Comparison of Once- or Twice-daily Bimatoprost with Twice-daily Timolol in Patients with Elevated IOP

A 3-Month Clinical Trial

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Objective: To compare the safety, tolerability, and efficacy of bimatoprost 0.03% instilled once daily or twice daily with timolol 0.5% twice daily.

Design: Multicenter, 3-month, randomized, double-masked, interventional comparison trial.

Participants: Patients diagnosed with ocular hypertension or glaucoma (n = 596).

Intervention: Patients received bimatoprost 0.03% ophthalmic solution once daily (8 PM, with vehicle control at 8 AM), bimatoprost 0.03% twice daily (8 AM; 8 PM), or timolol 0.5% twice daily (8 AM; 8 PM) in an uneven 2:2:1 randomization. Scheduled visits were at prestudy, baseline (day 0), weeks 2 and 6, and month 3. Intraocular pressure (IOP) was measured at 8 AM (predose), 10 AM, and 4 PM.

Main Outcome Measures: The primary outcome measure was reduction in IOP in the eye with higher IOP at baseline. Secondary outcome measures included safety variables (adverse events, ophthalmoscopy, biomicroscopy, iris pigmentation, laser-flare meter, visual acuity, visual fields, heart rate, blood pressure, blood chemistry, hematology, and urinalysis).

Results: At month 3, the mean reduction in IOP from baseline at 8 AM was 9.16 mmHg (35.2%) with bimatoprost once daily, 7.78 mmHg (30.4%) with bimatoprost twice daily, and 6.74 mmHg (26.2%) with timolol twice daily. At all follow-up visits, mean IOP reductions were significantly greater in the bimatoprost once daily group than in the timolol group at each time point (8 AM, 10 AM, and 4 PM; $P < 0.001$). Twice-daily dosing of bimatoprost also provided significantly greater mean reductions in IOP than timolol at most time points but was not as effective as once-daily dosing. Bimatoprost was associated with significantly more hyperemia and eyelash growth than timolol, whereas timolol was associated with significantly more burning and stinging sensation in eyes. Overall, bimatoprost was well tolerated with few discontinuations because of adverse events.

Conclusions: Bimatoprost 0.03% once daily was safe and statistically superior to timolol 0.5% twice daily in lowering IOP in patients with ocular hypertension or glaucoma. Bimatoprost given once daily consistently provided IOP reductions approximately 2 to 3 mmHg greater than those provided by timolol. Once-daily dosing of bimatoprost, 0.03%, demonstrated greater IOP-lowering effect and better ocular tolerability than twice-daily dosing. *Ophthalmology 2001;108:1023–1032 © 2001 by the American Academy of Ophthalmology.*

Bimatoprost (AGN 192024, previously referred to as an ocular Hypotensive Lipid) is a member of a new class of pharmacologically unique intraocular pressure (IOP)–lowering agents called prostamides.[1,2] The prostamides were originally discovered as biosynthetic products derived from anandamide, an endogenous membrane lipid.[3] These naturally occurring substances have been found in ocular tissue, suggesting a new intrinsic mechanism for IOP regulation. Bimatoprost is a synthetic analogue of these newly discovered naturally occurring substances and mimics the prostamides by demonstrating strong IOP-lowering activity.

In a previous 1-month dose-response study involving patients with primary open-angle glaucoma or ocular hy-

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pertension, the optimal concentration for bimatoprost therapy was found to be 0.03%. This concentration, used either once or twice daily, lowered IOP significantly more than timolol 0.5% twice daily.[4] In an additional 1-month study, bimatoprost 0.03% once daily was well tolerated and as or more effective than latanoprost 0.005% once daily in lowering IOP throughout the day.

In this report we introduce the 3-month results of a large, ongoing, randomized, double-masked, multicenter comparison trial in patients with glaucoma or ocular hypertension. The IOP-lowering efficacy, safety, and tolerability of bimatoprost 0.03% ophthalmic solution, administered once or twice daily, was compared with that of timolol 0.5% given twice daily. Bimatoprost achieves maximal IOP lowering 12 to 14 hours after the initial instillation, whereas timolol reaches maximal effect approximately 1 to 2 hours after instillation.[5] Thus, in this study, 8 AM IOP measurements represent peak effect for bimatoprost and trough effect for timolol, whereas the 10 AM measurements represent peak effect for both study medications.

Material and Methods

Study Design

This was a double-masked, randomized, parallel-group, active-control, comparison trial involving 30 centers in three countries (23 in the United States; 5 in Australia; 2 in New Zealand). The study is ongoing, with a planned extension of masked treatment to 1 year. It was conducted in accordance with the Declaration of Helsinki and guidelines set forth by the International Conference on Harmonisation (ICH) and United States Code of Federal Regulations CFR21. All investigators obtained appropriate institutional review board or ethics committee approval before initiating the study, and all patients provided written informed consent before any study-related procedures or changes in treatment.

