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Two-year Double-masked Comparison of Bimatoprost with Timolol in Patients with Glaucoma or Ocular Hypertension

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Abstract. The object of this study was to compare the long term efficacy and safety of bimatoprost with timolol in patients with glaucoma or ocular hypertension. In a 12-month extension of two identically designed 1-year, multicenter, randomized, double-masked clinical trials, patients were treated topically with bimatoprost 0.03% QD (n = 167), bimatoprost 0.03% BID (n = 131), or timolol 0.5% BID (n = 81). Main outcome measures were IOP at 8 AM and 10 AM and safety parameters. Bimatoprost QD provided significantly greater mean reduction from baseline IOP than did timolol at both measurements at each study visit ($P \leq .001$). At 10 AM (peak timolol effect) at month 24, the mean reduction from baseline IOP was 7.8 mm Hg with bimatoprost QD and 4.6 mm Hg with timolol ($P < .001$). Patients treated with bimatoprost QD also sustained significantly lower mean IOP than timolol-treated patients at every follow-up visit throughout the 2-year study period ($P \leq .006$). At 10 AM at month 24, a significantly greater proportion of bimatoprost QD than timolol patients achieved target pressures of ≤13–18 mm Hg ($P \leq .010$). Bimatoprost sustained an excellent safety profile during the second year of treatment. Most adverse events were mild, and there were no reports of increased iris pigmentation, uveitis, or CME. The incidence of hyperemia was significantly higher with bimatoprost QD (13.8%) than with timolol (2.5%) ($P = .006$). Mean reduction from baseline IOP with bimatoprost BID was not significantly different from that with timolol at month 24 at 10 AM ($P = .474$). We conclude that bimatoprost QD provides superior IOP lowering to timolol, and is safe and well tolerated over 24 months of treatment. (**Surv Ophthalmol 49(Suppl 1)**:S45–S52, 2004.

Key words. antihypertensive agents • bimatoprost • hypotensive lipids therapeutic use • intraocular pressure • ocular hypertension • open-angle glaucoma • timolol

Glaucoma is a progressive optic neuropathy causing deterioration of visual field and in some patients, blindness. Medical treatment of this disease has been dedicated to the goal of lowering intraocular pressure (IOP), a known risk factor for development and progressive worsening of glaucomatous damage.[1,6,9]

Since it was approved in the United States in 2001, bimatoprost 0.03% ophthalmic solution has been prescribed for the reduction of IOP in patients with glaucoma or ocular hypertension (OHT). Bimatoprost once daily was significantly more effective than timolol in reducing mean IOP throughout the day over the initial 12 months of the trial reported here.[8]

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Bimatoprost-treated patients were also significantly more likely to reach low target pressures than were timolol-treated patients.[8]

Because glaucoma is a lifelong disease, once diagnosed, the ideal glaucoma drug should maintain its efficacy over the long term without causing undue safety concerns. To study the long-term safety and efficacy of bimatoprost, we conducted a 12-month extension of the initial 12-month comparison of bimatoprost and timolol.[8]

Methods

STUDY DESIGN

This was a randomized, active-controlled, double-masked, parallel-group, extension of the 12-month clinical trial.[8] The extension study was conducted at 23 centers throughout the United States. The number of patients participating in this extension study was determined by the willingness of the sites that had participated in the first 12 months of the trial to enroll patients into the 12-month extension, and the number of patients from these sites who were willing to participate. Data on IOP and adverse events were stratified and tabulated by site comparing those patients and sites that enrolled in the 12-month extension with those who did not participate. Based on the examination of these data, there was no evidence of selection bias for patients continuing into this extension.

This study was conducted in compliance with the Declaration of Helsinki, 1996 and in accordance with Institutional Review Board (IRB) regulations (United States 21 Code of Federal Regulations Part 56.103). The original protocol for this extension study prospectively specified a month 18 endpoint. A subsequent amendment extended the study to month 24. Patients signed informed consent agreements at baseline of the initial 12-month trial, and at months 12 and 18. Patients who experienced lack of efficacy or an adverse event during the extension to month 18 and discontinued were not eligible to participate in the extension to month 24.

