Evaluation of Travoprost as Adjunctive Therapy in Patients With Uncontrolled Intraocular Pressure While Using Timolol 0.5%

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• PURPOSE: To evaluate the intraocular pressure–lowering efficacy and safety of travoprost 0.0015% and 0.004%, dosed daily in the evening compared with vehicle, in patients with open-angle glaucoma or ocular hypertension, whose intraocular pressure was not adequately controlled on timolol 0.5% twice daily (twice daily).

• METHODS: Subjects who qualified at screening began a run-in period dosing timolol twice daily for 3 weeks. If the subjects had an intraocular pressure of 24 to 36 mm Hg at 8 AM and 21 to 36 mm Hg at 10 AM and 4 PM in at least one eye on timolol, they were randomized to one of two concentrations of travoprost (0.0015% or 0.004%) or vehicle solution every day and were followed for 6 months. Four hundred twenty-six subjects were randomized. The mean intraocular pressure at 8 AM, 10 AM, and 4 PM in the patient's eye with the higher intraocular pressure was used for the analysis.

• RESULTS: Mean baseline values (25 mm Hg) for subjects at eligibility (while maintained on timolol) were not significantly different ($P < .0001$) among the treatment groups. The intraocular pressure was lowered an additional −5.7 to −7.2 mm Hg and −5.1 to −6.7 mm Hg in the travoprost 0.004% and 0.0015% concentrations, respectively. These changes were significantly ($P \leq .0001$) different from the vehicle group (−1.3 to −2.8 mm Hg). The intraocular pressure range on treatment at all visit times over the 6-month treatment period ranged from 17.9 to 19.2 mm Hg for travoprost 0.004% and 18.3 to 20.1 mm Hg for travoprost 0.0015% compared with 22.4 to 24.1 mm Hg for vehicle. Average hyperemia scores ranged from trace to mild (mean 0.5 on a scale of 0 = none/trace; 1= mild; 2 = moderate; 3 = severe) for all treatment groups. No iris pigmentation changes were observed in any patient during this study. There were no clinically or statistically significant changes from baseline in visual acuity, ocular cells and flare, fundus parameter, cup-to-disk ratio and visual field between the treatment groups. There were no serious adverse events reported for any treatment group.

• CONCLUSIONS: Travoprost produced clinically relevant and statistically significant additional intraocular pressure reductions from baseline when used adjunctively with timolol in subjects with open-angle glaucoma or ocular hypertension. (Am J Ophthalmol 2001;132: 860–868. © 2001 by Elsevier Science Inc. All rights reserved.)

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ELEVATED INTRAOCULAR PRESSURE IS A RISK FACTOR contributing to optic nerve damage and subsequent visual field loss in patients with glaucoma or ocular hypertension.[1–3] Since its introduction more than two decades ago, timolol has become first-line therapy for the reduction of intraocular pressure and is often used in combination with topical carbonic anhydrase inhibitors, α-agonist, or prostaglandin analogues in those patients whose control of intraocular pressure requires more than one medication.

Prostaglandin analogues represent a class of active ocu-

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lar hypotensive agents shown to reduce intraocular pressure as effectively as β-adrenergic antagonists, such as timolol.[4,5] The isopropyl ester precursor of travoprost is a synthetic prostaglandin $PGF_{2\alpha}$ analog of the FP class, which is rapidly hydrolyzed by esterases in the cornea to the biologically active free acid. This free acid, in nanomolar concentrations, has demonstrated preferential affinity and full agonist activity for the FP receptor with no meaningful affinity or activity at other receptors.[6–8] Binding of prostaglandins or prostaglandin analogues to the FP receptor are thought to lower intraocular pressure by a variety of mechanisms, including the relaxation of ciliary muscle,[9] the induction of matrix metalloproteinases[10] and the subsequent degradation of extracellular matrix proteins, and the release of endogenous prostaglandins.[11] FP receptors have been found in abundance on the iris sphincter and longitudinal ciliary muscle in the human eye.[6]