Patients

A list of the primary eligibility criteria is shown in Table 1. Eligible patients were age 21 years and older with a diagnosis of glaucoma or ocular hypertension. Patients had IOP ≥22 mmHg and ≤34 mmHg at 8 AM on day 0 after washout of glaucoma medications and best-corrected visual acuity 20/100 or better in each eye. Patients who had filtering surgery within the past 6 months or other intraocular surgery within the past 3 months, and patients who had demonstrated progressive visual field loss or who, in the opinion of the investigator, had functionally significant visual field loss within the past year, were excluded. Because the active control was timolol, patients with any contraindication to β-blockers, such as obstructive pulmonary disease, bronchial asthma, heart block more severe than first degree, or uncontrolled congestive heart failure, were excluded. Patients were asked whether they were taking oral β-blocker medication, but were excluded only for a planned alteration in the therapy. Women who were or might become pregnant were also excluded. Patients could be discontinued from the study medication because of adverse events, protocol violations, lack of efficacy, or for other medical reasons.

Table 1. Patient Eligibility Criteria

Primary Inclusion Criteria	Primary Exclusion Criteria
At least 21 yrs old	Any contraindication to β-blocker therapy
Diagnosis: chronic open-angle glaucoma, ocular hypertension, chronic angle-closure glaucoma with patent iridotomy, pseudoexfoliative glaucoma, or pigmentary glaucoma	Uncontrolled systemic disease
Bilateral treatment required	Anticipated alteration of ongoing therapy with agents that could interact with study medications or have a substantial effect on IOP or study outcomes
IOP in each eye ≥22 mmHg and ≤34 mmHg at 8 AM on day 0 (after washout)	Known allergy or hypersensitivity to either study medication or its components
Best-corrected visual acuity 20/100 or better in each eye	Required chronic use of ocular medications other than the study medications during the trial
Two reliable visual fields collected before dosing	Progressive or functionally significant visual field loss within the past year
	Filtering surgery within the past 6 mos or other intraocular surgery within the past 3 mos
	Females of childbearing potential who were not using reliable contraception; pregnant or nursing females

IOP = intraocular pressure.

Randomization, Masking, Intervention, and Timing

Patients taking ocular hypotensive medications underwent the following washout periods before study entry: 4 days for parasympathomimetics or carbonic anhydrase inhibitors; 2 weeks for sympathomimetics or topical α-adrenergic agonists; and 4 weeks for topical β-blockers, prostaglandins, and combination therapy (Fig 1). At baseline, patients were randomly assigned to one of three treatment groups: bimatoprost 0.03% once daily; bimatoprost 0.03% twice daily; or timolol 0.5% twice daily, in a 2:2:1 ratio of treatment allocation on the basis of a block size of 5 (Fig 1). The randomization schedule was generated using an SAS version 6.12 (SAS Inc., Cary, NC) program and stored in a locked cabinet. The treatment identity was not revealed at any investigational site. For the bimatoprost once-daily group, a vehicle control solution was administered in the morning to maintain masking. Medications were supplied in identical-appearing masked bottles and were color-coded for use in the morning or evening. Study medications were self-instilled (1 drop [~28 μl] in each eye) daily between 7 and 9 AM and between 7 and 9 PM for 3 months. On the morning of follow-up visits, medications were instilled by the study coordinator immediately after the examination. Visits, scheduled to begin between 7 and 9 AM, included a prestudy visit and study visits on day 0 (baseline), week 2, week 6, and month 3.

Outcome Measures

The primary efficacy measure was IOP reduction from baseline, measured by a single investigator with Goldmann applanation. Both eyes were tested. Measurements (two for each eye, or three if the measurements differed by more than 2 mmHg) were performed at approximately 8 AM (between 7 and 9 AM; immediately preceding instillation of the morning dose of study medication), and at 2, 8, and (at select sites) 12 hours after the morning dose.

