Clinical Ophthalmology

Dovepress
open access to scientific and medical research

Open Access Full Text Article

REVIEW

Role of fixed-combination brinzolamide 1%/timolol 0.5% in the treatment of elevated intraocular pressure in open-angle glaucoma and ocular hypertension

This article was published in the following Dove Press journal:
Clinical Ophthalmology
20 October 2009
Number of times this article has been viewed

Henny JM Beckers
Jan SAG Schouten
Carroll AB Webers

University Eye Clinic, Maastricht, The Netherlands

Abstract: Brinzolamide 1%/timolol 0.5% is a new fixed-combination for the treatment of open-angle glaucoma or ocular hypertension. Brinzolamide/timolol has a favorable safety profile, with an incidence of ocular burning and stinging <5%. Published data show that brinzolamide 1%/timolol 0.5% and dorzolamide 2%/timolol 0.5% have similar efficacies for lowering intraocular pressure (IOP). There is some evidence that brinzolamide/timolol may be more comfortable. Although patients receiving brinzolamide/timolol may experience more blurred vision on instillation, some data show a preference for brinzolamide/timolol over dorzolamide/timolol. Although available data to assess the role of brinzolamide/timolol in daily clinical practice are still limited, these first results suggest the agent to be a reasonable alternative for patients who do not reach target IOP with monotherapy.

Keywords: brinzolamide, dorzolamide, fixed combination, glaucoma, IOP, timolol

Introduction

Reduction of elevated intraocular pressure (IOP) is the only proven approach to protect against visual field loss in patients with open-angle glaucoma (OAG) or ocular hypertension (OHT), making ocular hypotensive agents critical to the management of these patients. First-line therapy for elevated IOP is typically a single topical agent from one of the following classes of drugs: alpha-2 adrenergic receptor agonists, beta-blockers, topical carbonic anhydrase inhibitors (CAIs), and prostaglandin derivatives/prostamides.[1] If single-agent therapy is effective but not sufficient to reach a patient's target IOP, a second hypotensive drug is added. Evidence shows that this strategy can produce an additional IOP decrease.[2] The 2-drug combination can be comprised of 2 individual agents or a fixed-combination product. A recent meta-analysis confirmed that these 2 types of glaucoma therapies produce equivalent efficacy.[3] In a large study (N = 3333) of patients taking glaucoma medications, the majority (79%) reported that they were satisfied with their eye drops; however, nearly 1 in 10 patients (9%) were likely to have their medication changed at their next visit due to side effects.[4] Each hypotensive agent has a characteristic side effect profile, but fixed-combination products as a group have a number of advantages over the instillation of 2 individual drugs.[5] First, a fixed-combination product requires dispensing from only 1 bottle, making it more convenient than dispensing 2 separate doses. The European Glaucoma Society recommended that fixed-combination products be used, whenever available, in place of 2 separate instillations.[1] Fixed-combination products

Correspondence: Henny JM Beckers
University Eye Clinic, Maastricht, The Netherlands
Tel +31 43 387 53 42
Fax +31 43 387 53 43
Email henny.beckers@mumc.nl

also avoid washout, which occurs when inadequate time is allowed between instillation of the first and second drugs.[6] Moreover, the lifetime exposure to preservatives is reduced with fixed-combination products. Because preservatives have been shown to be associated with both *in vitro* ocular toxicities (eg, cellular apoptosis, conjunctival inflammation),[7,8] and clinical signs and symptoms of ocular irritation (eg, dry eye, burning/stinging, discomfort),[9,10] reducing exposure to preservatives should facilitate the maintenance of ocular surface health in these patients requiring chronic topical therapies. Finally, costs and impact on quality of life can lead to non-compliance in patients who have to use multiple medications. Some of these disadvantages can also be reduced by using fixed combinations.[11]