PATIENTS

A detailed description of the methods used in this study has been published previously;[8] and is briefly summarized here. To qualify for participation in the initial 12-month phase 3 trial, patients had to have had a diagnosis of ocular hypertension, chronic open-angle glaucoma, chronic angle-closure glaucoma with patent iridotomy, pseudoexfoliative glaucoma, or pigmentary glaucoma requiring bilateral treatment. Key exclusion criteria in these trials included uncontrolled systemic disease, any contraindication to topical beta-blocker therapy, active ocular disease, or functionally significant visual field loss within the past year. In order to participate in the extension to 24 months, the patient had to have completed the month-12 visit of the initial studies.[8]

TREATMENT ASSIGNMENT AND DRUG ADMINISTRATION

At baseline (day 0) of the initial 12-month trial, patients were randomized to receive topically either bimatoprost 0.03% once-daily (QD), bimatoprost 0.03% twice daily (BID), or generic timolol maleate 0.5% BID. The randomization scheme that was established during the initial 12-month study (bimatoprost QD, bimatoprost BID, or timolol 0.5% BID in a 2:2:1 ratio) was maintained through this 12-month extension and all participating sites/patients remained masked to treatment assignments. Masking was achieved in the group that received bimatoprost QD by providing masked vehicle for the morning dose. Medications were supplied in identical-appearing bottles that were color-coded for use in the morning or evening.

Patients were instructed to self-instill their medication into both eyes at approximately 8 AM and 8 PM. During study visits, the morning dose was administered at the site, immediately after the first examination (at approximately 8 AM). Visits were scheduled at months 12 (entered into extension), 15, 18, 21, and 24.

EFFICACY AND SAFETY VARIABLES

The primary outcome measure was mean reduction from baseline IOP. IOP was measured at 8 AM and 10 AM using a Goldmann applanation tonometer affixed to a slit-lamp with the patient in a seated position. Two measurements were taken for each eye. If the two measurements differed by at least 2 mm Hg, a third measurement was required. The IOP value was taken to be the mean of the two measurements or the median of the three measurements. Other efficacy measures included mean IOP and percentage of patients reaching selected target pressures.

Safety variables included adverse events (AEs), visual acuity, visual field, biomicroscopy, ophthalmoscopy, cup/disc ratio, fasting laboratories (hematology, blood chemistry), and heart rate and blood pressure. The severity of AEs was assessed using a four-point scale: none, mild, moderate, or severe. Hyperemia could be reported by the patient and recorded as an adverse event, or be reported by the physician on the basis of comparison of the patient's eye with a laminated card showing photographs of eyes with trace, mild, moderate, or severe hyperemia. In addition, the protocol included a detailed written description of criteria for categorizing hyperemia.

Eyelash growth may have been reported by the patient as an adverse event, or by the physician on the basis of biomicroscopy. Fasting blood samples were drawn at months 18 and 24 for hematology and serum chemistry analyses. Blood and plasma samples were collected at the study sites and shipped to a central laboratory for analysis.

In order to assess changes in iris color pigmentation, each patient's eye was photographed under standardized conditions with a Polaroid Macro 5 SLR camera prior to fluorescein instillation at months 15, 18, 21, and 24. Investigators compared follow-up photographs with those from day 0 in the initial 1-year study and recorded any changes. At the end of month 24, all photographs were collected centrally and evaluated by two independent, masked reviewers, who reported a lower incidence of iris pigmentation than had been reported by the individual investigators.

ANALYSES

All efficacy results presented are from the intent-to-treat population with the last observation carried forward to subsequent missing visits (ITT-LOCF). This population included all patients who were enrolled in the extension from 12 to 24 months. Safety analyses included all patients who were enrolled and received at least one dose of study medication in the extension from 12 to 24 months.

Mean change from baseline IOP was the primary efficacy variable for this study. The baseline IOP for each participant in the 12-month extension was IOP at the start of the initial 12-month trial. Secondary efficacy parameters included mean IOP and mean percent change in IOP at 8 AM and 10 AM pressures at months 15, 18, 21, and 24. An additional efficacy variable was the percentage of patients reaching selected target pressures at the month-24 visit. IOP values were based on the worse eye (i.e., eye with greater IOP at day 0 or right eye if both the eyes had equal IOP at 8 AM).

