Clinical Ophthalmology

Dovepress
open access to scientific and medical research

Open Access Full Text Article

ORIGINAL RESEARCH

Comparison of the latanoprost 0.005%/timolol 0.5% + brinzolamide 1% versus dorzolamide 1%/timolol 0.5% + latanoprost 0.005%: a 12-week, randomized open-label trial

This article was published in the following Dove Press journal:
Clinical Ophthalmology
5 March 2012
Number of times this article has been viewed

Shunsuke Nakakura[1]
Hitoshi Tabuchi[1]
Yukio Baba[2]
Futoshi Maruiwa[2]
Nobuko Ando[2]
Takashi Kanamoto[3]
Yoshiaki Kiuchi[3]

[1]Department of Ophthalmology, Saneikai Tsukazaki Hospital, Himeji, Hyogo Prefecture, Japan; [2]Department of Ophthalmology, Baba Eye Clinic, Hiroshima, Japan, [3]Department of Ophthalmology and Visual Sciences, Graduate School of Biomedical Sciences, Hiroshima University, Hiroshima City, Japan

Objective: To compare the safety and effectiveness of fixed-combination regimes (latanoprost–timolol and brinzolamide 1% compared to dorzolamide 1%/timolol and latanoprost) in open-angle glaucoma patients after switching from a combination of three topical antiglaucoma eye drops.

Methods: We conducted an open, randomized 12-week multicenter prospective study. We randomly allocated 39 patients who had been treated with three antiglaucoma eye drops (prostaglandin $F_{2\alpha}$ analogues plus beta-blockers and carbonic anhydrase inhibitors) into two groups. Group A (n = 20) were treated with latanoprost–timolol and brinzolamide 1% therapy and Group B (n = 16) were treated with dorzolamide 1%/timolol and latanoprost. Thirty-six patients completed all 12 weeks of this study. The major clinical parameters measured were intraocular pressure (IOP), conjunctive hyperemia, superficial punctate keratopathy and hyperpigmentation of eyelid at baseline, 4, and 12 weeks. Additionally noted were adverse events and patient preferences, measured using a questionnaire at study initiation and at 12 weeks.

Results: At baseline, IOPs were (Group A: 14.1 ± 2.9 mmHg, B: 14.5 ± 2.9 mmHg; $P = 0.658$), (Group A: 13.8 ± 2.6 mmHg, B: 14.3 ± 2.8 mmHg; $P = 0.715$) at 4 weeks, and (Group A: 14.1 ± 2.7 mmHg, B: 14.2 ± 2.7 mmHg; $P = 0.538$) at 12 weeks. Among the groups, there was no significant difference at any time point after baseline ($P = 0.923$, 0.951, respectively). All adverse events were not remarkably different after therapy. In regards to patient preference before and after switching therapy, 10 patients (50%) in Group A and 10 patients (63%) in Group B preferred using fixed-combination eye drop therapy.

Conclusions: Effectiveness and safety were maintained in both groups after switching therapy. Overall, patients generally preferred using a fixed-combination therapy.

Keywords: glaucoma, latanoprost–timolol, dorzolamide–timolol, brinzolamide, fixed combination, intraocular pressure

Introduction

High intraocular pressure (IOP) is a risk factor for developing visual field deficits in patients with various forms of glaucoma, including normal-tension glaucoma.[1–3] Chauhan et al reported that for every 1 mmHg increment in IOP, the risk of glaucoma progression increases by 19%.[4] Reducing IOP is currently the only known strategy for preventing glaucoma progression.