The fixed-combination dorzolamide 2%/timolol 0.5% (Cosopt®; Merck & Co., Inc., Whitehouse Station, NJ, USA) has been shown to be at least as effective as separate instillations of the component drugs.[12] Side effects that have been described are ocular stinging and burning upon instillation and a bitter taste.[13] The safety profiles of the individual components show that the incidence of stinging and burning of the fixed-combination product is most similar to dorzolamide (Trusopt®; Merck & Co., Inc., Whitehouse Station, NJ, USA) alone.[14] Recently, the fixed combination dorzolamide/timolol has also become available in several countries in a preservative-free variant. Recently, a new fixed-combination product, brinzolamide 1%/timolol 0.5% (Azarga®; Alcon Laboratories, Inc., Fort Worth, TX, USA), has been introduced. The aim of this review article is to explore the molecular and clinical characteristics of brinzolamide/timolol to determine its potential role in the management of patients with OAG or OHT.

Brinzolamide 1%/timolol 0.5%

The brinzolamide/timolol fixed combination is comprised of the CAI brinzolamide and the beta-blocker timolol and is recommended to be dosed twice daily (bid).[15] It is delivered as a suspension with a pH of 7.2 and is preserved with benzalkonium chloride 0.01%.[15] The concentration of brinzolamide is 1% (10 mg/mL), equal to that of brinzolamide ophthalmic suspension (Azopt®; Alcon Laboratories, Inc., Fort Worth, TX, USA)[16] and the timolol concentration is 0.5% (5 mg/mL), equal to that of single-agent timolol.[17–19]

Mechanisms of action and pharmacokinetics

Brinzolamide is a highly specific, reversible inhibitor of carbonic anhydrase, an enzyme which is present in the lens, cornea, ciliary body and retina.[20,21] Blocking this enzyme is believed to reduce aqueous humor formation by slowing the formation of bicarbonate ions with subsequent reduction in sodium and fluid transport.[16] Brinzolamide-induced inhibition of CA II, a key carbonic anhydrase isoenzyme, occurs both during the day and at night, apparently not subjected to the circadian rhythm.[22,23] A single drop of brinzolamide can lower IOP for approximately 12 hours, and its washout time after chronic instillation is 7 days.[22]

Contraindications of topical carbonic anhydrase inhibitors are renal failure and sulfonamide allergy. Caution should be taken in patients with a compromised corneal endothelium.

Beta-adrenergic antagonists (beta blockers) reduce IOP through blocking of the B_1-adrenoreceptor (non-selective and selective beta blockers) and B_2-adrenoreceptors (non-selective beta blockers) of the ciliary body epithelium which leads to a reduced inflow of aqueous humor in the anterior chamber of the eye. Most beta blockers are dosed bid, although the gel-forming solutions are often equally efficacious in a once daily regime.[24–26] The activity of timolol is subject to circadian changes, showing less efficacy at night.[27] Contraindications for the use of timolol are asthma, obstructive pulmonary disease, sinus bradycardia and heart block.

Effect on ocular blood flow

Some aspects of ocular blood flow may be reduced in certain patients with glaucoma.[28] Reduced ocular perfusion pressure probably is an independent risk factor for the development of OAG.[29–34]

Numerous studies have shown that timolol does not affect ocular blood flow;[35–37] however, several studies have reported a possible increased resistance to blood flow.[38,39] Although there is no conclusive evidence, many studies have suggested that the topical carbonic anhydrase inhibitor dorzolamide probably has a positive effect on ocular blood flow. In addition, a positive effect on ocular blood flow for the fixed combination of dorzolamide/timolol has been shown.[40–46] The effect of brinzolamide on ocular blood flow is less well established, mainly due to a limited number of publications on the subject. Several studies have shown that brinzolamide positively affects ocular blood flow,[47–49] but others have shown no effect.[50,51] Until now, the effects of brinzolamide/timolol on ocular blood flow have been unclear. Studies on the effects of the combination brinzolamide/timolol (concomitant or fixed combination) on ocular blood flow are scarce.

