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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

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PURPOSE. *To compare the safety and efficacy of the fixed combination product with non-fixed combination use of the same active ingredients in separate bottles (bimatoprost once-daily [qd], and timolol twice-daily [bid]). A bimatoprost 0.03% qd treatment arm was used for validation of the study.*

METHODS. *This was a double-masked, randomized, parallel study in 445 patients with open-angle glaucoma or ocular hypertension. They were randomized in a ratio of 2:2:1 to receive bilateral treatment with the fixed combination, non-fixed combination treatment, or bimatoprost alone.*

RESULTS. *Comparing the fixed combination and non-fixed combination, the non-inferiority margin of 1.5 mmHg was met at all three timepoints for mean intraocular pressure (IOP), and a margin of 1.0 mmHg for mean diurnal IOP. The incidence of conjunctival hyperemia was statistically significantly lower (p=0.014) in the fixed combination group (8.5%, 15/176) compared with the bimatoprost group (18.9%, 17/90) and the non-fixed combination group (12.5%, 22/176).*

CONCLUSIONS. *The fixed combination of bimatoprost 0.03%/timolol 0.5% administered once daily was comparable in ocular hypotensive efficacy to the non-fixed combination. The lower propensity of the fixed combination to elicit conjunctival hyperemia suggests a superior comparative benefit/risk assessment of the fixed combination in the treatment of elevated IOP. (Eur J Ophthalmol 2007; 17: 53-62)*

KEY WORDS. *Bimatoprost, Timolol, Glaucoma, Intraocular pressure*

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INTRODUCTION

Elevated intraocular pressure (IOP) is a major risk factor in the progression of glaucomatous optic neuropathy. Studies show that there is a strong relationship between poor IOP control and glaucomatous visual field loss (1, 2). For patients with ocular hypertension (OHT), the risk of converting a normal visual field to a glaucomatous one increases with higher IOP (3).

Approximately 50% of patients eventually require multidrug therapy in order to control IOP (4, 5). However, use of two separate products is cumbersome, and requires patients to wait several minutes between administrations of the individual products. A fixed com-

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bination of two active ingredients in a single formulation could provide the benefit of combination therapy more conveniently, may be a regimen with which the patient can more readily comply (6), and could further benefit patients with a reduction in exposure to potentially harmful preservatives (7).

The two active agents selected for the fixed combination ophthalmic solution formulation under investigation in this study were bimatoprost 0.03% and timolol ophthalmic solution 0.5%. Bimatoprost, a synthetic prostamide analog, lowers IOP through enhancement of uveoscleral (nontraditional) and trabecular (traditional) outflow (8). Timolol lowers IOP through reduction of aqueous humor production (inflow) (9, 10). The combined use of these two agents was found effective in a double-masked, placebo-controlled study (11).

The concentration selected for bimatoprost, 0.03%, was the marketed strength and dosing frequency (12, 13). The dosage selected for timolol, 0.5%, bid, was the maximal marketed concentration and dosing regimen, based upon the premise the patients considered for dual therapy were likely to have been previously treated with maximal doses of monotherapy (14). The pharmaceutical properties, chemical stability, and preservative effectiveness of the combination product, critical factors in preparing a fixed combination ophthalmic product (15), were developed and assured by the manufacturer. There were no clinically relevant or unexpected systemic or ophthalmologic abnormalities detected in phase 1 study of bimatoprost 0.03%/timolol 0.5% in healthy normal volunteers (data on file, Allergan, Inc., 2006).

The present study was designed to compare the safety and efficacy of the fixed combination product with non-fixed combination use of the same active ingredients in separate bottles (bimatoprost qd and timolol bid). A bimatoprost 0.03% qd treatment arm was used for validation of the study.