Various kinds of antiglaucoma drugs have been successfully developed to date. However higher dose frequency, especially more than two administrations per day,

Correspondence: Shunsuke Nakakura
Department of Ophthalmology, Saneikai Tsukazaki Hospital, 68-1 Aboshi Waku, Himeji 671-1227, Japan
Tel +81 79 272 8555
Fax +81 79 272 8550
Email shunsukenakakura@yahoo.co.jp

is usually associated with increased glaucoma medication nonadherence.[5–9] Adherence to medication regimes is also attributable to side effects,[10,11] the cost of medication,[8,12] and noon-time doses.[13,14] Recently, various fixed-combination therapies have become available. These have decreased the daily dose frequency and proved equally or more effective compared with combination therapy.[15–19]

Because of the benefits, a regime of fixed-combination therapy plus one antiglaucoma eye drop may be considered to be the most convenient and maximally tolerable management strategy for glaucoma patients at present. To the best of our knowledge, there have been no studies which compare and evaluate which two administrations including fixed-combination therapy is most safe and effective.

Latanoprost 0.005% was the first prostaglandin $F_{2\alpha}$ analogue developed for use as a topical glaucoma medication and has been prescribed worldwide for more than 10 years. However, there have not yet been reports regarding which combination therapy; latanoprost–timolol + brinzolamide 1% or dorzolamide 1%–timolol + latanoprost is superior in effectively and safely lowering IOP.

The aim of this study was to compare the treatment regimes of latanoprost 0.005%–timolol 0.5% plus brinzolamide 1% (hereafter referred to as Regime A) versus dorzolamide 1%–timolol + latanoprost 0.005% (hereafter referred to as Regime B) to investigate their IOP reduction, ocular adverse effects, and patients' response.

In this study, we conducted a randomized, controlled trial to compare the two regimens after switching from a combination of three topical antiglaucoma eye drops (prostaglandin $F_{2\alpha}$ analogues plus beta-blockers and carbonic anhydrase inhibitors) to Regime A and Regime B in primary open-angle glaucoma patients.

Methods

Design

We conducted a randomized, open prospective multicenter study in which two groups were treated in parallel. The study received approval from the University Institutional Review Board in Hiroshima University and was conducted according to the tenets of the Declaration of Helsinki.

Patient selection

The purpose and nature of the trial was explained in detail to all patients and their informed consent was obtained. Patients were enrolled between April 2010 and January 2011 at three clinical sites in Japan, Tsukazaki Hospital, Baba Eye Clinic, and Hiroshima University Hospital. Inclusion criteria were: (1) primary open-angle glaucoma exhibiting characteristic glaucomatous visual-field loss and optic nerve head damage; (2) exhibition of a stable IOP for more than 3 months measured by Goldmann applanation tonometer by the same ophthalmologist; (3) no history of fixed-combination therapy; and (4) patients that were treated with three antiglaucoma eye drops (various preparations of prostaglandin $F_{2\alpha}$ analogues + beta-blockers + carbonic anhydrase inhibitors).

Exclusion criteria were: (1) patients with congenital or narrow-angle glaucoma; (2) patients who had undergone ocular surgery including laser surgery within the previous 6 months; (3) patients who have had any previous glaucoma surgery; (4) patients with ocular inflammation, neovascular glaucoma, or steroid-induced glaucoma; (5) patients with any other conditions that prevent use of the Goldmann applanation tonometer; (6) patients at risk of visual acuity and visual fields worsening during this study; and (7) allergy to preservatives. On the basis of these criteria, 39 patients were enrolled during the study period.

Procedures

Baseline visit assessments measured were: the best-corrected visual acuity; IOP by Goldmann applanation tonometer, slit-lamp examination (including fundoscopy), results of visual field tests (Humphrey 30-2 or 24-2 SITA program, Humphrey Field Analyzer; Carl Zeiss Meditec, Dublin, CA) within several months, age, sex, medical history, histories of cataract and glaucoma surgery, content of present antiglaucoma drugs, hyperpigmentation of eyelid, conjunctival hyperemia score and superficial punctate keratopathy (SPK, area–density [AD] classification).[20] A written questionnaire for using the present eye drops was administered to check the adverse effects.