IOP-lowering efficacy

We performed a systematic review of the IOP-lowering efficacy of the combination of brinzolamide and timolol. Articles were identified through a computerized search in Medline, Embase, and the Cochrane Controlled Trials Register. For details on search strategy, selection process and data extraction we refer to the papers of van der Valk et al[52] and Webers et al[2,53] Potentially eligible for inclusion in this systematic review were randomized clinical trials on the combination of timolol and brinzolamide written in English, French, German or Dutch and published between January 1995 and July 2009.

The initial search revealed 1169 papers. Based on the title, abstract and medical subject heading (MeSH) words, 1128 papers were excluded. The most important reasons for excluding articles were that the primary endpoint in the studies was not IOP but, for instance, side-effects, visual field outcome or impact on ocular blood flow, that articles reported on glaucoma topics other than IOP lowering of drugs, or that studies reported on IOP lowering of monotherapies. From the remaining 41 papers that were printed or photocopied 36 papers had to be excluded. The major reasons were a non-randomize design (n = 9), a combination of other drugs (n = 7) or a different outcome parameter (n = 9).

The results of the included studies[54–58] are shown in Table 1.

An earlier systematic review showed no significant differences between concomitant and fixed use of the combination of 0.5% timolol bid and 2% dorzolamide bid.[2] The mean additional IOP decrease of 2% dorzolamide bid or tid when added to 0.5% timolol bid was 15.7% at trough and 20.1% at peak.[53] The present study gives similar results for the IOP decrease of the concomitant use of 0.5% timolol bid and 1% brinzolamide bid or tid, varying between 13.2% at trough and 20.3% at peak. The 2 papers reporting on the fixed combination brinzolamide/timolol[57,58] revealed similar IOP-lowering results. These studies both used a washout design. Moreover, the Manni study[58] also reported similar IOP-lowering results for the brinzolamide/timolol combination when directly compared with the fixed combination dorzolamide/timolol.

Safety and tolerability

In the study by Kaback[57] et al a higher incidence of blurred vision was found in the group of patients treated with brinzolamide/timolol versus patients treated with timolol 0.5% alone; however, reported dysgeusia was markedly lower with the fixed combination. The Manni study showed similar safety profiles for brinzolamide/timolol and dorzolamide/timolol, with the exceptions of a lower incidence of any adverse events and fewer patients with ocular burning and stinging. In the brinzolamide/timolol group, a higher incidence of blurred vision was reported.[58]

A study by Vold and colleagues[59] directly examined the ocular discomfort associated with the use of brinzolamide/timolol or dorzolamide/timolol after 1 week of dosing. Mean ocular discomfort scores (judged from a scale of 0 [none] to 4 [very severe]) were significantly lower in patients receiving brinzolamide/timolol than in those receiving dorzolamide/timolol. Although this study had a very short follow-up period, the results confirm the results from the Manni study.

Because the beta-blocker component of the 2 CAI-containing fixed-combination products is identical, any dissimilarities in tolerability are likely due to differences in pH between brinzolamide and dorzolamide. Dorzolamide/timolol is formulated at an acidic pH of 5.65,[13] whereas brinzolamide/timolol has a near physiologic pH of 7.2.[15] This hypothesis is supported by results from 2 multicenter studies published in 2000 which used study designs similar to the Vold comfort study, comparing the ocular comfort of the single agents brinzolamide and dorzolamide.[60] Significantly more patients in both studies reported no ocular discomfort with brinzolamide than with dorzolamide. In an ocular discomfort study in which patients taking latanoprost, dorzolamide, and timolol combination therapy were randomized to switch the CAI component to brinzolamide or to continue dorzolamide, patients in the brinzolamide group, but not the control group, experienced a significant decrease in ocular irritation, although these patients had a numerical increase in blurred vision.[61] Another study from Michaud and colleagues, which compared brinzolamide and dorzolamide each given twice daily in addition to timolol 0.5%, also found significantly less ocular burning and stinging in the brinzolamide group.[55]

The results from the studies mentioned above suggest that brinzolamide/timolol may be more tolerable than (preserved) dorzolamide/timolol, at the cost of an increase in blurred vision. The authors are not aware of any studies comparing the ocular comfort of unpreserved dorzolamide/timolol to preserved dorzolamide/timolol or other topical medication.