Treatment group comparisons of mean change from baseline IOP and of mean IOP were performed using a two-way (treatments, sites) analysis of variance (ANOVA) model. If statistically significant baseline differences were detected the model incorporated baseline as a covariate (ANCOVA). Within-group changes from baseline were analyzed using paired t-tests. Nominal categorical variables were analyzed using Fisher's exact test, Pearson's chi-square test, or Cochran-Mantel-Haenszel methods. Ordinal categorical variables were analyzed with the Wilcoxon rank-sum test.

As noted earlier, the number of patients enrolled in this study was determined by the sites' and patients' willingness to continue into the extension. With the sample size achieved in this study (167 patients in the bimatoprost QD group and 81 patients in the timolol group), the resulting power was 72% to claim that bimatoprost QD was non-inferior to timolol with a non-inferiority margin of 1.5 mm Hg given the observed common standard deviation of approximately 4.3 mm Hg (maximum standard deviation observed across all timepoints for change from baseline in IOP).

The SAS computer program package (version 8.2 on Unix) (SAS Institute, Cary, North Carolina, USA) was used for computation and analysis of all variables.

Results

PATIENT POPULATION

A total of 23 sites (379 patients) agreed to enroll in this extension. Of these patients, 167 received bimatoprost QD, 131 received bimatoprost BID, and 81 received timolol (Table 1), according to their original randomization during year 1 of the trial. Results from a per-protocol (PP) population (not presented) mirrored those found with ITT-LOCF. Reasons for discontinuation are detailed in Table 1. Patient flow through year 2 of the study is shown in Fig. 1.

Based on the population who entered this extension study, there were no significant differences among the three treatment groups for any demographic or patient characteristic (Table 2). Ninety-six percent (364/379) of patients received one or

TABLE 1

Patient Disposition[a]

	Bimatoprost QD n (%)	Bimatoprost BID n (%)	Timolol BID n (%)
Enrolled	167	131	81
Completed at month 18[a]	19 (11.4)	19 (14.5)	2 (2.5)
Completed at month 24	130 (77.8)	88 (67.2)	66 (81.5)
Discontinued	18 (10.8)	24 (18.3)	13 (16.0)
Lack of Efficacy	3 (1.8)	7 (5.3)	3 (3.7)
Ocular AE	2 (1.2)	5 (3.8)	1 (1.2)
Nonocular AE	3 (1.8)	2 (1.5)	3 (3.7)
Protocol Violations	4 (2.4)	6 (4.6)	3 (3.7)
Administrative	3 (1.8)	2 (1.5)	1 (1.2)
Other	3 (1.8)	2 (1.5)	2 (2.5)

QD = once-daily; BID = twice-daily; AE = adverse events.

[a]Initial protocol was designed with a month 18 stopping point. Patients who had experienced lack of efficacy or an adverse event by the month 18 stopping point were not eligible to participate in the extension to month 24. In addition, some eligible patients elected not to participate in the extension to month 24.