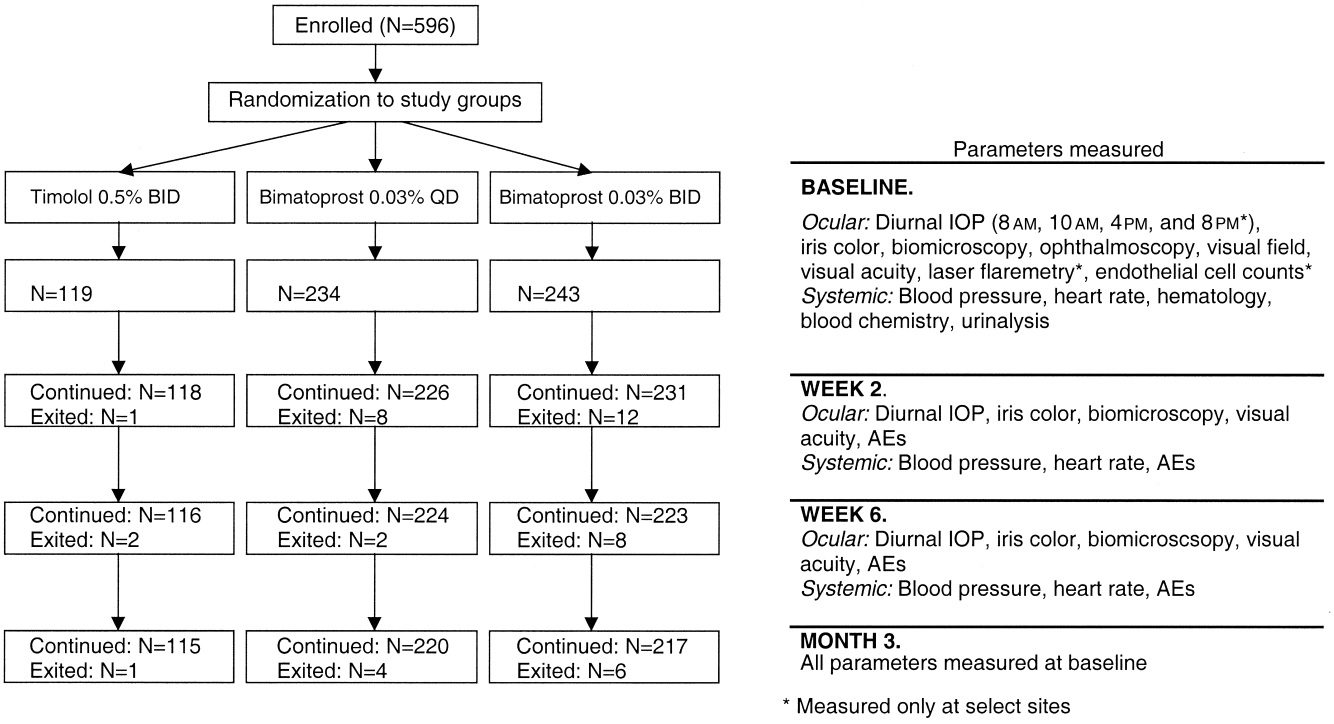

Figure 1. Study design and patient entry/exit status.

Analyses used only data from the eye with the worse IOP at baseline (8 AM). "Lack of efficacy" was defined as inadequate IOP lowering based on the opinion of the masked investigator.

Safety measures included adverse events, biomicroscopy, ophthalmoscopy, visual acuity, and visual fields. Before fluorescein instillation, color calibration strips were placed under patients' eyes, and each eye was photographed with the calibration strip using a Polaroid Macro 5® (Polaroid) camera. Each investigator assessed possible iris color change by comparing photographs of the eyes at baseline and follow-up study visits. To elicit adverse events, patients were asked a general, nondirected question, such as "How have you been feeling since the last visit?"' Directed questioning and examinations were then done as appropriate. Adverse events were reported whenever the patient or the examiner noted symptoms or findings. Slit-lamp biomicroscopic observations were graded on a numeric scale from 0 to 3, with 0 = none, 0.5 = trace, 1 = mild, 2 = moderate, and 3 = severe.[6] Ophthalmoscopic examinations (with pupil dilatation) were carried out to evaluate vitreous and retinal pathologic conditions, and the cup/disc ratio was measured. Visual field examinations were performed with a Humphrey 24-2 full threshold automated perimetry test. At select centers, the following additional measures of ocular safety were performed: (1) endothelial cell density was evaluated with a noncontact specular microscope; (2) laser flare meter (Kowa FM-500; Kowa Co, Ltd, Chuo-Ku, Tokyo, Japan) readings were performed before fluorescein instillation or pupil dilatation.

Evaluations of systemic safety included heart rate and blood pressure. In addition, urine and blood (fasting samples) were taken for urinalysis and hematology/serum chemistry analysis, respectively.

Statistical Analysis

Nominal categorical variables were analyzed by Fisher's exact test, Pearson's chi-square test, or Cochran-Mantel-Haenszel methods.[7] Ordinal categorical variables were analyzed with the Wilcoxon rank-sum test,[8] with within-group changes from baseline analyzed with the Wilcoxon signed-rank test.[9] Continuous variables were analyzed with analysis of variance; within-group changes from baseline were analyzed with paired *t* tests. Intent-to-treat with last-observation-carried-forward analyses were performed for IOP. All randomly assigned patients were included and, for patients who discontinued the study before the month 3 visit or who missed the month 3 visit, the last observed data were carried forward to subsequent time points in the analyses. Missing data between visits were not imputed. Analyses of IOP used only data from the eye with the higher IOP at 8 AM on day 0. For all pairwise between-group comparisons of IOP, tests of noninferiority and superiority[10] were performed, with a two-sided significance level of ≤ 0.05 considered statistically significant. Noninferiority of bimatoprost to timolol was claimed when the upper limit of the two-sided 95% confidence interval (CI) of the difference (bimatoprost—timolol) was ≤ 1 mmHg. Superiority was claimed when the upper limit of this 95% confidence interval was < 0 mmHg. Bimatoprost once daily was compared with bimatoprost twice daily using similar tests. All patients received at least one dose of study medication and were included in the safety analyses.