Patient preference

All of the clinical characteristics described above – efficacy, safety, and tolerability – probably affect patient preference. Patient preference, in turn, may improve adherence. Barnebey et al suggested that better patient adherence after

Table 1 Run-in medication, treatment combination after adding brinzolamide, baseline characteristics, time point(s) of intraocular pressure measurements and absolute (mmHg) and relative (%) decrease from baseline intraocular pressure for peak and trough time points

Trial	Run-in medication	Treatment combination after run-in	No. of patients baseline (% withdrawals)	Sex (M/F)	Mean age (y)	POAG (%)
Trough						
Shin 2000[54]	0.5% timolol bid	0.5% timolol bid and 1% brinzolamide tid	53 (11.3)	28/25	61	59
Michaud et al 2001[55]	0.5% timolol bid	0.5% timolol bid and 1% brinzolamide bid	104 (6.7)	54/50	nr	57
Martinez et al 2009[56]	0.5% timolol bid	0.5% timolol bid and 1% brinzolamide bid	76 (54)	41/35	64	100
Kaback et al 2008[57]	washout	0.5% timolol/1% brinzolamide bid (fixed)	171 (7.5)	80/91	nr	63
Manni et al 2009[58]	washout	0.5% timolol/1% brinzolamide bid (fixed)	220 (7.3)	96/124	65	78
Peak						
Shin 2000[54]	0.5% timolol bid	0.5% timolol bid and 1% brinzolamide tid	53 (11.3)	28/25	61	59
Michaud et al 2001[55]	0.5% timolol bid	0.5% timolol bid and 1% brinzolamide bid	104 (6.7)	54/50	nr	57
Martinez et al 2009[56]	0.5% timolol bid	0.5% timolol bid and 1% brinzolamide bid	76 (54)	41/35	64	100
Kaback et al 2008[57]	washout	0.5% timolol/1% brinzolamide bid (fixed)	171 (7.5)	80/91	nr	63
Manni et al 2009[58]	washout	0.5% timolol/1% brinzolamide bid (fixed)	220 (7.3)	96/124	65	78

a transition from dorzolamide to brinzolamide correlated with a patient preference for brinzolamide.[62] In a crossover study, Mundorf and colleagues found better comfort scores for brinzolamide/timolol than for dorzolamide/timolol.[63] Although the follow up in this study was very limited, a majoritiy of patients preferred brinzolamide/timolol. Ocular burning and stinging are very frequent side effects of topical glaucoma medications.[4] In a willingness-to-pay analysis of topical ocular medications, it was found that nearly 75% of patients would be willing to pay a premium for a medication that would eliminate stinging and burning upon instillation.[64]

Summary

Published data show that brinzolamide 1%/timolol 0.5% and dorzolamide 2%/timolol 0.5% have similar efficacies for lowering IOP. The main difference between these agents appears to be in the safety profiles, with dorzolamide/timolol producing more ocular burning and stinging, probably due to differences in pH. In several studies, brinzolamide/timolol was rated as the more comfortable medication for new users. Although patients receiving brinzolamide/timolol may experience more blurred vision upon instillation, some data suggest a preference for brinzolamide/timolol over dorzolamide/timolol in new users. However, the follow up of these studies was short or very short. Patients who have used their medication for a longer period may probably be more satisfied with their medication. The effect of excluding preservatives in dorzolamide/timolol on comfort and/or patient preference has not been studied.

Thus, although available data to assess the role of brinzolamide/timolol are still limited, its apparently similar efficacy and probably improved tolerability relative to dorzolamide/timolol make it a reasonable alternative for patients who do not reach target IOP with monotherapy.

Further evaluation of the fixed combination brinzolamide/timolol in daily clinical practice will elucidate how this novel combination agent will be accepted by physicians and ultimately incorporated into the management of patients with elevated IOP.