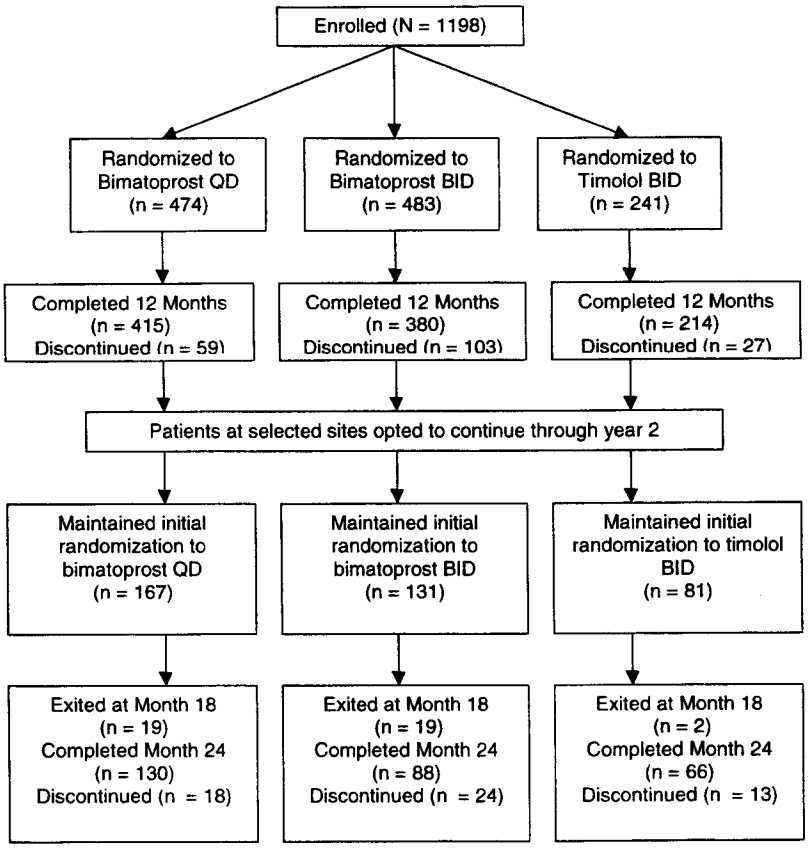

Fig. 1. Trial profile. QD = once-daily; BID = twice-daily.

more concomitant systemic medications between month 12 and month 24. There were no notable differences in the types or frequencies of concomitant systemic medication use among the 3 treatment groups, however, 16.8% of bimatoprost QD, 18.3% of bimatoprost BID, and 19.8% of timolol patients received concomitant systemic beta-blockers such as atenolol or metoprolol.

There were no significant differences in medical history among the treatment groups except for migraine (4.2% [7/167] of patients in the bimatoprost QD group, 3.1% [4/131] of patients in the bimatoprost BID group, and 11.1% [9/81] of patients in the timolol group; $P = .027$).

The most common ophthalmic history findings were cataract (58.0%, 220/379) and lid abnormalities (17.7%, 67/379). There were no significant differences in ophthalmic history among the treatment groups.

A statistically significant difference in mean IOP was detected at baseline at 10 AM between the bimatoprost QD group (25.0 mm Hg) and the timolol group (23.7 mm Hg) ($P = .028$).

IOP-LOWERING EFFICACY

Bimatoprost QD provided significantly greater mean reductions from baseline IOP than did timolol at both measurements at all follow-up visits during the extension to 24 months ($P \leq .001$). As has been reported previously, bimatoprost BID did not perform as well as bimatoprost QD.[4,8,12] The presentation of the efficacy data will focus on the bimatoprost QD group as this was the dosing regimen approved by regulatory authorities.

Typically, timolol reaches its peak effect approximately 2 hours after dosing. Because dosing occurred at 8 AM at each visit, this report will focus on treatment-group response at the 10 AM IOP measurement at each follow-up visit. At month 24 at 10 AM, the mean reduction from baseline IOP was 7.8 mm Hg with bimatoprost QD, compared to the mean reduction of 4.6 mm Hg with timolol ($P < .001$) (Fig. 2). Overall, mean IOP reduction from baseline was 2.5–3.0 mm Hg greater with bimatoprost QD than with timolol.

Patients treated with bimatoprost QD achieved significantly lower mean IOPs than did timolol-treated patients at 8 AM at every follow-up visit throughout the 2-year study period ($P \leq .002$). In addition, bimatoprost QD patients achieved significantly lower mean IOPs than did timolol-treated patients at 10 AM at every follow-up visit ($P \leq .006$) (Fig. 3). This result was confirmed by ANCOVA that included baseline IOP as a covariate. At month 24 at 10 AM, a