In three well-controlled phase 3 clinical studies, significant decreases in intraocular pressure were observed with travoprost when used as primary therapy.[12–14]

Although the exact mechanism by which travoprost reduces intraocular pressure has not been fully elucidated, it is thought to reduce intraocular pressure by increasing the outflow of aqueous humor through the uveoscleral pathway as observed with other $PGF_{2\alpha}$ analogue medications.[15,16]

Unlike travoprost and other prostaglandin analogues, β blockers lower intraocular pressure by decreasing the production of aqueous humor.[17–19] Because they work by different mechanisms, it was reasoned that using both travoprost and timolol would produce a greater reduction in intraocular pressure than could be achieved with either drug alone.

This study was designed to compare the intraocular pressure–lowering effect of two concentrations of travoprost (0.0015% and 0.004%) with vehicle solution in subjects with open-angle glaucoma or ocular hypertension, whose intraocular pressure was not well controlled on maintenance therapy with timolol. Safety was analyzed by recording and evaluating side effects and adverse events.

METHODS

THIS PROSPECTIVE, MULTICENTER, DOUBLE-MASKED, RANdomized, parallel group study was conducted in accordance with the principles set forth in the Declaration of Helsinki. Subjects or their legal representative read, signed, and dated an institutional review board–approved consent form before undergoing a screening examination and participation in the study.

The study population consisted of subjects of any race and either sex. Women were required to be 1 year postmenopausal or to have been surgically sterilized at least 3 months before starting the study. Contact lens use was permitted, but lenses were removed to instill medication and were also removed on follow-up examination days.

Subjects were excluded from the study for any of the following criteria: best-corrected visual acuity worse than 0.6 logarithm of minimal angle of resolution (logMAR) in either eye; chronic or recurrent severe inflammatory eye disease; ocular trauma within the past 6 months; ocular infection or ocular inflammation within the past 3 months; clinically significant progressive retinal disease; inability to undergo applanation tonometry; ocular disease precluding the use of topical β blockers or prostaglandins; cup-to-disk ratio greater than 0.80 in either eye; severe central visual field loss; intraocular surgery within past 6 months; laser surgery within past 3 months; severe hypersensitivity to study medications or vehicle; severe, unstable, or uncontrolled cardiovascular, hepatic, or renal disease in which the use of β blockers is contraindicated; bronchial asthma or chronic obstructive pulmonary disease; beginning any regular medication that might affect intraocular pressure less than 1 month before study entry; glucocorticoid use during the eligibility phase; current use of topical ocular nonsteroidal anti-inflammatory agents; any type of glaucoma other than open-angle glaucoma or ocular hypertension; anterior chamber angle grade less than 2; therapy with another investigational agent within 30 days of study start; inability to instill medication in both eyes; use of any other topical or systemic ocular hypotensive medication during the study.

Subjects who qualified at the screening examination and were taking ocular hypotensive medications other than timolol discontinued their use. All subjects were placed on single therapy timolol 0.5% twice daily (TIMOPTIC; Merck and Company, Inc, Whitehouse Station, New Jersey) for 3 weeks before the two eligibility examinations. To qualify for the study, subjects with open-angle glaucoma (with or without pigment dispersion or pseudoexfoliation) or ocular hypertension were required to have uncontrolled intraocular pressure defined as mean intraocular pressure of 24 to 36 mm Hg in at least one eye at 8 AM on both eligibility days and 21 to 36 mm Hg in at least one eye (the same eye) at 10 AM and 4 PM on both eligibility days while taking timolol. Subjects with intraocular pressure greater than 36 mm Hg in either eye during the eligibility phase were excluded on the basis of potential safety risk during this 6-month study. The primary efficacy variable was mean intraocular pressure at the 8 AM, 10 AM, and 4 PM time points for the patient's eye with the highest mean intraocular pressure, and this eye was used in the analysis.