OHT (%)	Endpoint of measurement (months)	Baseline IOP (mmHg) mean ± SD	Time point(s) of IOP measurements	IOP decrease (mmHg) mean ± SD	IOP decrease (%) mean ± SD
41	1	25.5 ± nr	+0 timolol +0 brinzolamide	–3.3 ± nr	–13.2 ± nr
37	1	25.5 ± 1.9	+0 timolol +0 brinzolamide	–3.6 ± 3.0	–14.1 ± 11.4
0	60	22.7 ± 1.2	nr	–4.3 ± nr	–18.9 ± nr
37	3	27.1 ± 2.7	+0 timolol +0 brinzolamide	–8.3 ± 3.8	–30.6 ± 13.6
22	3	27.3 ± nr	+0 timolol +0 brinzolamide	–9.1 ± nr	–33.3 ± nr
41	1	25.5 ± nr	+2 timolol +2 brinzolamide	–3.3 ± nr	–14.3 ± nr
37	1	25.5 ± 1.9	+2 timolol +2 brinzolamide	–4.9 ± 2.6	–20.3 ± 10.5
0	60	22.7 ± 1.2	nr	–4.3 ± nr	–18.9 ± nr
37	3	25.8 ± 3.0	+2 timolol +2 brinzolamide	–8.7 ± 3.9	–33.7 ± 14.7
22	3	25.9 ± nr	+2 timolol +2 brinzolamide	–9.1 ± nr	–34.9 ± nr

Abbreviations: M, male; F, female; Y, year; POAG, primary open-angle glaucoma; OHT, ocular hypertension; IOP, intraocular pressure; SD, standard deviation; bid, twice daily; tid, thrice daily; nr, not reported.

Acknowledgments and disclosures

Publication support was provided by Alcon Laboratories, Inc. The authors have no proprietary interest in the products discussed in this manuscript.

References

1. European Glaucoma Society. Terminology and guidelines for glaucoma. Sivona, Italy: Dogma; 2008.
2. Webers CA, Beckers HJ, Nuijts RM, Schouten JS. Pharmacological management of primary open-angle glaucoma: second-line options and beyond. *Drugs Aging*. 2008;25:729–759.
3. Cox JA, Mollan SP, Bankart J, Robinson R. Efficacy of antiglaucoma fixed combination therapy versus unfixed components in reducing intraocular pressure: a systematic review. *Br J Ophthalmol*. 2008;92:729–734.
4. Beckers HJ, Schouten JS, Webers CA, van der Valk R, Hendrikse F. Side effects of commonly used glaucoma medications: comparison of tolerability, chance of discontinuation, and patient satisfaction. *Graefes Arch Clin Exp Ophthalmol*. 2008;246:1485–1490.
5. Khouri AS, Realini T, Fechtner RD. Use of fixed-dose combination drugs for the treatment of glaucoma. *Drugs Aging*. 2007;24:1007–1016.
6 Fechtner RD, Realini T. Fixed combinations of topical glaucoma medications. *Curr Opin Ophthalmol*. 2004;15:132–135.
7. Baudouin C, Riancho L, Warnet JM, Brignole F. In vitro studies of antiglaucomatous prostaglandin analogues: travoprost with and without benzalkonium chloride and preserved latanoprost. *Invest Ophthalmol Vis Sci*. 2007;48:4123–4128.
8. Kahook MY, Noecker RJ. Comparison of corneal and conjunctival changes after dosing of travoprost preserved with sofZia, latanoprost with 0.02% benzalkonium chloride, and preservative-free artificial tears. *Cornea*. 2008;27:339–343.
9. Jaenen N, Baudouin C, Pouliquen P, Manni G, Figueiredo A, Zeyen T. Ocular symptoms and signs with preserved and preservative-free glaucoma medications. *Eur J Ophthalmol*. 2007;17:341–349.
10. Pisella PJ, Pouliquen P, Baudouin C. Prevalence of ocular symptoms and signs with preserved and preservative free glaucoma medication. *Br J Ophthalmol*. 2002;86:418–423.
11 Hommer A, Thygesen J, Ferreras A, et al. A European perspective on costs and cost effectiveness of ophthalmic combinations in the treatment of open-angle glaucoma. *Eur J Ophthalmol*. 2008;18:778–786.
12. Francis BA, Du LT, Berke S, Ehrenhaus M, Minckler DS. Comparing the fixed combination dorzolamide-timolol (Cosopt) to concomitant administration of 2% dorzolamide (Trusopt) and 0.5% timolol – a randomized controlled trial and a replacement study. *J Clin Pharm Ther*. 2004;29:375–380.
13. Cosopt® [package insert]. Whitehouse Station, NJ: Merck and Co., Inc.; 2006.
14. Trusopt® [package insert]. Whitehouse Station, NJ: Merck and Co., Inc.; 2005.
15. European Agency for the Evaluation of Medical Products. European public assessment report and product information on Azarga [online]. URL http://www.emea.europa.eu/humandocs/Humans/EPAR/azarga/azarga.htm. Accessed February 2, 2009.
16. Azopt® [package insert]. Fort Worth, TX: Alcon Laboratories, Inc.; 2008.