TABLE 2

Patient Demographics and Baseline Characteristics

	Bimatoprost QD $n = 167$	Bimatoprost BID $n = 131$	Timolol BID $n = 81$	P Value
Age (years)				
Mean	62.0	63.0	60.7	.375
Standard deviation	12.3	12.5	11.0	
Sex				
Male	73 (43.7%)	64 (48.9%)	34 (42.0%)	.565
Female	94 (56.3%)	67 (51.1%)	47 (58.0%)	
Race				
Caucasian	127 (76.0%)	99 (75.6%)	57 (70.4%)	
Black	28 (16.8%)	19 (14.5%)	13 (16.0%)	.871[a]
Asian	4 (2.4%)	6 (4.6%)	3 (3.7%)	
Hispanic	8 (4.8%)	7 (5.3%)	7 (8.6%)	
Other	0 (0.0%)	0 (0.0%)	1 (1.2%)	
Iris Color				
Light	86 (51.5%)	74 (56.5%)	34 (42.0%)	.119
Dark	81 (48.5%)	57 (43.5%)	47 (58.0%)	
Ophthalmic diagnosis				
Glaucoma	109 (65.3%)	77 (58.8%)	48 (59.3%)	.753
OHT	55 (32.9%)	51 (38.9%)	32 (39.5%)	
Glaucoma/OHT	3 (1.8%)	3 (2.3%)	1 (1.2%)	
Washout required				
Yes	110 (65.9%)	79 (60.3%)	42 (51.9%)	
No	57 (34.1%)	52 (39.7%)		
IOP at baseline Mean ± SD, mm Hg				
8 AM	26.4 ± 3.52	25.9 ± 3.15	25.4 ± 3.06	.052[b]
10 AM	25.0 ± 3.69	24.4 ± 3.64	23.7 ± 3.30	.028[b]
Body Weight				
Mean	78.8	83.6	84.6	.027[c]
Standard deviation	17.7	18.4	21.5	

[a] P value refers to comparison of black vs nonblack (Fisher's Exact Test).
[b] P values for the comparison of bimatoprost QD vs. timolol (two-way ANOVA).
[c] Not considered clinically meaningful.

significantly greater proportion of bimatoprost QD than timolol patients achieved target pressures of ≤13– ≤18 mm Hg ($P \leq .010$) (Fig. 4). For example, 56% of patients on bimatoprost QD achieved IOPs ≤17 mm Hg compared with 37% of timolol patients ($P = .004$).

Mean IOP in the bimatoprost BID group at baseline was 24.4 mm Hg at 10 AM. Mean reduction from baseline IOP at month 24 with bimatoprost BID was not significantly different from that with timolol at 10 AM ($P = .474$). At all measurements, there was no significant difference in mean IOP between bimatoprost BID and timolol patients. Mean change from baseline IOP with bimatoprost QD was significantly lower than with bimatoprost BID at 10 AM throughout the 12-month extension ($P < .001$).

SAFETY AND TOLERABILITY

The types of adverse events that were reported were similar among the three treatment groups. Conjunctival hyperemia and eyelash growth were significantly more frequent with bimatoprost QD than with timolol ($P = .006$ and $P < .018$, respectively) (Table 3).

There were no reports of any new onset of iris pigmentation or worsening of existing iris pigmentation during the second year of the trial (occurrence during year 1 among year-2 participants: bimatoprost QD, 1.2%; bimatoprost BID, 1.5%; timolol BID, 0%). Similarly, there were no reports of iritis or uveitis. Visual acuity in 83.6% (317/379) of patients either improved or did not change (defined as less than a two-line change from baseline) at month 24 (overall comparison $P = .098$).

The majority of non-ocular adverse events were unrelated to the study medications. No clinically relevant differences were noted among the three treatment groups on cardiovascular, neurological, or other systemic measures, and there were no negative trends observed with regard to pulse rate, blood pressure, or any laboratory tests.