Patients were randomly allocated into two groups without a washout period: Group A: latanoprost–timolol (Xalacom™; Pfizer, Inc, New York, NY) + brinzolamide 1% (Azopt™; Alcon Japan Limited, Tokyo, Japan) therapy (Regime A) and Group B: dorzolamide 1%–timolol (Cosopt™; Merck & Co, Inc, Whitehouse Station, NJ) + latanoprost (Xalatan™; Pfizer, Inc,) (Regime B). The various preparations of three antiglaucoma eye drops (prostaglandin $F_{2\alpha}$ analogues + beta-blockers + carbonic anhydrase inhibitors) are used.

Upon enrollment in the study, patients were advised to administer the medication according to the treatment regimen and were subsequently reevaluated at 4 and 12 weeks. Patients were instructed that latanoprost–timolol and latanoprost were to be self-administered once per day at night, and that brinzolamide and dorzolamide–timolol were self-administered twice per day. IOP was measured in the sitting position by

Goldmann applanation tonometer by the same experienced ophthalmologists. IOP, hyperpigmentation of the eyelid, conjunctival hyperemia and SPK were evaluated at baseline, 4, and 12 weeks. A questionnaire survey was evaluated at baseline and at 12 weeks. Each patient's preference before and after switching treatments was evaluated at 12 weeks. Conjunctival hyperemia was classified using a four-grade photographic scale; slight (0), mild (+1), moderate (+2), and severe (+3). Superficial punctate keratopathy was assessed by fluorescein staining observed using a blue-free filter and evaluated using AD classification.[20] The AD score is the adding of the area score (0–3) and density score (0–3).

Adverse effects in the written questionnaire were evaluated by six questions indicating patient experience of stinging/burning, foreign body sensation, blurred vision, conjunctival hyperemia, frequency of forgetting administration, and comfortableness when administered eye drops (Figure 1). Stinging/burning, foreign body sensation, blurred vision, and conjunctival hyperemia were judged by a three-point response: yes, no, or neither. Frequency of forgetting

A questionnaire before changing eye drops. Please co-operate.
Please check that the patient completes the questionnaire ☐

• Do you have "Stinging/burning" after administration?	☐ Yes	☐ No	☐ Neither
• Do you have "Foreign body sensation" after administration?	☐ Yes	☐ No	☐ Neither
• Do you have "Blurred vision" after administration?	☐ Yes	☐ No	☐ Neither
• Do you have "Conjunctival hyperemia" after administration?	☐ Yes	☐ No	☐ Neither
• How often do you forget administration per week?	☐ Never	☐ Within two times per week	☐ More than three times per week
• Comfortableness when you administered	☐ Comfortable	☐ Neither	☐ Uncomfortable

A questionnaire after changing eye drops after 12 weeks. Please cooperate.
Please check that the patient completes the questionnaire ☐

• Do you have "Stinging/burning" after administration?	☐ Yes	☐ No	☐ Neither
• Do you have "Foreign body sensation" after administration?	☐ Yes	☐ No	☐ Neither
• Do you have "Blurred vision" after administration?	☐ Yes	☐ No	☐ Neither
• Do you have "Conjunctival hyperemia" after administration?	☐ Yes	☐ No	☐ Neither
• How often do you forget administration per week?	☐ Never	☐ Within two times per week	☐ More than three times per week
• Comfortableness when you administered	☐ Comfortable	☐ Neither	☐ Uncomfortable
• Which do you prefer before or after changing therapy?	☐ Before	☐ Same	☐ After

Figure 1 Questionnaire.

administration was judged as never, once or twice per week, or more than three times per week. Comfortableness was judged by comfortable, neither comfortable nor uncomfortable, or uncomfortable. Patients who treated both eyes received the randomly chosen regimen in both eyes and the right eye was analyzed in this study.