17. Betimol® [package insert]. Jacksonville, FL: Vistakon Pharmaceuticals, LLC; 2006.
18. Timoptic® [package insert]. Whitehouse Station, NJ: Merck and Co., Inc.; 2005.
19. Istalol® [package insert]. Irvine, CA: Ista Pharmaceuticals, Inc.; 2005.
20. Iester M. Brinzolamide. *Expert Opin Pharmacother*. 2008;9:653–662.
21. Sugrue MF. Pharmacological and ocular hypotensive properties of topical carbonic anhydrase inhibitors. *Prog Retin Eye Res*. 2000;19: 87–112.
22. Holló G. Use of topical carbonic anhydrase inhibition in glaucoma treatment. In: Pharmacotherapy in glaucoma. Bern, Switzerland: Hans Huber Verlag; 2000.
23. Liu JH, Medeiros FA, Slight JR, Weinreb RN. Comparing diurnal and nocturnal effects of brinzolamide and timolol on intraocular pressure in patients receiving latanoprost monotherapy. *Ophthalmology*. 2009;116:449–454.
24. Konstas AG, Mantziris DA, Maltezos A, Cate EA, Stewart WC. Comparison of 24 hour control with Timoptic 0.5% and Timoptic-XE 0.5% in exfoliation and primary open-angle glaucoma. *Acta Ophthalmol Scand*. 1999;77:541–543.
25. Kumar H, Sudan R, Sethi HS, Sony P. Timolol maleate 0.5% versus timolol maleate in gel forming solution 0.5% (Timolol GFS) in open angle glaucoma in India. Preliminary safety and efficacy study. *Indian J Ophthalmol*. 2002;50:21–23.
26. Shedden A, Laurence J, Tipping R. Efficacy and tolerability of timolol maleate ophthalmic gel-forming solution versus timolol ophthalmic solution in adults with open-angle glaucoma or ocular hypertension: a six-month, double-masked, multicenter study. *Clin Ther*. 2001;23:440–450.
27. Orzalesi N, Rossetti L, Invernizzi T, Bottoli A, Autelitano A. Effect of timolol, latanoprost, and dorzolamide on circadian IOP in glaucoma or ocular hypertension. *Invest Ophthalmol Vis Sci*. 2000;41:2566–2573.
28. Rojanapongpun P, Drance SM, Morrison BJ. Ophthalmic artery flow velocity in glaucomatous and normal subjects. *Br J Ophthalmol*. 1993;77:25–29.
29. Tielsch JM, Katz J, Sommer A, Quigley HA, Javitt JC. Hypertension, perfusion pressure, and primary open-angle glaucoma. A population-based assessment. *Arch Ophthalmol*. 1995;113:216–221.
30. Asrani S, Zeimer R, Wilensky J, Gieser D, Vitale S, Lindenmuth K. Large diurnal fluctuations in intraocular pressure are an independent risk factor in patients with glaucoma. *J Glaucoma*. 2000;9:134–142.
31. Bergea B, Bodin L, Svedbergh B. Impact of intraocular pressure regulation on visual fields in open-angle glaucoma. *Ophthalmology*. 1999;106:997–1004; discussion 1004–1005.
32. Nouri-Mahdavi K, Hoffman D, Coleman AL, et al. Advanced Glaucoma Intervention Study. Predictive factors for glaucomatous visual field progression in the Advanced Glaucoma Intervention Study. *Ophthalmology*. 2004;111:1627–1635.
33. Liu JH, Kripke DF, Twa MD, et al. Twenty-four-hour pattern of intraocular pressure in the aging population. *IOVS*. 1999;40:2912–2917.
34. Caprioli J. Intraocular pressure fluctuation: an independent risk factor for glaucoma? *Arch Ophthalmol*. 2007;125:1124–1125.
35. Carenini AB, Sibour G, Boles Carenini B. Differences in the longterm effect of timolol and betaxolol on the pulsatile ocular blood flow. *Surv Ophthalmol*. 1994;38 Suppl:S118–S124.
36. Lubeck P, Orgul S, Gugleta K, Gherghel D, Gekkieva M, Flammer J. Effect of timolol on anterior optic nerve blood flow in patients with primary open-angle glaucoma as assessed by the Heidelberg retina flowmeter. *J Glaucoma*. 2001;10:13–17.
37. Harris A, Spaeth GL, Sergott RC, Katz LJ, Cantor LB, Martin BJ. Retrobulbar arterial hemodynamic effects of betaxolol and timolol in normal-tension glaucoma. *Am J Ophthalmol*. 1995;120:168–175.
38. Yoshida A, Ogasawara H, Fujio N, et al. Comparison of short- and long-term effects of betaxolol and timolol on human retinal circulation. *Eye*. 1998;12:848–853.