There were no significant among-group differences in the frequency of serious adverse events ($P = .836$), nor were any treatment-related serious adverse events reported. One patient (bimatoprost

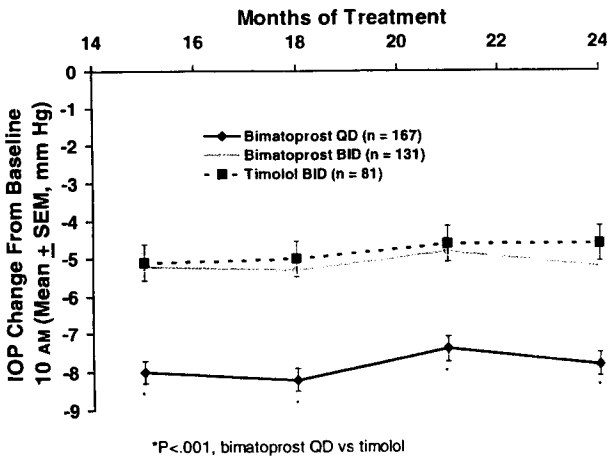

Fig. 2. Mean change from baseline IOP during second year of treatment at 10 AM (peak effect for timolol; 14 hours post-dose for bimatoprost). Mean change from baseline IOP with bimatoprost QD is significantly lower than with timolol at all measurements. Mean change from baseline IOP with bimatoprost BID is numerically larger than with timolol at all measurements, but the differences are not statistically significant.

QD group) died from injuries sustained as a passenger in a motor vehicle accident, but this was not related to the study drug.

Discussion

The bimatoprost efficacy findings discussed here focus on the QD data because bimatoprost has been approved for once-daily dosing.

The most important result of this study is that bimatoprost QD sustained significantly better IOP control

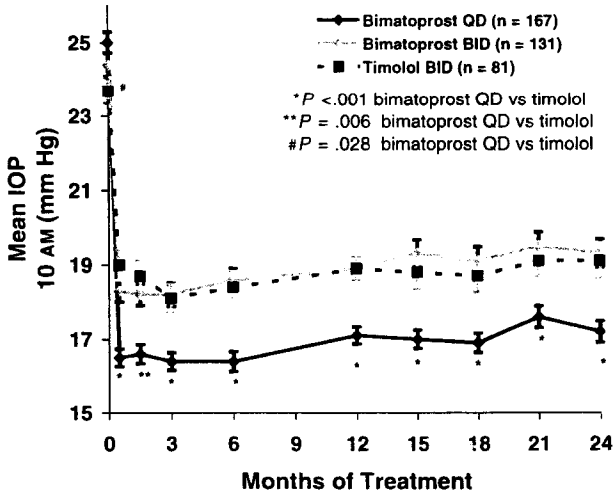

Fig. 3. Mean IOP, baseline through month 24 at 10 AM (peak effect for timolol; 14 hours post-dose for bimatoprost). Mean IOP with bimatoprost QD was significantly lower than with timolol at all measurements. Mean IOP with bimatoprost BID was not statistically different than with timolol.

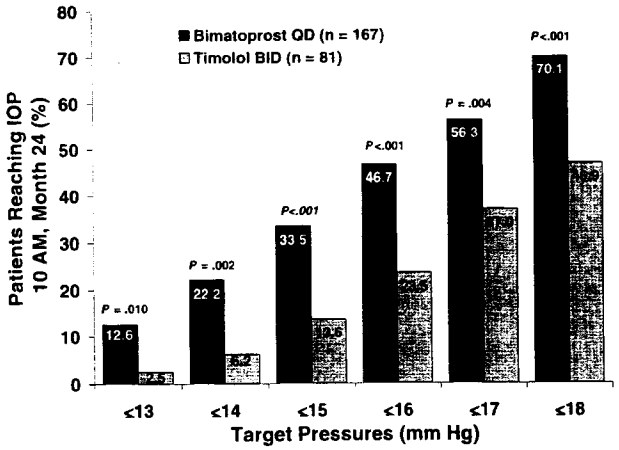

Fig. 4. Patients reaching low IOP at month 24 at 10 AM (peak effect for timolol; 14 hours post-dose for bimatoprost). Significantly more bimatoprost QD than timolol patients achieved IOP at or below the designated values.

than did timolol at all follow-up measurements for 24 months, confirming the results of the first year of this trial.[8,12] IOP-lowering with bimatoprost QD exceeded that of timolol by (2.4 mm Hg at both timepoints at all study visits, and this was sustained throughout the second year of treatment with no evidence of long-term drift of IOP. In addition, bimatoprost QD enabled a greater percentage of patients to achieve clinically relevant low target pressures (between 13 and 18 mm Hg). For example, 19.3% more bimatoprost QD than timolol patients achieved a target of <17 mm Hg.