Statistics

Statistical analyses were performed using JMP software (version 6.0.3; SAS Institute Inc, Cary, NC). Values are shown as mean ± standard deviation (SD). Values for patient characteristics were statistically analyzed by χ^2 test and Student's *t*-test. IOP differences between the groups were evaluated by Student's *t*-test and one-way analysis of variance (ANOVA) was used to analyze the differences between IOP at individual time points before and after treatment in both groups. Patients' distribution between regimes and settings were analyzed by the χ^2 test. For the values regarding SPK (AD score) and conjunctival hyperemia, a Mann–Whitney *U* test was used between the two groups and a Kruskal–Wallis test was used to compare the differences between scores at individual time points before and after treatment in both groups. All questions in the questionnaire were evaluated by the χ^2 test. *P* values less than 0.05 were considered statistically significant.

Results

Patients

Thirty-nine patients were enrolled in this study. Twenty out of 21 patients in Group A and 16 out of 18 patients in Group B followed the study to completion. One patient was lost at 12 weeks in Group A and two patients withdrew from Group B at 12 weeks because of hospitalization for heart disease (1 patient) and an orthopedic issue (1 patient).

Fifteen patients (n = 7 in Group A, n = 8 in Group B) from Tsukazaki Hospital, 11 patients from Baba Eye Clinic (n = 6 in Group A, n = 5 in Group B), and 10 patients from Hiroshima University Hospital (n = 7 in Group A, n = 3 in Group B) were enrolled ($P = 0.514$). Baseline demographic characteristics at 12 weeks of patients who completed the study are shown in Table 1. There were no statistically significant differences between the two groups in age, the proportion of males and females, visual acuity, degrees of visual field disturbance and lens (χ^2 test and Student's *t*-test).

Previous medications

Details of the various preparations of three antiglaucoma eye drops (prostaglandin $F_{2\alpha}$ analogues + beta-blockers + carbonic anhydrase inhibitors) are shown in Table 1.

Table 1 Patient characteristics and previous medications

Characteristic	Group A : N = 20 Regime A	Group B : N = 16 Regime B	*P* value
Age (yrs)	70.5 (12.1)	71.9 (12.8)	0.862[b]
Male/Female	9/11	10/6	0.296[a]
Mean Deviation (dB)	−10.8 (7.6)	−15.2 (9.8)	0.077[b]
Visual Acuity	0.14 (0.33)	0.22 (0.76)	0.664[b]
Cataract	Phakic 13/IOL 7	Phakic 13/IOL 3	0.279[a]
Combination (PG + β blocker + CAI)			
Lat + Tim + Bri	5	6	
Lat + TimG + Bri	5	4	
Lat + Car + Bri	2	2	
Lat + TimG + Dor	0	2	
Lat + Tim + Dor	0	2	
Bim + Tim + Bri	3	0	
Bim + Tim + Dor	1	0	
Taf + Tim + Bri	3	0	
Lat + Car + Dor	1	0	

Notes: Mean ± SD (standard deviation); [a]χ^2 test; [b]Student's *t*-test.
Abbreviations: IOL, intraocular lens; Group A, latanoprost–timolol fixed combination + brinzolamide (Regime A); Group B, dorzolamide 1%–timolol fixed combination + latanoprost (Regime B); PG, prostaglandin $F_{2\alpha}$ analogues; CAI, carbonic anhydrase inhibitors; Lat, latanoprost 0.005%; Tim, timolol maleate 0.5%; TimG, timolol maleate gel-forming ophthalmic solution 0.5%; Bri, brinzolamide 1.0%; Car, carteolol 2%; Dor, dorzolamide 1.0%; Bim, bimatoprost 0.03%; Taf, tafluprost 0.0015%.