METHODS

Design

This study was conducted at 35 academic centers and private practices in the United States, Canada, Austria, and Germany. In this double-masked, randomized, parallel study, patients were randomized in a ratio of 2:2:1 to receive bilateral treatment with the fixed combination, non-fixed combination treatment, or bimatoprost alone. Randomization was stratified by the average of IOP between the two eyes at hour 0 of day 0 (~08:00 hours at baseline) as ≤26 mmHg versus >26 mmHg. A validated remote automated randomization system was used to assign the appropriate treatment group which had been generated by PROC PLAN (SAS® version 8.2, Cary, NC). Masking was maintained by the use of bottles containing vehicle as appropriate (Tab. I).

Patients

Included in the study were adult patients with bilateral ocular hypertension or glaucomatous disease (chronic open-angle glaucoma, chronic angle-closure glaucoma with patent iridotomy/iridectomy, pseudoexfoliative glaucoma, or pigmentary glaucoma). Patients were required to be treatment-naïve to topical or systemic ocular hypotensive medications. Patients

TABLE I - TREATMENT GROUPS AND MEDICATIONS DISPENSED TO MAINTAIN DOUBLE-MASKING

Treatment group	Fixed combination	Non-fixed combination	Bimatoprost
Morning (08:00) bottle	Fixed combination	Timolol	Vehicle
Evening (20:00) bottle			
Bottle 1 of 2	Vehicle	Bimatoprost	Bimatoprost
Bottle 2 of 2	Vehicle	Timolol	Vehicle

Timolol was preserved with 0.01% benzalkonium chloride. All other clinical trial materials were preserved with 0.005% benzalkonium chloride. Morning bottles had a sun on the label, and evening bottles had a moon on the label.

Fixed combination = Bimatoprost 0.03% and timolol 0.5%; Bimatoprost = 0.03% Bimatoprost (Lumigan®, Allergan, Inc., Irvine, CA); Timolol = 0.5% timolol maleate ophthalmic solution; Vehicle = Bimatoprost vehicle

were required to have visual acuity of 20/100 or better, in each eye, and IOP of 24 to 34 mmHg in each eye with an interocular difference of 5 mmHg or less at hour 0. Exclusion criteria were similar to previous studies (12, 16) (e.g., individuals with contraindications or known hypersensitivity to any components of the test medications, uncontrolled systemic or ocular disease other than glaucoma or ocular hypertension, functionally significant visual field loss or evidence of progressive visual field loss within the last year, and recent ophthalmic procedures). Women of childbearing potential were required to have a negative urine pregnancy test at entry, and to use reliable contraception during the study. The study was approved by governing institutional review boards, and all patients provided written informed consent.

Visits and examinations

Eligible individuals underwent a pre-study examination that included consent, history, measurement of heart rate and blood pressure, and a complete eye examination. Goldmann applanation tonometry was performed using a repeated, two-person method to mask the value. Pachymetry was performed by ultrasound up to 6 months pre-study, although most had this performed at the pre-study examination. An automated threshold perimetric test (Humphrey Field Analyzer, program 24-2 preferred, Zeiss Meditec, Dublin, CA) was required within the 6 months prior to study entry. Individuals were scheduled to return for a baseline (day 0) visit 2 to 28 days later. At the baseline visit (to occur between 07:00 and 09:00 hours), IOP was measured. Individuals meeting the IOP entry criteria were randomized at hour 0. IOP was measured at hour 2 (~10:00 hours) and hour 8 (~16:00 hours). These study patients were to begin dosing in the evening of the day of the day 0 visit (between 19:00 and 21:00). Patients were instructed to instill their morning dose between 07:00 and 09:00 hours, and their evening doses between 19:00 and 21:00 hours, except on the morning of the week 3 visit. For the evening instillation, the bimatoprost drop was to be instilled first, followed 5 minutes later by the timolol or vehicle drop. Patients returned 3 weeks after randomization at the same time of day for a repeat examination at hour 0, plus measurement of IOP at hours 2 and 8. At this visit, the morning dose of study medication was to be instilled immediately following the hour 0 examination in the investigator's office.