With 200 patients in each bimatoprost group and 100 patients in the timolol group, the power was 0.85 to claim noninferiority of bimatoprost to timolol on the basis of a maximum difference of 1.5 mmHg and using the estimated variability determined in a prior study.[4]

Results

Five hundred ninety-six patients were enrolled and randomly assigned to receive bimatoprost once daily (n = 234), bimatoprost twice daily (n = 243), or timolol twice daily (n = 119; Fig 1). There were no statistically significant among-group differences in demographic characteristics, clinical diagnosis, or mean IOP at

Table 2. Patient Characteristics

	Bimatoprost Once Daily (n = 234)	Bimatoprost Twice Daily (n = 243)	Timolol (n = 119)	P Value
Age (yrs)				0.479
Mean ± SD	63.1 ± 12.9	61.9 ± 11.7	62.0 ± 12.1	
Gender				0.212
Male	41.9% (98)	48.1% (117)	39.5% (47)	
Female	58.1% (136)	51.9% (126)	60.5% (72)	
Race				0.750
Caucasian	75.6% (177)	74.1% (180)	73.9% (88)	
Black	20.1% (47)	18.5% (45)	16.8% (20)	
Asian	1.7% (6)	4.9% (12)	3.4% (4)	
Hispanic	1.7% (4)	2.1% (5)	5.0% (6)	
Other	0	0.4% (1)	0.8% (1)	
Iris color				0.922
Blue	24.2% (57)	20.2% (49)	21.0% (25)	
Brown	37.2% (87)	35.0% (85)	35.3% (42)	
Green	2.1% (5)	4.5% (11)	7.6% (9)	
Dark brown	11.1% (26)	11.9% (29)	10.9% (13)	
Yellow-brown	12.4% (29)	13.2% (32)	10.1% (12)	
Gray	1.7% (4)	0.8% (2)	0.8% (1)	
Blue-gray	6.4% (15)	6.2% (15)	5.9% (7)	
Green-brown	3.0% (7)	4.1% (10)	3.4% (4)	
Blue/gray-brown	0.9% (2)	2.9% (7)	2.5% (3)	
Other	0.9% (2)	1.2% (3)	2.5% (3)	
Ophthalmic diagnosis				0.842
Glaucoma	62.8% (147)	60.9% (148)	65.5% (78)	
OHT	36.3% (85)	37.9% (92)	34.5% (41)	
Glaucoma/OHT	0.9% (2)	1.2% (3)	0	
Washout required				0.502
Yes	65.8% (154)	70.0% (170)	64.7% (77)	
No	34.2% (80)	30.0% (73)	35.3% (42)	
Systemic β-blocker therapy				0.159
Yes	15.8% (37)	10.7% (26)	10.1% (12)	
No	84.2% (197)	89.3% (217)	89.9% (107)	
Mean IOP (±SD) at baseline				
8 AM	26.1 ± 3.3	25.6 ± 3.2	25.7 ± 3.3	0.117
10 AM	24.7 ± 3.5	24.4 ± 3.5	24.1 ± 3.4	0.090
4 PM	23.7 ± 3.8	23.4 ± 3.8	23.3 ± 3.9	0.266
8 PM*	22.4 ± 3.4	22.1 ± 3.6	22.3 ± 4.4	0.742

*IOP measurements at 8 PM at selected sites only.

IOP = intraocular pressure; OHT = ocular hypertension; SD = standard deviation.

baseline (Table 2). Most patients were white with brown or blue eyes and a diagnosis of glaucoma. Approximately 10% to 15% of patients in each treatment group were taking concurrent oral β-blocker medication. Exclusion of these patients from the analyses did not affect the statistical significance of the results. The 3-month study was completed by 220 of 234 (94.0%) patients in the bimatoprost once-daily group; 221 of 243 (89.3%) patients in the bimatoprost twice-daily group; and 115 of 119 (96.6%) patients in the timolol group (Table 3). Only one patient was lost to follow-up. The percentage of patients who completed the study was comparable in the bimatoprost once-daily and timolol groups.

IOP-lowering Efficacy

Patients receiving either bimatoprost regimen had significantly lower mean IOP at 8 AM at every follow-up visit ($P < 0.001$; Table 4) than patients receiving timolol twice daily. Mean IOP at 8 AM ranged from 16.9 to 17.2 mmHg in the bimatoprost once-daily group, from 17.4 to 17.7 mmHg in the bimatoprost twice-daily group, and from 19.0 to 19.2 mmHg in the timolol group (Fig 2). Similarly, mean percent reductions (Fig 3) and mean reductions from baseline IOP at 8 AM were significantly greater with bimatoprost, 0.03%, once daily and twice daily than with timolol 0.5% twice daily at all follow-up visits ($P \leq 0.013$). Mean reductions from baseline IOP at 8 AM ranged from 8.9 to 9.2 mmHg (34.0%–35.2%) in the bimatoprost once-daily group compared with 6.5 to 6.7 mmHg (25.4%–26.2%) in the timolol group. Mean reductions in the bimatoprost twice-daily group ranged from 7.8 to 8.2 mmHg

Table 3. Patient Disposition at Month 3

	Bimatoprost Once Daily (%)	Bimatoprost Twice Daily (%)	Timolol (%)
Enrolled	234	243	119
Completed	220 (94.0)	221 (89.3)	115 (96.6)
Discontinued	14 (6.0)	26 (10.7)	4 (3.4)
Lack of efficacy	2 (0.9)	1 (0.4)	1 (0.8)
Adverse events	6 (2.6)	18 (7.4)	3 (2.5)
Ocular	3 (1.3)	17 (7.0)	1 (0.8)
Systemic	3 (1.3)	3 (1.2)	2 (1.7)
Protocol violation	1 (0.4)	0	0
Administrative	4 (1.7)	6 (2.5)	0
Other	1 (0.4)	1 (0.4)	0