IOP

IOPs in Group A were 14.1 ± 2.9 mmHg at baseline, 13.8 ± 2.6 mmHg at 4 weeks, and 14.1 ± 2.7 mmHg at 12 weeks. There was no significant difference between each of the time points (one-way ANOVA; $P = 0.923$). IOPs in Group B were 14.5 ± 2.9 mmHg at baseline, 14.3 ± 2.8 mmHg at 4 weeks and 14.2 ± 2.7 mmHg at 12 weeks. There was no significant difference between each of the time points (one-way ANOVA; $P = 0.951$). Between the groups, there is no significant difference at baseline ($P = 0.658$), at 4 weeks ($P = 0.715$), or at 12 weeks ($P = 0.538$) by Student's *t*-test (Figure 2). Power analysis of the test between the groups gave 0.05 (least significant number = 8664) at 4 weeks and 0.07 (least significant number = 802) at 12 weeks.

Superficial punctate keratopathy and conjunctival hyperemia

The level of SPK as assessed by using the AD classification score and measuring conjunctival hyperemia was shown in Table 2. There was no significant difference at each of the time points either within or between the groups (Kruskal–Wallis test and Mann–Whitney *U* test).

Hyperpigmentation of eyelid

At baseline, five patients in Group A and six patients in Group B showed hyperpigmentation of eyelid. At week 12, only one

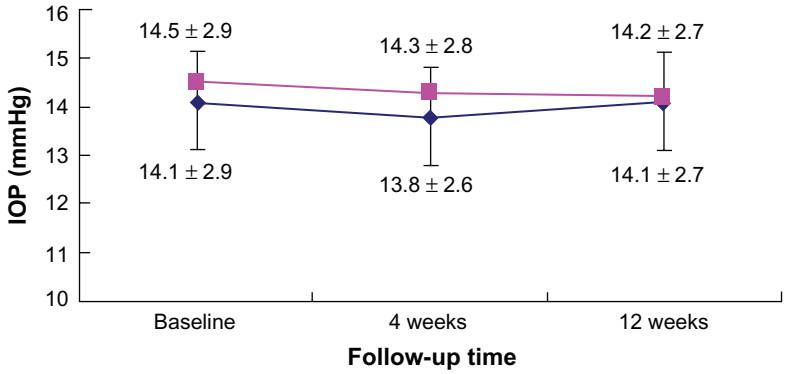

Figure 2 Mean IOP at baseline, 4, and 12 weeks.
Notes: There were no significant differences at any of the time points either within or between the groups. Diamonds indicate Group A: latanoprost–timolol fixed combination + brinzolamide (Regime A). Squares indicate Group B: dorzolamide 1%–timolol fixed combination + latanoprost (Regime B).

patient in Group A showed increasing hyperpigmentation (total of six patients). There were no remarkable changes in Group B.

Results of the questionnaire

A 78-year-old female patient in Group A was excluded from the question "frequency of forgetting administration" because the drugs were administered by her family because of physical disability.

In the questionnaire, there was no significant difference either within or between the groups in any of the responses at baseline and 12 weeks. However a slight increase (three patients in Group A and two patients in Group B; $P = 0.43$ and 0.48, respectively) was observed in responses to the question regarding experiences of "stinging/burning". On the other hand, a slight decrease was observed (three patients in Group B; $P = 0.43$) in the question regarding experiences of "blurred vision". No change was observed in the responses to the other questions (Table 3).

Table 2 Superficial punctate keratopathy and conjunctival hyperemia

	Group A	Group B	*P* value
SPK (A + D score)			
Baseline	0.80 (1.40)	0.38 (0.81)	0.262[b]
4 w	0.55 (1.00)	0.13 (0.50)	0.108[b]
12 w	0.45 (0.94)	0.13 (0.50)	0.195[b]
P value	0.605[a]	0.426[a]	
Hyperemia score			
Baseline	0.16 (0.35)	0.17 (0.39)	0.767[b]
4 w	0.16 (0.35)	0.17 (0.39)	0.767[b]
12 w	0.11 (0.32)	0.11 (0.36)	0.815[b]
P value	0.868[a]	0.863[a]	

Notes: [a]Kruskal–Wallis test; [b]Mann–Whitney *U* test.
Abbreviations: Group A, latanoprost–timolol fixed combination + brinzolamide (Regime A); Group B, dorzolamide 1%–timolol fixed combination + latanoprost (Regime B).