Statistics

This study was designed to assure that the fixed combination product was not inferior in efficacy to each component administered adjunctively. The primary efficacy measure was mean IOP. The assessment of non-inferiority was based upon the between group difference (fixed combination minus non fixed combination) using the upper limit of the 95% confidence interval (CI). A priori, both the non-inferiority margins of 1.0 and 1.5 mmHg were tested using a two-way analysis of variance (ANOVA) model including factors for treatment and investigator.

A superiority hypothesis was tested using a two-way ANOVA model including factors for treatment and investigator. A two-sided test was performed in which $p \leq 0.05$ was considered statistically significant. A mean diurnal IOP for each visit was calculated as the average IOP at hours 0, 2, and 8. Missing values were imputed using the method of last observation carried forward (LOCF) from the previous visit.

In a priori power calculations, a standard deviation of 4.2 mmHg was assumed, and a sample size of 415 patients was calculated to detect the stated clinically significant difference (a=0.05, two-sided; nQuery Advisor, Version 5.0, ©1995–2002, Janet D. Elashoff, Statsol, Saugus, MA).

In general, categorical variables were analyzed using Fisher exact test, Pearson chi-square test, or Cochran-Mantel-Haenszel methods. Continuous variables were analyzed using ANOVA models. All analyses were performed using SAS (SAS Institute, Cary, NC, version 8.2).

RESULTS

Pre-study characteristics

Enrolled into the study were 445 patients (178 in fixed combination, 177 in non-fixed combination, and 90 bimatoprost treatment groups). The total population had a mean age of 60 years, was 55% female, and 56% had light irides. Race as stated by the subjects was 80% white, 14% black, and 5% Hispanic

(Tab. II). The proportion of patients diagnosed with ocular hypertension was 68.1% (303/445). Mean cup-disc ratio was 0.43±0.21, and mean corneal thickness was 571±41 µm (range: 456–716 µm). Overall, 84.3% (375/445) of patients received one or more concomitant medications during the study.

Disposition

The disposition of the study population is shown in Table III. Overall, 96.6% (430/445) of patients successfully completed the study. There were no patients discontinued for inadequate efficacy. The proportion of discontinued patients was similar among the three treatment groups: 3.4% (6/178) of patients in the fixed-combination group, 4.0% (7/177) of patients in the non-fixed combination group, and 2.2% (2/90) of patients in the bimatoprost group. The most frequently reported reason for discontinuation of the study was adverse events in 1.6% (7/445)– 3 (1.7%) in the fixed combination group (allergic conjunctivitis, conjunctival hyperemia, and eye pain and worsened visual acuity), 3 (1.7%) in the non-fixed combination group (stinging, burning, and asthma and rash), and 1 (1.1%) in the bimatoprost group (allergic conjunctivitis).

Efficacy

Mean IOP at each timepoint is shown in Table IV. At baseline, mean values of IOP at each hour ranged from 23.7 to 26.4 mmHg with no statistically significant difference in mean values of IOP for any of the three pairwise comparisons (p=0.300 to 0.973). At week 3, the upper limit of the 95% CI for the between group difference in mean IOP (fixed combination – non-fixed combination) was 1.28 mmHg at hour 0, 1.29 mmHg at hour 2, and 0.51 mmHg at hour 8. The criteria for non-inferiority at the 1.5 mmHg level was met at all three timepoints at week 3, and for the more rigorous 1.0 mmHg level at one timepoint. In addition, the difference in mean IOP between the fixed combination and non-fixed combination groups was 0.60, 0.61, and –0.15 mmHg. Mean IOP values at week 3 were statistically significantly lower in each of the fixed combination and non-fixed combination groups compared with the bimatoprost group at hour 0 and hour 8 (p≤0.007),

TABLE II - DEMOGRAPHICS (INTENT-TO-TREAT)

