

Comparison of Travoprost 0.0015% and 0.004% with Timolol 0.5% in Patients with Elevated Intraocular Pressure

A 6-Month, Masked, Multicenter Trial

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Objective: To compare the safety and intraocular pressure (IOP)-lowering efficacy of once-daily travoprost (0.0015% and 0.004%) to twice-daily timolol 0.5%.

Design: Prospective, 6-month, randomized, controlled, multicenter, double-masked, phase III study.

Participants: Six hundred five patients with open-angle glaucoma or ocular hypertension.

Methods: Patients with an 8 AM IOP between 24 to 36 mmHg in at least one eye (the same eye) at two eligibility visits received either travoprost 0.0015%, travoprost 0.004% (dosed every day), or timolol 0.5% (dosed twice daily).

Main Outcome Measures: Mean IOP at 8 AM, 10 AM, and 4 PM in the patient's eye with the higher baseline IOP.

Results: The mean IOP was significantly lower for both concentrations of travoprost compared with timolol. Travoprost was statistically superior to timolol at 9 of 13 visits, with differences in IOP reductions ranging from 0.9 to 1.8 mmHg (0.0015%) and 10 of 13 visits with differences in IOP reductions from 0.9 to 2.4 mmHg (0.004%). Mean IOP changes from baseline ranged from -6.0 to -7.5 mmHg (0.0015%), -6.5 to -8.0 mmHg (0.004%), and -5.2 to -7.0 mmHg for timolol. Hyperemia was experienced at rates of 29.2% (59 of 202) for travoprost 0.0015%, 42.8% (86 of 201) for travoprost 0.004%, and 8.9% (18 of 202) for timolol. Iris pigmentation changes were observed in 1.0% (2 of 200) of patients receiving travoprost 0.004% with no changes noted in the travoprost 0.0015% group or the timolol group. A decrease in pulse and systolic blood pressure was observed in the timolol group. There were no other clinically relevant or statistically significant changes from baseline in ocular signs or laboratory values, and no serious, related, unexpected adverse events were reported for any group.

Conclusions: Travoprost (0.0015% and 0.004%), dosed once daily in the evening, is statistically superior or equal to timolol 0.5% dosed twice daily at all treatment visits during this 6-month study. IOP reductions of up to 2.0 mmHg greater than timolol were found in the travoprost 0.004% pooled data group. Travoprost is safe and well tolerated in patients with open-angle glaucoma or ocular hypertension. *Ophthalmology* 2002;109:998-1008 © 2002 by the American Academy of Ophthalmology.

Elevated intraocular pressure (IOP) is a risk factor contributing to optic nerve damage and subsequent visual field loss. Therefore, control of IOP in patients with glaucoma or ocular hypertension is the primary goal of successful glaucoma therapy.¹⁻⁴

Topical nonselective β -blockers, such as timolol

(Timoptic, Merck and Company, Inc., Whitehouse Station, NJ) have been used as first-line therapy for elevated IOP because of their familiarity and IOP-lowering efficacy. The potential side effects of nonselective β -blockers on pulmonary, cardiovascular, and central nervous system function are well known. A reduction in cardiovascular output caused by heart block and/or fall in blood pressure may

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occur secondary to systemic absorption of topical nonselective β -blockers.^{5,6} Patients with reactive airway disease and chronic obstructive pulmonary disease may be at significant risk for further airway compromise.⁷⁻⁹ Consequently, this class of drugs is usually contraindicated in these patients.

Prostaglandin (PG) analogues represent a class of potent ocular hypotensive agents shown to effectively reduce IOP equivalent to nonselective β -adrenergic antagonists without the side effects associated with β -blockers.¹⁰

The most common side effects associated with PG analogues are ocular hyperemia, increased eyelash growth, eyelid skin darkening, and change in iris pigmentation. Anterior uveitis¹¹ and cystoid macular edema (CME)^{12,13} have been reported in some patients using PG analogues; thus their use may be contraindicated in those patients with a history of uveitis or recent ocular surgery.

Travoprost (Travatan, Alcon Research, Ltd., Fort Worth, Texas) is a synthetic PG analogue. The isopropyl ester prodrug is rapidly hydrolyzed by esterases in the cornea to the biologically active, free acid that is structurally similar to other PGF_{2 α} analogues. It has demonstrated preferential affinity and full agonist activity for the FP receptor in the nanomolar range, with no meaningful affinity for or activity on other receptors.¹⁴⁻¹⁶ The reduction of IOP by PGF_{2 α} is largely caused by increased uveoscleral outflow of aqueous humor^{17,18}; and because travoprost is a PGF_{2 α} analogue, it is thought that reduction of IOP by travoprost is primarily through the uveoscleral pathway.

This study was designed to evaluate the safety and IOP-lowering efficacy of two concentrations of travoprost (0.0015% and 0.004%) compared with timolol 0.5% in patients with open-angle glaucoma or ocular hypertension.

Patients and Methods

This 6-month, randomized, controlled, multicenter, double-masked, prospective, parallel group study was conducted in accordance with the ethical principles in the Declaration of Helsinki, the United States Code of Federal Regulations (21 CFR), and the guidelines in the International Conference of Harmonization under an Investigational New Drug (IND) exemption. Institutional review board approval was obtained at each site, and all patients or their legal representatives read, signed, and dated an institutional review board-approved consent form before study participation.