Patient preference in the questionnaire

At 12 weeks, two patients (10%) preferred combination therapy of three antiglaucoma eye drops, eight patients (40%) preferred the regimes equally, and ten patients (50%) preferred combination therapy using fixed-combination eye drop in Group A.

In Group B, no patients preferred combination therapy of three antiglaucoma eye drops. Six patients (37%) preferred the regimes equally and ten patients (63%) preferred combination therapy using fixed-combination eye drops. There was no significant difference between the preferences of the groups ($P = 0.394$).

Discussion

In glaucoma patients, achieving a healthy IOP by monotherapy is the most desirable outcome, however, many patients need second-line antiglaucoma eye drops in order to combine different mechanisms of action. Second-line therapies are not uniform and various kinds of antiglaucoma eye drops are prescribed in the United States.[21] Third-line therapy, however, almost always consists of prostaglandin $F_{2\alpha}$ analogues with beta-blockers and carbonic anhydrase inhibitors. Nasser et al reported that 75% of ophthalmologists prescribed the combination of prostaglandin $F_{2\alpha}$ analogues with dorzolamide 2%–timolol fixed combination (prostaglandin $F_{2\alpha}$ analogues–timolol fixed combination is not yet available in the United States).[21] Meanwhile, various fixed-combination therapies have become available in European and Asian countries. Despite this, until this study no group had investigated or discussed whether third-line therapies including fixed combination were superior to other regimes. To make therapies which combine two different mechanisms-of-action drugs from three antiglaucoma eye drops is important for patients' adherence.[5–9]

Table 3 Results of the questionnaire

Question	Group A			Group B		
	Baseline	12 w	*P* value	Baseline	12 w	*P* value
Stinging/burning						
Yes	5	8	0.43	4	6	0.48
No	14	10		11	10	
Neither	1	2		1	0	
Foreign body sensation						
Yes	1	1	0.60	4	2	0.37
No	19	18		12	14	
Neither	0	1		0	0	
Blurred vision						
Yes	8	8	1.00	5	2	0.43
No	11	11		9	11	
Neither	1	1		2	3	
Conjunctival hyperemia						
Yes	3	0	0.18	1	0	0.60
No	16	18		14	15	
Neither	1	2		1	1	
Frequency of forgetting administration						
None	16	17	0.83	14	14	1.00
Within two times per week	2	1		2	2	
More than three times per week	1	1		0	0	
Comfortableness						
Comfortable	5	5	0.60	3	3	1.00
Neither	15	14		13	13	
Uncomfortable	0	1		0	0	

Notes: A 78-year-old female in Group A was excluded from the question "frequency of forgetting administration" because her drugs were administered by her family.
Abbreviations: Group A, latanoprost–timolol fixed combination + brinzolamide (Regime A); Group B, dorzolamide 1%–timolol fixed combination + latanoprost (Regime B).

In our study, we evaluated two groups treated with regimes that both included latanoprost and achieved similar effects on IOP. Furthermore adverse effects were similar in both groups; therefore we recommend that either combination is appropriate.