Table 4. Between-group Differences in Mean Intraocular Pressure Values (with 95% Confidence Intervals) at 8 AM for Each Study Visit

Study Visit	Statistic	Bimatoprost Once Daily–Timolol	Bimatoprost Twice Daily–Timolol	Bimatoprost Once Daily–Bimatoprost Twice Daily
Baseline (day 0)	Difference	0.51 mmHg	−0.06 mmHg	0.57 mmHg*
	95% CI	(−0.19, 1.21)	(−0.75, 0.64)	(0.00, 1.13)
Wk 2	Difference	−1.71 mmHg†	−1.67 mmHg†	−0.04 mmHg‡
	95% CI	(−2.50, −0.93)	(−2.45, −0.90)	(−0.68, 0.59)
Wk 6	Difference	−1.66 mmHg†	−1.27 mmHg†	−0.38 mmHg‡
	95% CI	(−2.43, −0.89)	(−2.04, −0.51)	(−1.01, 0.24)
Mo 3	Difference	−1.89 mmHg†	−1.11 mmHg†	−0.78 mmHg§
	95% CI	(−2.70, −1.09)	(−1.91, −0.31)	(−1.44, −0.13)

*Statistically significant difference between groups ($P = 0.05$).

†Bimatoprost superior to timolol ($P \leq 0.007$).

‡Bimatoprost once daily at least as effective as bimatoprost twice daily.

§Bimatoprost once daily superior to bimatoprost twice daily.

CI = confidence interval.

(30.4%–32.1%). Once-daily dosing of bimatoprost was significantly more effective than twice-daily dosing at the week 6 and month 3 visits ($P < 0.005$) and was at least as effective as twice-daily dosing at week 2.

Diurnal IOP results were also consistent across the follow-up visits. Bimatoprost once daily provided significantly lower mean IOP than timolol at each time of the day (8 AM, 10 AM, and 4 PM) and at each follow-up visit ($P < 0.001$). At month 3, mean IOP values ranged from 16.1 to 16.9 mmHg with bimatoprost once daily, versus 17.9 to 19.0 mmHg with timolol (Fig 4; Table 5). Mean IOP values ranged from 17.3 to 17.8 mmHg with bimatoprost twice daily. Although the mean IOP provided by bimatoprost twice daily was consistently lower than that provided by timolol, once-daily dosing of bimatoprost was as effective or significantly more effective than twice-daily dosing at each time of the day and at each follow-up visit.

At month 3, mean reductions from baseline IOP at time points throughout the day (8 AM, 10 AM, and 4 PM) ranged from 7.1 to 9.2 mmHg (30.0%–35.2%) with bimatoprost once daily compared with 5.1 to 6.7 mmHg (21.7%–26.2%) with timolol. Bimatoprost once daily provided mean IOP reductions significantly greater than those provided by timolol at each time point and at each follow-up visit ($P < 0.001$).

IOP was measured at 8 PM (just before medication dosing) for a subset of 214 patients. At the follow-up visits, mean IOP at 8 PM ranged from 16.1 to 16.4 mmHg with bimatoprost once daily versus 18.3 to 18.4 mmHg with timolol. Mean IOP ranged from 16.3 to 16.4 mmHg with bimatoprost twice daily. Mean reductions in IOP from baseline at 8 PM ranged from 5.8 to 6.1 mmHg (26.1%–27.9%) with bimatoprost once daily and from 3.9 to 4.1 mmHg (17.5%–18.2%) with timolol. Mean IOP reductions ranged from 5.68 to 5.74 mmHg (25.7%–26.0%) with bimatoprost twice daily. Because of the smaller sample sizes at 8 PM, there was low power for pairwise comparisons between groups. Despite this low power, statistical analyses demonstrated that the bimatoprost regimens provided mean IOP reductions as great or significantly greater than those provided by timolol at 8 PM at each follow-up

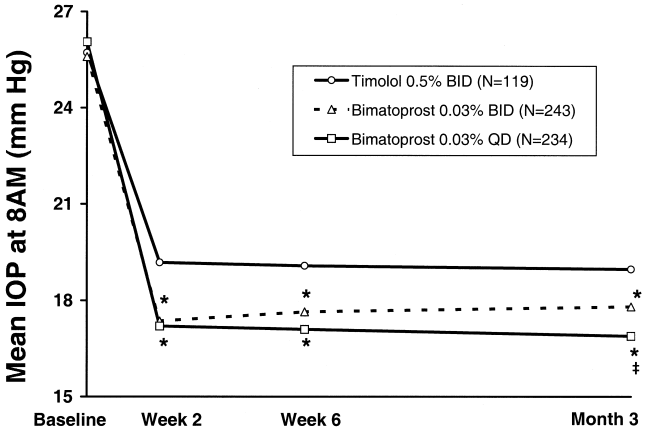

Figure 2. Mean intraocular pressure (IOP) values at 8 AM at each scheduled visit. Mean IOP values were statistically significantly lower in the bimatoprost groups than in the timolol group at each follow-up visit. *$P < 0.007$ vs. timolol; ‡$P = 0.019$ vs. bimatoprost twice daily