Eligibility evaluations were conducted as follows: best-corrected visual acuity (logMAR scale), biomicroscopy, resting pulse and blood pressure, dilated fundus examination, automated perimetry, gonioscopy, bilateral intraocular pressure measurements at 8 AM, 10 AM, and 4 PM using Goldmann applanation tonometry, ocular hyperemia assessment, cells and flare assessment, and iris/eyelash photographs.

Subjects who met the eligibility criteria were assigned a patient number and sequentially randomized to one of the three treatment groups in an approximately equal 1:1:1 ratio by means of a computer-generated randomization schedule prepared by the Alcon Biostatistics Department.

Subjects, investigators, and study staff were masked to the treatment received by subjects. All study medications (travoprost 0.0015%, travoprost 0.004%, [TRAVATAN; Alcon Research, Ltd, Fort Worth, Texas] and travoprost vehicle) were packaged in identical containers. The vehicle solution contained the same ingredients as the active formulation except for the active test drug, travoprost. The investigator was supplied with sealed envelopes containing the description of the medication for each patient. The treatment code was not broken at any time during this study.

Subjects continued to dose one drop of open-label timolol in each eye at approximately 8 AM and 8 PM. Five minutes after the evening dose of timolol, they instilled one drop of masked study medication from a container labeled "evening dose." Subjects were re-examined at week 2 and after 1.5, 3, 4.5, and 6 months of treatment. At these visits, intraocular pressure was measured at 8 AM, 10 AM, and 4 PM (except at the 1.5-month and 4.5-month visits, when the 4 PM measurement was omitted).

During the study, adverse events were defined as any change from baseline in a patient's ophthalmic or medical health, as identified by observations made by the investigator or complaints solicited from subjects. Adverse event and safety monitoring included measuring resting pulse and blood pressure and examining subjects for evidence of hyperemia, ocular flare or inflammatory cells, and best-corrected visual acuity. Slit-lamp examination, funduscopy, and iris/eyelash photographs were also performed. Baselines were recorded at the second eligibility visit, and monitoring occurred regularly throughout treatment.

Two trained individuals, a reader and an operator, using a recently calibrated Goldmann applanation tonometer (Haag Streit, Bern, Switzerland) measured intraocular pressure. Hyperemia was assessed in ambient light, before intraocular pressure measurements and instillation of fluorescein. Throughout the study, the same masked observer assessed the degree of hyperemia by comparing photographs of subjects' eyes with a standard set of photographs depicting ocular hyperemia. Hyperemia was graded on a scale of 0 to 3—0 = none/trace; 1 = mild; 2 = moderate; 3 = severe—and could be reported in 0.5-U increments. A clinically significant change from baseline in ocular hyperemia was defined as an increase of one or more units from the maximum hyperemia score recorded at any of the prerandomization visits.

Iris and eyelash changes were assessed at a central reading center by a group of masked ophthalmologists and scientists who had not examined the subjects nor were investigators in the study by comparing photographs obtained at baseline with photographs obtained during treatment. Changes were confirmed at the last patient visit.

Visual field evaluations were performed with either a Humphrey Field Analyzer (24-2 or 30-2) (Humphrey Instruments, Inc, San Leandro, California) equipped with STATPAC or FASTPAC or an Octopus (Program G1 or G1X) (Interzeag AG, Schlierien, Switzerland). Standard logMAR visual acuity was recorded. Macular edema was assessed by fundoscopy examination.

The statistical objectives for this study were to demonstrate superiority of travoprost 0.0015% and travoprost 0.004% to vehicle in lowering intraocular pressure and to determine if travoprost 0.004% was superior to 0.0015% in lowering intraocular pressure. Statistical analysis was based on measuring changes in mean intraocular pressure in the patient's eye with the highest mean intraocular pressure at baseline. Because the statistical objective was to determine the superiority of treatment with travoprost 0.0015% and 0.004% compared with treatment with vehicle, the statistical inferences were based on two-sided hypothesis tests using intent-to-treat data. Hypothesis tests were performed using repeated measures analysis of variance. Mean intraocular pressure was estimated by the least squares means from the repeated measures analysis of variance. The analysis plan was reviewed before database lock and breaking the mask for randomized treatment assignment to ensure compliance with the Principles for Statistical Analysis of Clinical Trials established by the International Conference on Harmonization. Clarifications to the plan were made at the time of review to address recent understanding of the regulatory interpretation for this study,[20,21] but the primary efficacy and safety analyses developed in the original analysis plan remained unchanged.