As for adverse effects, in self-reported "stinging/burning", a slight increase was observed in both groups, however no significant difference was observed between them at 12 weeks ($P = 0.394$). In line with this, Konstas et al reported in their crossover study that latanoprost and dorzolamide 2%–timolol fixed-combination treatment (18 of 31 patients) reported more "burning/stinging" compared with a single dorzolamide 2%–timolol fixed combination (7 of 31 patients) or latanoprost–timolol fixed combination (4 of 31 patients) ($P < 0.001$).[22] Shin et al also reported in 2004 that more patients with dorzolamide 2%–timolol fixed combination reported "burning/stinging" compared with latanoprost–timolol fixed combination (11.7% vs 4.0%, respectively; $P = 0.034$).[23] The mechanism of increasing sensations of "burning/stinging" is probably because of the low pH. Latanoprost–timolol fixed combination has a pH of 5.8–6.2 and dorzolamide 2%/timolol fixed combination has a pH of 5.5–5.8. They have a lower pH compared to latanoprost (pH 6.5–6.9), timolol (pH 6.5–7.5), brinzolamide (pH 7.5), and bimatoprost (pH 6.9–7.5). In addition to these drugs, clinicians also should take care to factor the sensations of other fixed-combination drugs. For example, bimatoprost–timolol fixed combination has a pH of 7.2–7.4, a brinzolamide–timolol fixed combination has a pH of 6.5–7.5 and brimonidine–timolol fixed combination has a pH of 6.5–7.3.

A limitation of this study is that dorzolamide is used at 1% concentrations in Japan, however 2% solutions are used in European countries and the Americas. So our data may not directly compare with previous reports or future studies coming from those areas. However, Kitazawa et al reported in their dose-response study that the percentage reduction from baseline was greater after treatment with 0.5%, 1%, or 2% dorzolamide than after treatment with 0.2% dorzolamide.[24] They concluded that IOP-lowering activity dose-response curve of dorzolamide may reach a plateau at concentrations equal to or above 0.5%. Furthermore, adverse effects of smarting and mild hyperemia were the most frequent following 2% dorzolamide (74.1% and 18.5%, respectively). Lippa et al also reported in the dose-response study that there is no

significant difference in IOP-lowering effects between 0.75, 1.45, and 2% dorzolamide.[25] Therefore, we consider that our results may be comparable with previous reports, and that 1% dorzolamide may be superior to 2% dorzolamide in decreasing glaucoma medication nonadherence.

Our study reported short-term results in a small group of patients and was an open trial. Further long-term, large-scale, double-blinded, crossover studies are needed to compare the difference between the effects of Regime A and Regime B.

Conclusion

The efficiency and safety were maintained in both groups after switching therapy. Patients generally preferred using fixed-combination therapy compared with a combination of three antiglaucoma eye drops. Decreasing the numbers of eye drops using fixed-combination therapy may be useful for patients' adherence.

Disclosure

The authors have no financial interest in this study, and report no other conflicts of interest in this work.