Physicians set therapeutic goals for their glaucoma or OHT patients to establish and maintain a target IOP set within the ranges shown to be protective of vision in long-term, prospective studies.[1,6,9] Recent studies have shown that among newly detected, previously untreated glaucoma patients, every 1 mm Hg of IOP lowering decreases the risk of disease progression by approximately 10%.[7,10] Thus, in the population studied while treated with bimatoprost QD or timolol BID, our data translates into a potential 24% lower risk of glaucomatous progression for bimatoprost QD-treated patients. This long-term comparison of bimatoprost with timolol is of special clinical importance because of the long recognized phenomenon that many patients treated with timolol over the long term will experience tachyphylaxis.[3,13] In addition, the effectiveness of timolol may also be compromised because of drug interactions, particularly with systemic beta-blockers.[11]

Bimatoprost QD was safe and well tolerated during the 12-month extension period. The safety profile seen from month 12 to month 24 was similar to the first year of treatment. The most frequent adverse event, conjunctival hyperemia, was generally well tolerated and mild in severity. In light of the evidence

TABLE 3

Most Common Adverse Events[a], Month 12 to Month 24

	Bimatoprost QD (n = 167)		Bimatoprost BID (n = 131)		Timolol BID (n = 81)
Adverse Event (AE)	n (%)	*P* value vs. Timolol	n (%)	*P* value vs. Timolol	n (%)
Conjunctival hyperemia	23 (13.8)	.006	26 (19.8)	<.001	2 (2.5)
Infection	13 (7.8)	NA	9 (6.9)	NA	2 (2.5)
Cataract	11 (6.6)	NA	4 (3.1)	NA	4 (4.9)
Eyelash growth	11 (6.6)	.018	8 (6.1)	.025	0 (0.0)
Systemic hypertension	11 (6.6)	NA	8 (6.1)	NA	6 (7.4)

NA = Not available.

[a]Summarized are all AEs (regardless of causality) that occurred in ≥5% of patients in any treatment group with onset dates on or after month 12, AEs with onset dates before month 12 that increased in severity after month 12, and AEs with onset dates prior to month 12 that were not previously reported.

that suggests that iris pigmentation in heterochromatic irides (e. g., green-brown, hazel, and yellow-brown eyes) worsens with increasing duration of latanoprost treatment,[2,5,14,15] it is notable that there were no reports of changes in iris pigmentation during the second year of bimatoprost treatment. The determination of iris pigmentation may not have been consistent across all sites (iris pigmentation was evaluated at each site rather than by sending masked photographs to a centralized site), but it was consistent with the methods used in the first year of the trial. There were no reports of bimatoprost-induced iritis or uveitis with onset in the second year.

Bimatoprost BID provided lowered IOP as effectively as timolol and less effectively than bimatoprost QD, but it was associated with a significantly higher incidence of certain adverse events than was bimatoprost QD. These results further support the appropriateness of once-daily use of this drug.

Every effort was made to ensure that no selection bias was introduced in the course of this trial. There were no significant differences in IOP or adverse events among the participating sites between those who enrolled in the extension and those who did not.

Conclusions

Bimatoprost 0.03% ophthalmic solution administered once daily and twice daily is efficacious over 24 months of treatment in patients with open-angle glaucoma or ocular hypertension, with no evidence of long-term drift in IOP. Bimatoprost QD treatment showed superior efficacy to both bimatoprost BID and timolol. Bimatoprost sustained an excellent safety profile during the second year of treatment. Most adverse events were mild, and there were no reports of increased iris pigmentation. The most common adverse event in the bimatoprost treatment groups was conjunctival hyperemia.

Method of Literature Search

A MEDLINE search was conducted for all years (1966–2003) using the keywords: *antihypertensive agents, bimatoprost, glaucoma, intraocular pressure, lipids, ocular hypertension, timolol.* Only those references that were directly relevant to the comparison of bimatoprost and timolol were included. Citations in foreign languages were ignored.

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