Status	Fixed combination	Non-fixed combination	Bimatoprost	Total
N	17	177	90	445
Age, yr				
Mean	61.2	59.6	57.5	59.8
SD	11.95	13.10	12.15	12.51
Median	62.0	61.0	56.5	61.0
Min	24	21	18	18
Max	87	84	80	87
>65 (%)	64 (36.0)	65 (36.7)	25 (27.8)	154 (34.6)
Sex, n (%)				
Female	88 (49.4)	109 (61.6)	49 (54.4)	246 (55.3)
Male	90 (50.6)	68 (38.4)	41 (45.6)	199 (44.7)
Race, n (%)*				
White	141 (79.2)	140 (79.1)	74 (82.2)	355 (79.8)
Black	26 (14.6)	26 (14.7)	10 (11.1)	62 (13.9)
Hispanic	9 (5.1)	8 (4.5)	6 (6.7)	23 (5.2)
Other	2 (1.1)	1 (0.6)	0 (0.0)	3 (0.7)
Asian	0 (0.0)	2 (1.1)	0 (0.0)	2 (0.4)
Iris color, n (%)†				
Light	102 (57.3)	94 (53.1)	52 (57.8)	248 (55.7)
Dark	76 (42.7)	83 (46.9)	38 (42.2)	197 (44.3)

*Other includes White/Hispanic, Filipino, and Indian. p value for race calculated as black vs non-black.

†Light includes blue, green, gray, blue-gray, green-brown, and hazel. Dark iris color includes brown

with the non-fixed combination group also being statistically significantly lower than the bimatoprost group at hour 2 (p=0.008).

Mean diurnal IOP is shown in Table V. Baseline mean diurnal IOP was similar in all treatment groups, ranging from 24.9 to 25.2 mmHg, with no statistically significant difference for any of the three pairwise comparisons (p=0.291 to 0.791). At week 3, the mean diurnal IOP was 16.1, 15.6, and 17.1 mmHg in the fixed combination, non-fixed combination, and bimatoprost groups, respectively. The between group difference in mean diurnal IOP (fixed combination – non-fixed

TABLE III - PATIENT DISPOSITION

Status	Fixed combination	Non-fixed combination	Bimatoprost	Total
Entered	178	177	90	445
Completed, n (%)	172 (96.6)	170 (96.0)	88 (97.8)	430 (96.6)
Discontinued, n (%)	6 (3.4)	7 (4.0)	2 (2.2)	15 (3.4)
Inadequate efficacy	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Adverse event	3 (1.7)	3 (1.7)	1 (1.1)	7 (1.6)
Administrative reason	1 (0.6)	3 (1.7)	0 (0.0)	4 (0.9)
Lost to follow-up	0 (0)	1 (0.6)	0 (0.0)	1 (0.2)
Personal reasons	1 (0.6)	2 (1.1)	0 (0.0)	3 (0.7)
Protocol violation	1 (0.6)	1 (0.6)	1 (1.1)	3 (0.7)
Other (patient did not use medication)	1 (0.6)	0 (0.0)	0 (0.0)	1 (0.2)

TABLE IV - MEAN INTRAOCULAR PRESSURE (INTENT-TO-TREAT, LAST OBSERVATION CARRIED FORWARD) (mmHg)

	Timepoint	Fixed combination (n=178)	Non-fixed combination (n=177)	Bimatoprost (n=90)	Fixed combination vs non-fixed combination, p value, difference (95% CI)	Fixed combination vs bimatoprost, p value, difference (95% CI)	Non-fixed combination vs bimatoprost, p value, difference (95% CI)
	Hour 0	26.2	26.4	26.2	0.410 -0.18 (-0.62, 0.25)	0.923 -0.03 (-0.56, 0.50)	0.562 0.16 (-0.38, 0.69)
Baseline	Hour 2	24.9	25.2	25.1	0.300 -0.29 (-0.83, 0.26)	0.530 -0.21 (-0.86, 0.45)	0.821 0.08 (-0.58, 0.73)
	Hour 8	23.7	23.9	23.8	0.400 -0.26 (-0.85, 0.34)	0.466 -0.27 (-0.99, 0.45)	0.973 -0.01 (-0.74, 0.71)
	Hour 0	16.5	15.8	17.7	0.084 0.60 (-0.08, 1.28)	0.007* -1.15 (-1.97, -0.32)	<0.001* -1.75 (-2.58, -0.92)
Week 3	Hour 2	16.2	15.5	16.8	0.077 0.61 (-0.07, 1.29)	0.216 -0.52 (-1.34, 0.30)	0.008* -1.13 (-1.96, -0.30)
	Hour 8	15.4	15.5	16.8	0.663 -0.15 (-0.80, 0.51)	0.001* -1.32 (-2.12, -0.52)	0.004* -1.17 (-1.97, -0.38)