39. Liu JH, Li R, Nelson TR, Weinreb RN. Resistance to blood flow in the rabbit ophthalmic artery after topical treatment with timolol. *J Ocul Pharmacol Ther*. 2007;23:103–109.
40. Siesky B, Harris A, Sines D, et al. A comparative analysis of the effects of the fixed combination of timolol and dorzolamide versus latanoprost plus timolol on ocular hemodynamics and visual function in patients with primary open-angle glaucoma. *J Ocul Pharmacol Ther*. 2006;22:353–361.
41. Brogliatti B, Rolle T, Vizzeri GM, Cipullo D. Comparison of the efficacy on intraocular pressure and retinal blood flow of a beta-blocker (timolol maleate) against the fixed association of a topical carbonic anhydrase (dorzolamide) and a beta-blocker (timolol maleate). *Acta Ophthalmol Scand*. 2000;232:47–49.
42. 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*. 2008;22:1172–1179.
43. Martínez A, Sánchez M. A comparison of the effects of 0.005% latanoprost and fixed combination dorzolamide/timolol on retrobulbar haemodynamics in perviously untreated glaucoma patients. *Curr Med Res Opin*. 2006;22:67–73.
44. Uva MG, Longo A, Reibaldi M, Reibaldi A. The effect of timolol-dorzolamide and timolol-pilocarpine combinations on ocular blood flow in patients with glaucoma. *Am J Ophthalmol*. 2006;141:1158–1160.
45. Janulevicinë I, Harris A, Kagemann L, Siesky B, McCranor L. A comparison of theeffects 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.
46. 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.
47. Barnes GE, Li B, Dean T, Chandler ML. Increased optic nerve head blood flow after 1week of twice daily topical brinzolamide treatment in Dutch-belted rabbits. *Surv Ophthalmol*. 2000;44(Suppl 2):S131–S140.
48. Iester M, Altieri M, Michelson G, Vittone P, Traverso CE, Calabria G. Retinal peripapillary blood flow before and after topical brinzolamide. *Ophthalmologica*. 2004;218:390–396.
49. Siesky B, Harris A, Cantor LB, et al. A comparative study of the effects of brinzolamide and dorzolamide on retinal oxygen saturation and ocular microcirculation in patients with primary open-angle glaucoma. *Br J Ophthalmol*. 2008;92:500–504.
50. Kaup M, Plange N, Niegel M, Remky A, Arend O. Effects of brinzolamide on ocular haemodynamics in healthy volunteers. *Br J Ophthalmol*. 2004;88:257–262.
51. Klemm M, Zeitz O, Reuss J, Matthiessen ET, Richard G. Therapy of normal tension glaucoma: effect of brinzolamide on ocular haemodynamics. *Klin Monatsbl Augenheilkd*. 2003;220:330–333.
52. van der Valk R, Webers CA, Schouten JS, et al. Intraocular pressure-lowering effects of all commonly used glaucoma drugs: a meta-analysis of randomized clinical trials. *Ophthalmology*. 2005;112: 1177–1185.
53. Webers CA, van der Valk R, Schouten JS, et al. Intraocular pressure-lowering effect of adding dorzolamide or latanoprost to timolol: a meta-analysis of randomized clinical trials. *Ophthalmology*. 2007;114:40–46.
54. Shin D. Adjunctive therapy with brinzolamide 1% ophthalmic suspension (Azopt) in patients with open-angle glaucoma or ocular hypertension maintained on timolol therapy. *Surv Ophthalmol*. 2000;44 Suppl 2:S163–S168.
55. Michaud JE, Friren B; International Brinzolamide Adjunctive Study Group. Comparison of topical brinzolamide 1% and dorzolamide 2% eye drops given twice daily in addition to timolol 0.5% in patients with primary open-angle glaucoma or ocular hypertension. *Am J Ophthalmol*. 2001;132:235–243.
56. Martinez A, Sanchez Salorio M. A comparison of the long-term effects of dorzolamide 2% and brinzolamide 1%, each added to timolol 0.5%, on retrobulbair hemodynamics and intraocular pressure in open-angle glaucoma patients. *J Ocul Pharmacol Ther*. 2009;25:239–248.