With 110 subjects per group, there was more than 90% power to detect a difference of 1.54 mm Hg between treatments. The sample sizes were based on a standard deviation of intraocular pressure of 3.5 mm Hg and a two-sample *t* test conducted at a 5% chance of a type 1 error.

RESULTS

FOUR HUNDRED TWENTY-SEVEN SUBJECTS WERE RANDOMized to travoprost 0.0015% (n = 142), travoprost 0.004% (n = 145), and vehicle (n = 139). Seventeen subjects had no data recorded while on treatment and thus were excluded from the intent-to-treat analysis (three in 0.0015%, nine in 0.004%, and five in vehicle groups).

Sixty-five subjects were excluded from the per protocol analysis because of protocol violations (20 in 0.0015%, 23 in 0.004%, and 22 in vehicle groups), which included nonqualifying intraocular pressure, inadequate time interval from dosing to intraocular pressure measurement, contraindicated concomitant medication, improper dosing

TABLE 1A. Demographic Comparisons: Age

Treatment	Mean	SD	N	Minimum	Maximum
Travoprost 0.0015%	63.9	11.7	139	11	84
Travoprost 0.004%	63.9	11.1	137	29	89
Vehicle	63.3	11.3	134	37	88

P = .8780 from analysis of variance for test of mean age differences among groups.

TABLE 1B. Demographic Comparisons: Statistics by Treatment Group

	Travoprost 0.0015%		Travoprost 0.004%		Vehicle		
	N	%	N	%	N	%	*P* Value
Age							
<65	70	50.4	65	47.4	71	53.0	.659*
≥65	69	49.6	72	52.6	63	47.0	
Age (≥65)							
≥65–<75	45	65.2	47	65.3	39	61.9	.721†
≥75–<85	24	34.8	23	31.9	24	34.9	
≥85–<95	0	0.0	2	2.8	2	3.2	
Sex							
Male	59	42.4	65	47.4	56	41.8	.588*
Female	80	57.6	72	52.6	78	58.2	
Race							
Caucasian	103	74.1	89	62.8	94	70.1	.301†
Black	27	19.4	35	25.5	32	23.9	
Asian	—	—	2	1.5	1	0.7	
Other	9	6.5	14	10.2	7	5.2	
Iris color							
Brown	72	51.8	85	62.0	64	47.8	.309*
Hazel	17	12.2	16	11.7	17	12.7	
Green	6	4.3	2	1.5	5	3.7	
Blue	44	31.7	33	24.1	46	34.3	
Grey	—	—	1	0.7	2	1.5	
Diagnosis							
Ocular hypertension	8	5.8	14	10.2	13	9.7	.447†
Open-angle glaucoma	126	90.6	118	86.1	116	86.6	
Pigmentary glaucoma	4	2.9	1	0.7	2	1.5	
Pseudoexfoliation glaucoma	1	0.7	4	2.9	3	2.2	

*P values from chi-square test of independence.
†P values from Fisher's exact test.

of timolol, inadequate run-in, improper dosing of study medication, laser surgery before a study visit, noncompliance to study medication, discontinued study medication, and one patient who did not receive study medications. Twenty-one of the twenty-four subjects who discontinued because of inadequate control of intraocular pressure were in the vehicle group. Tests on efficacy were based on the remaining 410 subjects. No significant demographic differences were noted among treatment groups. The groups were similar for age, sex, race, iris color, and diagnosis (Table 1).

Mean baseline values (mm Hg) for subjects at eligibility (while maintained on timolol) were not significantly different ($P < .0001$) in the study groups. Additional clinically relevant decreases in intraocular pressure in subjects already on timolol were observed with mean intraocular pressures ranging from 18.3 to 20.1 mm Hg for travoprost 0.0015% and 17.9 to 19.6 mm Hg for travoprost 0.004% compared with 22.4 to 24.1 mm Hg for vehicle (Table 2).