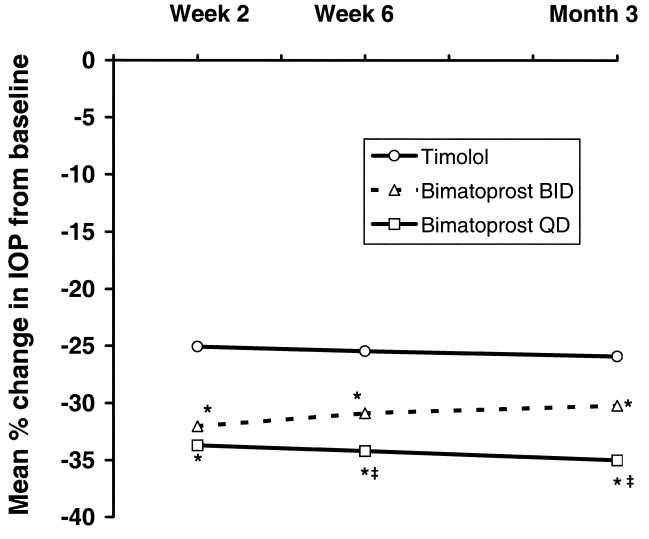

Figure 3. Mean percent intraocular pressure (IOP) changes from baseline at 8 AM at each scheduled visit. Mean percent changes in IOP from baseline were statistically significantly greater in the bimatoprost groups than in the timolol group at each follow-up visit. *$P < 0.003$ vs. timolol; ‡$P < 0.011$ vs. bimatoprost twice daily

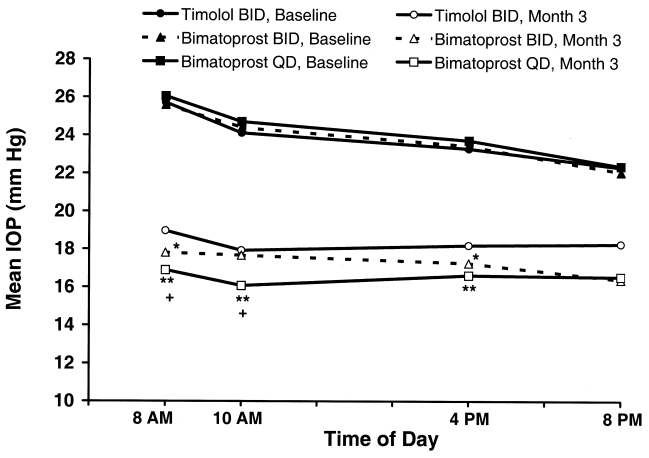

Figure 4. Diurnal intraocular pressure (IOP) mean values (mmHg) at baseline and month 3. The bimatoprost once daily regimen provided significantly lower mean IOP than timolol 0.5% twice daily at 8 AM, 10 AM, and 4 PM and was as effective or more effective than bimatoprost twice daily. Because the 8 PM measurement was performed only at select sites, there was inadequate power for statistical comparisons. However, at 8 PM, mean IOP in the bimatoprost once daily group was at least as low as in the timolol group (95% confidence interval of the between-group difference was from −2.28 to +0.66), and mean IOP in the bimatoprost twice daily group was significantly lower than in the timolol group ($P = 0.031$). Sporadic statistically significant between-group differences in mean IOP at baseline ($P = 0.05$ for bimatoprost once daily vs. bimatoprost twice daily at 8 AM; $P = 0.032$ for bimatoprost once daily versus timolol at 10 AM) were small and not clinically relevant. $^{**}P < 0.001$ vs. timolol; $^{*}P < 0.018$ vs. timolol; $^{+}P < 0.019$ vs. bimatoprost twice daily.

visit. The bimatoprost once-daily regimen consistently provided mean IOP reductions approximately 2 mmHg greater than those provided by timolol at 8 PM at each follow-up visit.

Frequency analysis of IOP after treatment demonstrated that a higher percentage of patients in the bimatoprost groups than in the timolol group had sufficient IOP lowering to achieve desirable target IOP levels. Table 6 shows response rates at month 3 at 10 AM (peak timolol effect). A higher percentage of bimatoprost patients than timolol patients achieved target IOP levels. For example, a target IOP of ≤17 mmHg was achieved by 70.9% of patients in the bimatoprost once-daily group compared with 46.1% of patients in the timolol group. Few patients in any treatment group discontinued because of lack of efficacy (2 of 234 [0.9%] in the bimatoprost once-daily group; 1 of 243 [0.4%] in the bimatoprost twice-daily group; 1 of 119 [0.8%] in the timolol group).

Adverse Events and Ocular Safety

All treatment regimens were safe and well-tolerated. No serious treatment-related adverse events were reported. Most treatment-related adverse events were ocular or periocular and mild in severity. The frequency of discontinuations because of adverse events in the bimatoprost once-daily and timolol groups was comparable (2.6% vs. 2.5%), whereas there were more discontinuations because of adverse events in the bimatoprost twice-daily group (7.4%, $P < 0.062$).