57. Kaback M, Scoper SV, Arzeno G, et al. Intraocular pressure-lowering efficacy of brinzolamide 1%/timolol 0.5% fixed combination compared with brinzolamide 1% and timolol 0.5%. *Ophthalmology*. 2008;115:1728–1734.
58. 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.
59. Vold SD, Evans RM, Stewart RH, Walters T, Mallick S. A one-week comfort study of BID-dosed brinzolamide 1%/timolol 0.5% ophthalmic suspension fixed combination compared to BID-dosed dorzolamide 2%/timolol 0.5% ophthalmic solution in patients with open-angle glaucoma or ocular hypertension. *J Ocul Pharmacol Ther*. 2008;24:601–605.
60. Silver LH. Ocular comfort of brinzolamide 1.0% ophthalmic suspension compared with dorzolamide 2.0% ophthalmic solution: results from two multicenter comfort studies. Brinzolamide Comfort Study Group. *Surv Ophthalmol*. 2000;44(Suppl 2):S141–S145.
61. Tsukamoto H, Noma H, Mukai S, Ikeda H, Mishima HK. The efficacy and ocular discomfort of substituting brinzolamide for dorzolamide in combination therapy with latanoprost, timolol, and dorzolamide. *J Ocul Pharmacol Ther*. 2005;21:395–399.
62. Barnebey H, Kwok SY. Patients' acceptance of a switch from dorzolamide to brinzolamide for the treatment of glaucoma in a clinical practice setting. *Clin Ther*. 2000;22:1204–1212.
63. Mundorf T, Rauchman S, Williams R, Notivol R. 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.
64. Jampel HD, Schwartz GF, Robin AL, Abrams DA, Johnson E, Miller RB. Patient preferences for eye drop characteristics: a willingness-to-pay analysis. *Arch Ophthalmol*. 2003;121:540–546.