Both concentrations of travoprost reduced intraocular pressure below baseline values obtained after subjects had

TABLE 2. Mean Intraocular Pressure Comparisons of Travoprost 0.004% and Vehicle, Travoprost 0.0015% and Vehicle; and Travoprost 0.0015% and 0.004%

	IOP comparison between travoprost 0.004% and vehicle															
	Combined			Week 2			Month 1.5		Month 3			Month 4.5		Month 6		
Treatment	8 AM	10 AM	4 PM	8 AM	10 AM	4 PM	8 AM	10 AM	8 AM	10 AM	4 PM	8 AM	10 AM	8 AM	10 AM	4 PM
IOP comparison between travoprost 0.0014% and vehicle																
Travoprost 0.004%	19.2	18.1	18.5	19.3	18.1	18.4	18.8	17.9	19.2	17.9	17.9	19.0	18.3	19.6	18.3	18.9
Vehicle	23.8	22.9	22.8	24.1	23.1	22.6	23.6	22.8	23.8	22.9	22.4	23.6	22.8	23.8	23.0	23.1
0.004%–vehicle	−4.6	−4.8	−4.2	−4.8	−5.0	−4.2	−4.8	−4.8	−4.7	−5.0	−4.5	−4.6	−4.5	−4.2	−4.7	−4.2
P value	.0001	.0001	.0001	.0001	.0001	.0001	.0001	.0001	.0001	.0001	.0001	.0001	.0001	.0001	.0001	.0001
Upper 95% CI	−3.76	−3.95	−3.30	−3.77	−3.96	−3.22	−3.82	−3.85	−3.67	−4.00	−3.50	−3.56	−3.50	−3.21	−3.70	−3.17
Lower 95% CI	−5.44	−5.64	−5.17	−5.76	−5.95	−5.21	−5.81	−5.84	−5.66	−5.99	−5.49	−5.55	−5.49	−5.20	−5.69	−5.16
IOP comparison between travoprost 0.0015% and vehicle																
Travoprost 0.0015%	19.9	18.6	18.7	20.1	18.9	18.7	19.9	18.5	19.8	18.5	18.3	19.4	18.3	20.1	18.8	19.1
Vehicle	23.8	22.9	22.8	24.1	23.1	22.6	23.6	22.8	23.8	22.9	22.4	23.6	22.8	23.8	23.0	23.1
.0015%–vehicle	−3.9	−4.3	−4.1	−4.0	−4.2	−4.0	−3.7	−4.3	−4.0	−4.4	−4.1	−4.1	−4.5	−3.7	−4.2	−4.0
P value	.0001	.0001	.0001	.0001	.0001	.0001	.0001	.0001	.0001	.0001	.0001	.0001	.0001	.0001	.0001	.0001
Upper 95% CI	−3.06	−3.48	−3.16	−2.96	−3.18	−2.96	−2.73	−3.27	−3.02	−3.45	−3.07	−3.14	−3.52	−2.69	−3.20	−3.03
Lower 95% CI	−4.74	−5.15	−5.03	−4.94	−5.17	−4.94	−4.71	−5.25	−5.01	−5.43	−5.06	−5.12	−5.50	−4.68	−5.19	−5.02
IOP comparison between travoprost 0.004% and 0.0015%																
Travoprost 0.0015%	19.9	18.6	18.7	20.1	18.9	18.7	19.9	18.5	19.8	18.5	18.3	19.4	18.3	20.1	18.8	19.1
Travoprost 0.004%	19.2	18.1	18.5	19.3	18.1	18.4	18.8	17.9	19.2	17.9	17.9	19.0	18.3	19.6	18.3	18.9
0.004%–0.0015%	−0.7	−0.5	−0.1	−0.8	−0.8	−0.3	−1.1	−0.6	−0.7	−0.6	−0.4	−0.4	0.0	−0.5	−0.5	−0.1
P value	.0987	.2591	.7643	.1047	.1233	.5953	.0293	.2459	.1947	.2701	.3894	.3908	.9819	.3048	.3214	.7731
Upper 95% CI	0.13	0.35	0.79	0.17	0.21	0.72	−0.11	0.40	0.33	0.43	0.55	0.55	1.00	0.47	0.49	0.84
Lower 95% CI	−1.54	−1.31	−1.07	−1.80	−1.76	−1.25	−2.08	−1.57	−1.64	−1.54	−1.42	−1.42	−0.97	−1.50	−1.48	−1.13