p-value and 95% confidence interval (CI) were from pair-wise contrasts from a two-way analysis of variance model at each timepoint with factors for treatment and investigator.

* Significant between-group difference, p ≤ 0.050.

N= Number of randomized patients

combination) was 0.38 mmHg, with the upper limit of the 95% CI being 0.98 mmHg, falling within the 1.0 mmHg level. The mean diurnal IOP at week 3 was statistically significantly lower in the fixed combination and non-fixed combination groups each compared with the bimatoprost group (p≤0.009).

Safety

Of the 445 patients enrolled in the study, 442 patients were confirmed to have received at least one dose of study medication and were included in the safety population (n=176, 176, and 90 in the fixed com-

TABLE V - MEAN DIURNAL INTRAOCULAR PRESSURE (IOP) (INTENT-TO-TREAT, LAST OBSERVATION CARRIED FORWARD) (mmHg)

Timepoint	Fixed combination (n=178)	Non-fixed combination (n=177)	Bimatoprost (n=90)	Fixed combination vs non-fixed combination, p value, difference (95% CI)	Fixed combination vs bimatoprost, p value, difference (95% CI)	Non-fixed combination vs bimatoprost, p value, difference (95% CI)
Baseline	24.9	25.2	25.0	0.291 -0.24 (-0.69, 0.21)	0.545 -0.17 (-0.71, 0.37)	0.791 0.07 (-0.47, 0.62)
Week 3	16.1	15.6	17.1	0.222 0.38 (-0.23, 0.98)	0.009* -0.98 (-1.71, -0.24)	<0.001* -1.35 (-2.09, -0.62)

Mean diurnal IOP is the mean IOP at hours 0, 2, and 8 averaged for the baseline visit and for the week 3 visit. p value and 95% confidence interval (CI) were from pairwise contrasts from a two-way analysis of variance model at each visit with factors for treatment and investigator.
*Significant between-group difference, p≤0.050.
N = number of randomized patients

TABLE VI - NUMBER (%) OF PATIENTS WITH TREATMENT-RELATED ADVERSE EVENTS: MOST FREQUENTLY REPORTED

Adverse event (preferred term)	Body system	Fixed combination (n=176)	Non-fixed combination (n=176)	Bimatoprost (n=90)	p value
Overall		62 (35.2%)	74 (42.0%)	34 (37.8%)	0.417
Conjunctival hyperemia	Special senses	34 (19.3%)	45 (25.6%)	25 (27.8%)	0.218
Burning sensation in eye	Special senses	12 (6.8%)	25 (14.2%)	5 (5.6%)	0.022*
Stinging sensation eye	Special senses	6 (3.4%)	8 (4.5%)	1 (1.1%)	0.343
Foreign body sensation	Special senses	6 (3.4%)	3 (1.7%)	2 (2.2%)	0.632†
Eye pruritus	Special senses	5 (2.8%)	6 (3.4%)	3 (3.3%)	0.950
Visual disturbance	Special senses	4 (2.3%)	5 (2.8%)	0 (0.0%)	0.311†
Eye pain	Special senses	4 (2.3%)	2 (1.1%)	0 (0.0%)	0.330†
Headache	Body as a whole	3 (1.7%)	0 (0.0%)	0 (0.0%)	0.232†
Dizziness	Nervous system	2 (1.1%)	0 (0.0%)	1 (1.1%)	0.426†
Eyelid edema	Special senses	2 (1.1%)	0 (0.0%)	0 (0.0%)	0.357†