The only treatment-related adverse events occurring in more than 5% of patients treated with the bimatoprost once-daily regimen were conjunctival hyperemia, eyelash growth, and eye pruritus. Mild conjunctival hyperemia was reported in 93 (39.7%) of bimatoprost once-daily patients, 121 (49.8%) of bimatoprost twice-daily patients, and 10 (8.4%) of timolol patients. Greater than mild conjunctival hyperemia was reported in 14 (6.0%) of the bimatoprost once-daily patients, 25 (10.3%) of bimatoprost twice-daily patients, and 3 (2.5%) of timolol patients. On slit-lamp biomicroscopy, conjunctival hyperemia was present at baseline, before receiving study medication, in 48 (20.5%) patients receiving bimatoprost once daily, 40 (16.5%) patients receiving bimatoprost twice daily, and 11 (9.2%) patients receiving timolol. Greater than a mild (1 grade) increase in the severity of conjunctival hyperemia after 3 months of therapy was noted in 6 (2.8%) patients treated with bimatoprost once daily compared with 0 (0%) patients treated with timolol ($P = 0.10$). Eyelash growth was reported in 60 (25.6%) bimatoprost once-daily patients, 82 (33.7%) bimatoprost twice-daily patients, and 2 (1.7%) timolol patients. Although conjunctival hyperemia and eyelash growth were significantly more frequent in the bimatoprost groups than in the timolol group ($P < 0.001$), their incidence was significantly lower with bimatoprost once daily than with twice-daily dosing ($P = 0.002$ and $P = 0.053$, respectively). Eye pruritus was reported in 21 (9.0%) bimatoprost once-daily patients, 37 (15.2%) bimatoprost twice-daily patients, and 4 (3.4%) timolol patients; there was a trend for a higher incidence with bimatoprost once daily than with timolol ($P = 0.052$). Burning and stinging sensation in the eye were significantly more frequent with timolol (9.2% and 2.5%, respectively) than with bimatoprost once daily (3.4% and 0%, $P = 0.022$ and $P = 0.038$, respectively).

Adverse effects were not associated with sequelae and led to few discontinuations. A comparable percentage of patients in the bimatoprost once-daily group (0.9%, 2 of 234) and in the timolol

Table 5. Between-group Differences in Diurnal Mean Intraocular Pressure Values (with 95% Confidence Intervals) at Month 3

Hour	Statistic	Bimatoprost Once Daily–Timolol	Bimatoprost Twice Daily–Timolol	Bimatoprost Once Daily–Bimatoprost Twice Daily
8 AM	Difference	−1.89 mmHg*	−1.11 mmHg*	−0.78 mmHg
	95% CI	(−2.70, −1.09)	(−1.91, −0.31)	(−1.44, −0.13)
10 AM	Difference	−1.71 mmHg*	−0.32 mmHg†	−1.39 mmHg
	95% CI	(−2.52, −0.90)	(−1.12, 0.48)	(−2.04, −0.74)
4 PM	Difference	−1.43 mmHg*	−0.94 mmHg*	−0.50 mmHg
	95% CI	(−2.22, −0.65)	(−1.71, −0.16)	(−1.13, 0.14)
8 PM‡	Difference	−0.81 mmHg†	−1.64 mmHg*	0.83 mmHg
	95% CI	(−2.28, 0.66)	(−3.13, −0.15)	(−0.41, 2.08)

*Bimatoprost superior to timolol ($P \leq 0.031$).

†Bimatoprost at least as effective as timolol.

‡8 PM measurements only at selected sites (timolol: n = 45; bimatoprost once daily: n = 83; bimatoprost twice daily: n = 84).

Table 6. Response Rates. The Percentage of Patients with Intraocular Pressure at or Below Target Intraocular Pressure Levels Is Shown for the 10 AM Measurement at the Month 3 Visit

Target Intraocular Pressure (mmHg)	Bimatoprost Once Daily (n = 234)	Bimatoprost Twice Daily (n = 243)	Timolol (n = 119)	*P* value
≤12	12.4%	7.4%	4.2%	0.021
≤13	18.4%	13.6%	8.4%	0.031
≤14	30.3%	21.0%	13.4%	<0.001
≤15	44.9%	29.6%	23.5%	<0.001
≤16	62.0%	39.5%	35.3%	<0.001
≤17	70.9%	44.9%	46.2%	<0.001
≤18	77.8%	58.4%	61.3%	<0.001
≤19	82.1%	69.1%	67.2%	<0.001
≤20	88.9%	79.4%	78.2%	0.002

group (0.8%, 1 of 119) discontinued because of conjunctival hyperemia. In the bimatoprost twice-daily group, 4.1% (10 of 243) of patients discontinued because of conjunctival hyperemia, and 1 patient discontinued because of growth of eyelashes.

Iritis was reported for one patient in the bimatoprost twice-daily group, but no associated cells or flare were noted, suggesting that the case might have been extremely mild or misdiagnosed. Another patient receiving bimatoprost twice daily was noted to have darker iris in both eyes at the month 3 examination. There were no reports of cystoid macular edema. There were no significant differences among groups in ophthalmoscopy, visual acuity, visual fields, cup/disc ratio, laser flare meter readings, and endothelial cell counts.