IOP = intraocular pressure. CI = confidence interval; least squares means and confidence intervals from the repeated measures analysis of variance.

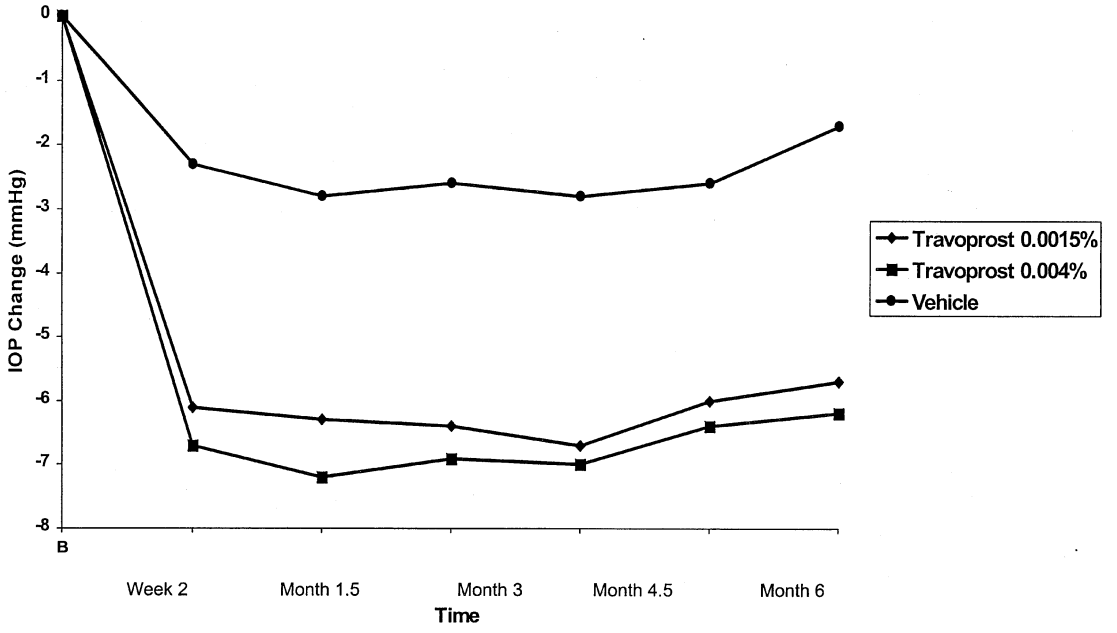

FIGURE 1. Intraocular pressure change at 8 AM. Mean intraocular pressure reductions were greatest in the travoprost 0.004% group with changes ranging from −5.7 to −7.2 mm Hg (23.1% to 27.7%) compared with −5.1 to −6.7 mm Hg (20.8% to 25.9%) for travoprost 0.0015%, and −1.3 to −2.8 mm Hg (5.4% to 10.9%) for vehicle ($P = .0001$). All intraocular pressure changes are least squares means from the corresponding diurnal baseline. Mean baseline values (mm Hg) were 25.0 (travoprost 0.0015%), 25.0% (travoprost) 0.004%, and 25.2 (placebo).

been treated twice daily for 3 weeks with timolol. Mean reductions were greatest in the travoprost 0.004% group with changes ranging from −5.7 to −7.2 mm Hg (23.1% to 27.7%) compared with −5.1 to −6.7 mm Hg (20.8% to 25.9%) for travoprost 0.0015%, and −1.3 to −2.8 mm Hg (5.4% to 10.9%) for vehicle (Figure 1; $P = .0001$). The reductions in mean intraocular pressure were present on all days for both concentrations of travoprost and were maintained for the entire 6-month study period. Although travoprost 0.004% produced a slightly greater reduction in mean intraocular pressure (up to 1.1 mm Hg greater) than travoprost 0.0015% on most study days, the difference between the two concentrations was not statistically significant ($P < .9819$; Table 2).