Presented are events with a frequency of 1% or greater in the fixed combination group.
p value: Pearson chi-square test was performed to evaluate the equality of proportions among treatment groups, except where the expected cell size was less than 5 in more than 25% of the cells, in which case a Fisher exact test was used†.
*Significant among-group difference, p ≤0.050

bination, non-fixed combination, and bimatoprost treatments, respectively). There was no statistically significant difference in the overall incidence of adverse events among treatment groups (p=0.380) or in the incidence of adverse events in any individual body system (p=0.097 to >0.999). One or more adverse events were reported for 40.3% (71/176), 46.6% (82/176), and 47.8% (43/90) of patients in the fixed combination, non-fixed combination, and bimatoprost treatments, respectively, irrespective of causality. Most of these adverse events were ocular in nature–37.5% (66/176), 43.2% (76/176), and 41.1% (37/90) of patients in fixed combination, non-fixed combination, and bimatoprost groups, respectively–and mild to moderate in severity.

The most frequently reported treatment-related adverse event in the study was conjunctival hyperemia, reported in 19.3% (34/176) of patients in the fixed combination group, 25.6% (45/176) of patients in the non-fixed combination group, and 27.8% (25/90) of patients in the bimatoprost group (Tab. VI). The incidence of this event was the lowest in the fixed combination group among treatment groups, although the among-group difference was not statistically significant (p=0.218). The incidence of burning sensation in eye was statistically significantly higher in the non-fixed combination group (14.2%, 25/176) than in fixed combination (6.8%, 12/176, p=0.024) and bimatoprost groups (5.6%, 5/90, p=0.035), whereas there was no statistically significant difference for this adverse event between the fixed combination and bimatoprost groups (p=0.690). No serious adverse events were reported.

Overall, 12.5% (22/176) of patients in the fixed combination group, 17.6% (31/176) of patients in the non-fixed combination group, and 23.3% (21/90) of patients in the bimatoprost group had one or more biomicroscopic and ophthalmic findings that increased by at least one severity grade from baseline (p=0.075). Of these findings, there was a statistically significant difference for the incidence of conjunctival hyperemia (increased by at least one severity grade) identified in the biomicroscopic examination among treatment groups (p=0.050). The incidence of conjunctival hyperemia was statistically significantly lower (p=0.014) in the fixed combination group (8.5%, 15/176) compared with the bimatoprost group (18.9%, 17/90). The incidence of conjunctival hyperemia in the fixed combination group was also lower than with the non-fixed combination group (12.5%, 22/176), although the difference was not statistically significant. There were no notable changes in mean heart rate or blood pressure.

DISCUSSION

A growing number of published reports of large, controlled trials has demonstrated a relationship between high IOP and the risk of visual field deterioration in patients with glaucoma, or the conversion of OHT to glaucoma (1-3). Thus, there is a growing trend towards more aggressive lowering of IOP in patients with elevated IOP. That trend may involve the use of more than one topical ocular hypotensive agent.

We investigated the efficacy and safety of a fixed combination of bimatoprost and timolol. Both of the medications are effective ocular hypotensive agents as monotherapy, and their different mechanisms of action on aqueous humor dynamics makes them good prospects for combined use. The present study was designed as a non-inferiority study, with mean IOP as the primary efficacy measure, and non-inferiority margins of 1.0 and 1.5 mmHg selected. The non-inferiority margin of 1.5 mmHg was met at all three timepoints. The fixed combination treatment provided consistent IOP control, similar to that observed in the non-fixed combination treatment group.