References

1. Collaborative Normal-Tension Glaucoma Study Group. The effectiveness of intraocular pressure reduction in the treatment of normal-tension glaucoma. *Am J Ophthalmol*. 1998;126:498–505.
2. Stewart WC, Chorak RP, Hunt HH, Sethuraman G. Factors associated with visual loss in patients with advanced glaucomatous changes in the optic nerve head. *Am J Ophthalmol*. 1993;116:176–181.
3. Kass MA, Heuer DK, Higginbotham EJ, et al. The Ocular Hypertension Treatment Study: a randomized trial determines that topical ocular hypotensive medication delays or prevents the onset of primary open-angle glaucoma. *Arch Ophthalmol*. 2002;120:701–713.
4. Chauhan BC, Mikelberg FS, Balazi AG, et al. Canadian Glaucoma Study: risk factors for the progression of open-angle glaucoma. *Arch Ophthalmol*. 2008;126:1030–1036.
5. Pappa C, Hypthantis T, Pappa S, et al. Psychiatric manifestation and personality traits associated with compliance with glaucoma treatment. *J Psychosom Res*. 2006;61:609–617.
6. Mackean JM, Elkington AR. Compliance with treatment of patients with chronic open-angle Glaucoma. *Br J Ophthalmol*.1983;67:46–49.
7. Olthoff CMG, Schouten JSAG, van de Borne BW, et al. Noncompliance with ocular hypotensive treatment in patients with glaucoma or ocular hypertension. *Ophthalmology*. 2005;112:953–961.
8. Patel SC, Spaeth GL. Compliance in patients prescribed eyedrops for glaucoma. *Ophthalmic Surg*. 1995;26:233–236.
9. Djafari F, Lesk MR, Harasymowycz PL, et al. Determination of adherence to glaucoma medical therapy in a long-term patient population. *J Glaucoma*. 2009;18:238–243.
10. Chawla A, McGalliard J, Batterbury M. Use of eyedrops in glaucoma: how can we help to reduce non-compliance? *Acta Ophthalmol Scand*. 2007;85:464.
11. Servat JJ, Bemardino CR. Effects of common topical antiglaucoma medications on the ocular surface, eyelids and periorbital tissue. *Drugs Aging*. 2011;28:267–282.
12. Sleath B, Robin A, Covert D, et al. Patient-reported behavior and problems using glaucoma medications. *Ophthalmology*. 2006;113:431–436.
13. MacKean JM, Elkington AR. Compliance with treatment of patients with chronic open-angle glaucoma. *Br J Ophthalmol*. 1983;67:46–49.
14. Granstrom PA. Glaucoma patients not compliant with their drug therapy: clinical and behavioural aspects. *Br J Ophthalmol*. 1982;66:464–474.
15. Barnebey HS, Orengo-Nania S, Flowers BE, et al. Safety and efficiency of travoprost 0.004%/timolol 0.5% fixed combination ophthalmic solution. *Am J Ophthalmol*. 2005;140:1–7.
16. Higginbothanm EJ, Feldman R, Stiles M, et al. Latanoprost and timolol combination therapy vs monotherapy: one-year randomized trial. *Arch Ophthalmol*. 2002;120:915–922.
17. Diestelhorst M, Larsson LI. A 12-week, randomized double-masked, multicenter study of the fixed combination of latanoprost and timolol in the evening versus the individual components. *Ophthalmology*. 2006;113:70–76.
18. Storhmaier K, Snyder E, DuBiner H, et al. The efficiency and safety of the dorzalamide-timolol combination versus the concomitant administration of its components. Dorzolamide-Timolol Study Group. *Ophthalmology*. 1998;105:1936–1944.
19. Hommer A; Ganfort Investigators Group I. A double-masked, randomized, parallel comparison of a fixed combination of bimatoprost 0.03%/timolol 0.5% with non-fixed combination use in patients with glaucoma or ocular hypertension. *Eur J Ophthalmol*. 2007;17:53–62.
20. Miyata K, Amano S, Sawa M, et al. A novel grading method for superficial punctate keratopathy magnitude and its correlation with corneal epithelial permeability. *Arch Ophthalmol*. 2003;121:1537–1539.
21. Nasser QJ, Stewart WC. Glaucoma treatment and diagnostic trends. *Rev Ophthalmol*. 2006;13:87–93.
22. Konstas AG, Mikropoulos D, Dimopoulos AT, et al. Second-line therapy with dorzolamide/timolol or latanoprost/timolol fixed combination versus adding dorzolamide/timolol fixed combination to latanoprost monotherapy. *Br J Ophthalmol*. 2008;92:1498–1502.
23. Shin DH, Feldman RM, Sheu WP; Fixed Combination Latanoprost/Timolol Study Group. Efficacy and safety of the fixed combinations latanoprost/timolol versus dorzolamide/timolol in patients with elevated intraocular pressure. *Ophthalmology*. 2004;111:276–282.
24. Kitazawa Y, Azuma I, Iwata K, et al. Dorzaloamide, a topical carbonic anhydrade inhibitor: a two-week dose-response study in patients with glaucoma or ocular hypertension. *J Glaucoma*. 1994;3:275–279.
25. Lippa EA, Carlson LE, Ehinger B, et al. Dose response and duration of action of dorzolamide, a topical carbonic anhydrase inhibitor. *Arch Ophthalmol*. 1992;110:495–499.