in subjects with glaucoma or ocular hypertension [abstract no. E434-B169]. *Invest Ophthalmol Vis Sci*. 2006:47.
59. Zabriskie N, Netland PA. Comparison of brimonidinee/latanoprost and timolol/dorzolamide: two randomized, double masked, parallel clinical trials. *Adv Ther*. 2003;20:92–100.
60. Sverrisson T, Gross R, Pearson J, et al. The dorzolamide/timolol combination versus timolol plus pilocarpine: patient preference and impact on daily life. United States Patient Preference Study Group. International Patient Preference Study Group. *J Glaucoma*. 1999;8:315–324.
61. Kalzuny J, Szaflik J, Czechowicz-Janicka K. Timolol 0.5%/ dorzolamide 2% fixed combination versus timolol 0.5%/pilocarpine 2% fixed combination in primary open angle glaucoma or ocular hypertensive patients. *Acta Ophthalmol Scand*. 2003;81: 349–354.
62. Shin DH, Feldman RM, Sheu WP. Efficacy and safety of the fixed combinations latanoprost/timolol versus dorzolamide/timolol in patients with elevated intraocular pressure. *Ophthalmology*. 2004;111: 276–282.
63. Konstas AG, Kozobolis VP, Lallos N, et al. Daytime diurnal curve comparison between the fixed combinations of latanoprost 0.005%/ timolol maleate 0.5% and dorzolamide 2%/timolol maleate 0.5%. *Eye*. 2004;18:1264–1269.
64. Cvenkel B, Stewart JA, Nelson LA, Stewart WC. Dorzolamide/timolol fixed combination versus latanoprost/timolol fixed combination in patients with primary open-angle glaucoma or ocular hypertension. *Curr Eye Res*. 2008;33:163–168.

65. Manni G, Denis P, Chew P, et al. The safety and efficacy of brinzolamide 1%/timolol 0.5% fixed combination versus dorzolamide 2%/timolol 0.5% in patients with open-angle glaucoma or ocular hypertension. *J Glaucoma*. 2009;18:293–300.
66. Mundorf TK, Rauchman SH, Williams RD, Notivol R. Brinzolamide/Timolol Preference Study Group. A patient preference comparison of Azarga (brinzolamide/timolol fixed combination) vs Cosopt (dorzolamide/timolol fixed combination) in patients with open-angle glaucoma or ocular hypertension. *Clin Ophthalmol*. 2008;2:623–628.
67. Teus MA, Miglior S, Laganovska G, et al. Efficacy and safety of travoprost/timolol vs dorzolamide/timolol in patients with open-angle glaucoma or ocular hypertension. *Clin Ophthalmol*. 2009;3:629–636.
68. Hatanaka M, Reis A, Sano ME, Susanna R Jr. Additive Intraocular pressure reduction effect of fixed combination of maleate timolol 0.5%/dorzolamide 2% (Cosopt) on monotherapy with latanoprost (Xalatan) in patients with elevated intraocular pressure: a prospective, 4-week, open-label, randomized, controlled clinical trial. *J Glaucoma*. 2009 Sep 2. [Epub ahead of print].
69. Fechtner RD, McCarroll KA, Lines CR, et al. Efficacy of the dorzolamide/timolol fixed combination versus latanoprost in the treatment of ocular hypertension or glaucoma: combined analysis of pooled data from two large randomized observer and patient-masked studies. *J Ocul Pharmacol Ther*. 2005;21:242–249.
70. Tsai JC, McClure CA, Ramos SE, et al. Compliance barriers in glaucoma: a systematic classification. *J Glaucoma*. 2003;12:393–398.