Per protocol data were analyzed to estimate and compare the percentage of subjects with a clinically relevant intraocular pressure response to treatment (test drug or vehicle) while maintained on timolol therapy. In the original analysis plan, a clinically relevant response to treatment was defined as a decrease from baseline of 6 mm Hg or greater or an intraocular pressure of 20 mm Hg or less. The percentage of subjects meeting these criteria over visit times and visit days in the travoprost 0.0015% group ranged from 66.2% to 82.7% and 73.0% to 86.9% in the travoprost 0.004% group compared with 23.1% to 43.3% for those who received vehicle. In addition, an analysis using more stringent criteria for response to treatment (30% or greater intraocular pressure reduction from diurnal baseline or a final intraocular pressure of 17 mm Hg or less) was conducted. Subjects treated with travoprost (0.0015% and 0.004%) had a significantly greater intraocular pressure response to treatment than subjects in the vehicle group ($P < .0001$). Subjects in the travoprost 0.0015% and 0.004% had an overall response to treatment of 40.2% and 47.8%, respectively, compared with 9.9% for subjects in the vehicle group. The response in the travoprost 0.004% group was marginally greater than in the 0.0015% group ($P = .0524$; Figure 2).

The most frequent side effect of treatment was ocular hyperemia. This occurred more frequently in the travoprost treatment groups than in subjects receiving only vehicle solution (Table 3). However, in all groups, mean hyperemia scores were less than 0.50 (on a scale from 0 to 3) during the 6-month treatment period. Hyperemia was more common with travoprost 0.004%, but compared with the 0.0015% concentration, the difference was not statistically significant ($P = .0516$.) Only one patient in the travoprost 0.0015% group, and two in the travoprost 0.004% group, discontinued treatment because of hyperemia.

Eyelash changes (color, length, density, and thickness) occurred more frequently in subjects receiving travoprost than in those receiving vehicle solution and were captured as an adverse event only if the patient discontinued the study because of these changes. No patient discontinued treatment because of eyelash changes. However, 51 of the 136 patients (37.5%) receiving travoprost 0.0015% and 72 of the 139 patients (51.8%) receiving travoprost 0.004%