These results are particularly noteworthy since the total daily dose of timolol in the non-fixed combination group was twice that received by patients randomized to fixed combination treatment. Also, the combination was placed at a disadvantage when compared with non-fixed combination therapy in that drugs were administered in the morning after the hour 0 IOP reading. At this timepoint, the combination was at its trough effect (24 hours after instillation), but bimatoprost in the non-fixed combination group, administered 12 hours earlier, was at its peak effect. Similarly, at the hour 2 IOP reading, non-fixed combination treatment was still favored, with bimatoprost still near its peak effect, but only timolol near peak effect for the fixed combination. The fixed combination also showed some superiority over the bimatoprost treatment group.

This finding of non-inferiority of the fixed combination of bimatoprost/timolol to the non-fixed combination (involving twice-daily timolol) is, to our

knowledge, a unique finding amongst prostaglandin analog/β–adrenoceptor antagonist combinations. It was not seen for a fixed combination of travoprost and timolol (dosed in the morning) (17), nor for a fixed combination of latanoprost and timolol (dosed in the morning) (18). Only when dosed in the evening was a fixed combination of latanoprost and timolol non-inferior to the non-fixed combination (19).

The decrease in IOP observed for bimatoprost treatment in this population, which had not previously received IOP lowering therapy, from 24 to 26 mmHg at baseline to 17 to 18 mmHg at week 3, was in keeping with values seen in previous studies of bimatoprost (12, 13, 20-24). Thus, the present study was validated in that the positive control showed ocular hypotensive efficacy similar to that previously reported. While not an objective of this study, a comparison between the fixed combination and bimatoprost alone was made. The magnitude of this difference was approximately 1 mmHg for mean diurnal IOP. However, the variance on this measure suggests that many patients experienced a greater difference. As well, in a report of two large studies, the fixed combination decreased mean diurnal IOP by more than 20% in 81.8% (436/533) of patients, relative to 72.1% (191/265) of patients in the bimatoprost group (p=0.001) (Brandt et al, manuscript in preparation), suggesting that there is a clinically relevant ocular hypotensive benefit of the fixed combination.

The fixed combination product was safe and well tolerated when administered in the current study, once daily for 3 weeks, and had fewer overall adverse events compared with the other groups. At a minimum, this is supportive that combining bimatoprost and timolol in one bottle has no worse safety potential than the two active ingredients administered separately, and may even have a lower potential for hyperemia. The comfort of the fixed combination was not of concern, as the incidence of burning sensation in the eye was actually lower in the fixed combination group (6.8%, 12/176) than in the non-fixed combination group (14.2%, 25/176; p=0.024). Of interest was the lower incidence of conjunctival hyperemia in the fixed combination group (19.3%, 34/176) than in the non-fixed combination (25.6%, 45/176) and the bimatoprost (31.1%, 28/90) groups. Similar overall conclusions could be drawn from the biomicroscopy examination findings. The reason for the decreased incidence of conjunctival hyperemia seen in the combination group is still unclear. It may be that the immediate co-application of timolol, a β-adrenoceptor antagonist, may reduce the development of hyperemia by reducing the vasodilatory effects of endogenous catecholamines at β_2-adrenoceptors in the conjunctiva (25).

The study population was similar to populations in other pharmacologic studies of ocular hypotensive medications, with the exception that the mean age was 60 years, approximately 5 years younger than some other study populations (17-19). However, it is unlikely that their response to these medications would be different from that of a slightly older population.

In summary, the present study demonstrated that the fixed combination of bimatoprost 0.03%/timolol 0.5% administered once daily was comparable in ocular hypotensive efficacy to the non-fixed combination. The fixed combination treatment was safe and well tolerated in patients with glaucoma and ocular hypertension. The fixed combination group had less overall adverse events and treatment-related adverse events compared with each of the non-fixed combination and bimatoprost groups, thereby suggesting a superior comparative benefit/risk assessment of the fixed combination in the treatment of these patients.

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The study was approved by the governing institutional review boards/ethics committees for the 35 study sites prior to enrollment. Registered with www.clinicaltrials.org as Study # NCT00332059.

APPENDIX

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