Systemic Safety

There were no clinically significant effects of bimatoprost on heart rate or blood pressure or on any hematology, blood chemistry, or urinalysis parameters. Timolol consistently caused a decrease in heart rate, and the mean change from baseline was statistically significantly different from that in the bimatoprost once-daily group at week 6 and month 3 ($P \leq 0.007$). There were no significant among-group differences in mean changes from baseline systolic and diastolic blood pressure.

Discussion

This study demonstrates that bimatoprost 0.03% once daily is superior to timolol in IOP lowering. The IOP reductions provided by bimatoprost 0.03% were greater than those provided by timolol at all times during the day, and the magnitude of the difference in mean IOP lowering, approximately 2 to 3 mmHg, was statistically significant and clinically relevant. Furthermore, a higher percentage of bimatoprost patients than timolol patients responded to treatment with a substantial reduction in IOP and achieved target IOP levels. One purpose of this trial was to evaluate the relative effectiveness of once-daily versus twice-daily dosing of bimatoprost. The IOP results clearly demonstrated that once-daily dosing of bimatoprost was superior in IOP lowering and safer, and that bimatoprost is a once-daily medication. Therefore, this discussion of the efficacy and safety of bimatoprost will focus on the bimatoprost once-daily regimen.

It has been reported that patients taking oral β-blockers may show a blunted IOP response to topical timolol.[11] However, only 12 patients in the timolol group (10.1%) were taking oral β-blockers. Furthermore, the IOP lowering found with timolol in this study (22%–26%) is consistent with previous reports of the ocular hypotensive efficacy of timolol at trough and peak effect.[6,12–16] Most importantly, exclusion of patients taking oral β-blockers from the analysis did not affect the statistical significance of the results. Therefore, the superiority of bimatoprost to timolol did not result from a lack of patient responsiveness to timolol, but rather to a superior IOP-lowering response to bimatoprost. Bimatoprost once daily consistently provided significantly greater IOP lowering compared with timolol throughout the day, even at the 10 AM measurement of peak timolol effect.

Studies suggest that after the optic nerve is damaged, progression of glaucoma can occur unless IOP is lowered.[17] A major strategy for the management of glaucoma is to lower IOP to a target IOP that may vary on the basis of the amount of damage to the optic nerve. In this trial, the response rates with bimatoprost were substantial. Few patients were discontinued because of lack of efficacy even in the timolol group, perhaps because patients were required to be likely to be controlled on monotherapy. Many patients required washout of glaucoma medications, therefore, there may have been a selection bias for patients responsive to ocular hypotensive agents. Nonetheless, patients treated with bimatoprost were significantly more likely than timolol patients to demonstrate substantial IOP reductions and achieve low target pressures.

It is clear that optimal treatment of glaucoma depends on adequate control of IOP over 24 hours. To minimize optic nerve damage, ideal glaucoma medications should not only provide a large peak IOP-lowering effect but also keep IOP low throughout the day. The results of this trial demonstrate that bimatoprost keeps IOP low throughout the day and provides superior diurnal IOP control compared with timolol.

All three regimens were well tolerated, and few patients discontinued because of adverse events from the bimatoprost once-daily group. Most adverse events (>96%) were rated as mild to moderate in severity. More patients treated with bimatoprost (particularly with the twice-daily regimen) experienced adverse events. However, timolol-related adverse events may have been underreported in this study, because patients likely to have side effects from topical β-blockers were excluded.

Conjunctival hyperemia was the most common adverse event, but 20% of the patients in the bimatoprost once-daily group had conjunctival hyperemia at baseline, and few demonstrated more than a mild increase in redness with therapy. Only two patients (0.9%) were discontinued from the bimatoprost once-daily group because of conjunctival hyperemia. Importantly, conjunctival hyperemia was not associated with intraocular inflammation or other sequelae. In the bimatoprost once-daily group, there were no reports of iritis or uveitis, and there were no reports of cystoid macular edema.

For the last two decades, topical application of timolol has been the standard for IOP-lowering therapy. However, many patients have contraindications to the use of β-blockers. The possibility of serious cardiopulmonary side effects and loss of efficacy over time can limit the usefulness of these agents for IOP lowering.[18–21] The development of new ocular hypotensive agents with increased efficacy and/or more favorable safety/tolerability profiles would be beneficial for the management of glaucoma and ocular hypertension. Bimatoprost has recently been demonstrated to lower IOP by increasing both pressure-sensitive and pressure-insensitive outflow.[22] This dual mechanism of action may contribute to the substantial IOP-lowering efficacy of bimatoprost.

In this clinical trial, bimatoprost demonstrated excellent IOP-lowering efficacy as a monotherapeutic agent for the management of glaucoma and ocular hypertension. Bimatoprost 0.03% ophthalmic solution, given once daily or twice daily, was safe and well tolerated and provided statistically significant and clinically relevant greater IOP lowering than timolol 0.5% twice daily. The bimatoprost 0.03% once-daily regimen was more effective than the twice-daily regimen, demonstrating greater IOP-lowering efficacy and better ocular tolerability. Not only were IOP reductions significantly greater with bimatoprost than with timolol, but the percentage of patients achieving target pressure and diurnal control was also significantly greater with bimatoprost 0.03% once daily than with timolol 0.5% twice daily.

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