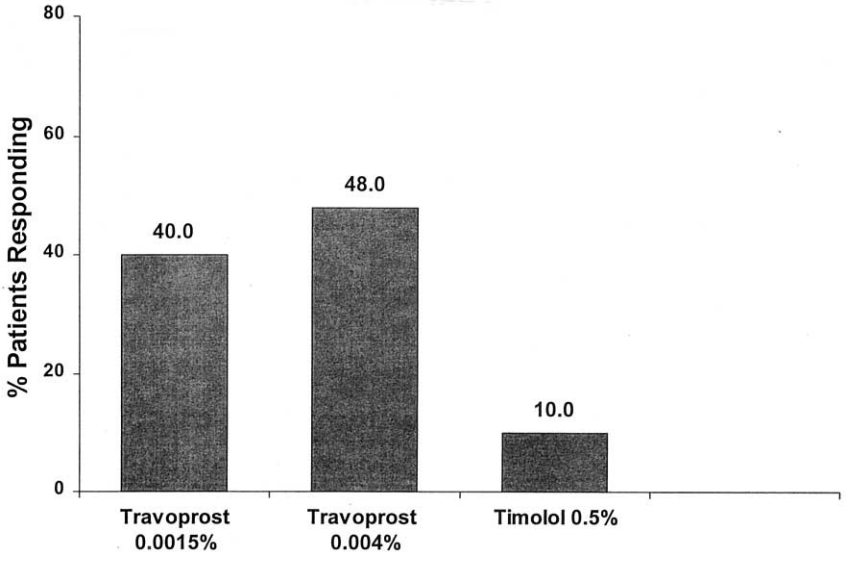

FIGURE 2. Responder analyses for travoprost (0.0015% and 0.004%) and timolol. The responder analyses were based on percent intraocular pressure reduction (30% or greater) or mean intraocular pressure (17 mm Hg or less). Subjects treated with travoprost (0.0015% and 0.004%) had a significantly greater intraocular pressure response to treatment than subjects in the vehicle group ($P < .0001$).

had eyelash changes noted by masked observers over the course of the study.

No patient experienced iris pigmentation changes during this 6-month study, and no clinically visible cystoid macular edema was reported. Among treatment groups, no clinically relevant or statistically significant differences were noted for pulse, systolic or diastolic blood pressure, visual acuity, inflammatory cells, aqueous flare, fundus parameters, cup-to-disk ratio, or visual fields. Other side effects were infrequent with no serious, unexpected adverse events.

DISCUSSION

TO OUR KNOWLEDGE, THIS IS THE LARGEST AND LONGEST controlled, clinical trial assessing the ability of a prostaglandin analogue to further lower intraocular pressure when used adjunctively with timolol. Significant additional intraocular pressure reductions from baseline of up to 28% were observed with both concentrations of travoprost in subjects whose intraocular pressure remained high despite timolol therapy.

Although the mechanism(s) of action of travoprost has not been determined, it is likely that increased uveoscleral outflow accounts for the decrease in intraocular pressure as has been observed with other $PGF_{2\alpha}$ analogues.[15] Therefore, when added to such drugs as timolol, which control intraocular pressure by the reduction of aqueous humor, it may be expected that there would be an additional intraocular pressure–lowering effect.

These findings suggest that travoprost has important benefits as adjunctive therapy. Although timolol has been considered first-line therapy for the control of intraocular pressure in patients with glaucoma, many require additional drugs to achieve adequate control. This study indicates that travoprost is effective in further lowering intraocular pressure in subjects already on timolol.

Furthermore, the study results suggest that travoprost is safe with no systemic effect on pulse, blood pressure, or airway responsiveness. Hyperemia is the most common side effect and is usually mild. Travoprost produced clinically relevant and statistically significant additional intraocular pressure reductions from baseline when used adjunctively with timolol, in subjects with open-angle glaucoma or ocular hypertension.

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TABLE 3. Frequency and Incidence of Adverse Events

	Travoprost 0.0015% (N = 142)		Travoprost 0.004% (N = 145)		Vehicle (N = 139)	
	N	%	N	%	N	%
Ocular						
Aqueous flare	5	3.5	0	0	0	0
Anterior chamber cells	7	4.9	6	4.1	1	0.7
Blurred vision	3	2.1	3	2.1	2	1.4
Discomfort	7	4.9	7	4.8	3	2.2
Dry eye	1	0.7	8	5.5	1	0.7
Foreign body sensation	3	2.1	4	2.8	1	0.7
Hyperemia	33	23.2	52	35.9	13	9.4
Keratitis	7	4.9	3	2.1	5	3.6
Lid disorder	0	0	3	2.1	0	0
Pain	3	2.1	6	4.1	1	0.7
Photophobia	0	0	4	2.8	0	0
Pruritus	4	2.8	5	3.4	2	1.4
Tearing	1	0.7	3	2.1	0	0
Visual acuity decrease	4	2.8	6	4.1	5	3.6
Nonocular						
Cold syndrome	4	2.8	3	2.1	1	0.7
Infection	7	4.9	3	2.1	3	2.2
Sinusitis	3	2.1	3	2.1	2	1.4
Surgical/medical procedure	5	3.5	4	2.8	6	4.3
Urinary tract infection	0	0	3	2.1	1	0.7

Includes all adverse events (related and nonrelated combined) reported at an incidence of 2.0% or greater. All N values represent numbers of patients.

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