To be enrolled, patients were 21 years of age or older, of any race and either gender, diagnosed with ocular hypertension (OH) or open-angle glaucoma (OAG), with or without pseudoexfoliation or pigment dispersion component. Patients underwent a 5-day to 3-week washout from all ocular hypotensive therapy, followed by two diurnal IOP eligibility examinations. Patients were required to have an 8 AM entry IOP of 24 to 36 mmHg in at least one eye (the same eye) at both of the eligibility visits to provide a suitable target treatment population with a clinically significant elevation in IOP.

Exclusion criteria were chosen primarily for patient safety concerns and to further characterize the study population. Patients with IOP >36 mmHg in either eye during the eligibility phase were excluded on the basis of potential safety risk during this 6-month study. In addition, patients were excluded from the study if they had visual acuity worse than 0.60 logarithm of the minimum angle of resolution (logMAR) in either eye, a cup/disc ratio greater than 0.80 or severe central field loss in either eye, gonioscopy measured angle grade less than 2, a history of chronic or

recurrent inflammatory eye disease, severe retinal disease, or any abnormality that prevented reliable applanation tonometry or dosing in either eye. Patients who had experienced ocular trauma or had undergone incisional ocular surgery within the past 6 months or laser surgery within the past 3 months were also excluded. Patients had to discontinue contact lens wear before study medication instillation and up to 15 minutes after instillation, as well as on study visit days. Women of childbearing potential and patients with severe, unstable, or uncontrolled cardiovascular, hepatic, or renal disease; a history of bronchial asthma or advanced chronic obstructive pulmonary disease; or clinically significant hematologic, electrolyte, renal, or hepatic abnormalities were excluded. Patients with a history of hypersensitivity to any component of the test medications were also excluded. Patients were excluded if they were using any glucocorticoid during the eligibility phase or were on adjunctive therapy, either topical or systemic, for lowering IOP. At the time this study was planned, it was not known whether the use of topical, ocular nonsteroidal antiinflammatory agents would affect efficacy or safety; so patients using these drugs were excluded. Patients using any systemic medications that would affect IOP had to be on a stable dosing regimen for at least 1 month before the screening visit.

Safety assessments were selected to examine those parameters generally associated with the use of topical β -blockers, such as cardiovascular parameters of pulse and blood pressure, and topical PGs, such as ocular hyperemia, flare, and iris pigmentation or eyelash changes. Safety assessments also included visual acuity measurements and slit-lamp biomicroscopy. Dilated fundus examinations and visual field assessments were included to monitor the normal progression of glaucoma. Laboratory assessments of blood chemistry, hematology, and urinalysis were conducted to evaluate potential systemic effects. A change of one or more units from baseline values for any of these parameters was identified and reported as an adverse event.

Best-corrected visual acuity was measured as logMAR values at 8 AM, 10 AM, and 4 pm at the eligibility visits. The maximum change in visual acuity for the worse eye in each patient (either the right or the left eye that had the greatest decrease in visual acuity) was calculated as the change in logMAR lines (0.1 = 1 logMAR line) from baseline to the final visit. Any clinically significant decrease in visual acuity (3 or more logMAR lines) from baseline was identified and reported as an adverse event.

Two different, trained individuals (a reader and an operator) determined IOP measurements with a recently calibrated Goldmann applanation tonometer (Haag-Streit, Bern, Switzerland). Assessment of hyperemia was made in ambient light, before IOP measurements and instillation of fluorescein, by the same masked observer throughout the study using a standard set of photographs depicting ocular hyperemia. The hyperemia scale was 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 OH was defined as an increase of 1 or more units from the maximum hyperemia score recorded at any of the prerandomization visits.

Photographs (Polaroid Macro 5 SLR Camera, Polaroid 990 film, Polaroid Corp., Cambridge, MA) of each eye were taken to determine whether there were any changes in iris pigmentation or eyelash characteristics. Subsequent photographs were evaluated for any change from baseline by a group of ophthalmologists and scientists (masked) who had not examined the patients or were investigators in the study. All changes were confirmed at the last patient visit.

The visual field evaluation was performed with either a Humphrey Field Analyzer (Humphrey Instruments, Inc, San Leandro, CA) (24-2 or 30-2) equipped with STATPAC or FASTPAC or an Octopus perimeter (Interzeag AG, Schlieren, Switzerland) (Pro-

gram G1 or G1X). One-way analysis of variance was used to analyze change from screening baseline in visual field to the exit visit, and separate analyses were performed for each visual field device used. SmithKline Beecham Clinical Laboratories Clinical Trials Center analyzed all laboratory specimens (blood chemistry, hematology, and urinalysis), with each site receiving common training on collecting, processing, and shipping of specimens. Laboratory reports were evaluated, and out-of-range values were assessed.

Adverse events, defined as any change from baseline in a patient's ophthalmic or medical health during the course of the study, were obtained as solicited complaints or investigator observations and recorded by the investigator at each patient's visit. Patients were discontinued from the study if the investigator considered the patient at risk or the patient chose to discontinue the study for any reason.

Patients who met inclusion criteria at the screening visit and were currently on glaucoma therapy were subjected to the following washout periods: 3 weeks for topical β -blockers or PGs; 2 weeks for topical sympathomimetics or alpha agonists; and 5 days for miotics or carbonic anhydrase inhibitors (topical or oral).

The following eligibility evaluations were conducted and documented: best-corrected visual acuity (logMAR scale); biomicroscopy; resting pulse and blood pressure; dilated fundus examination; cup/disc ratio, automated perimetry; gonioscopy; bilateral IOP measurements at 8 AM, 10 AM, and 4 PM using Goldmann applanation tonometry; hematology and blood chemistry analysis; urinalysis; ocular hyperemia assessment; flare and cell assessment; and iris/eyelash photography.

Patients who met all study eligibility criteria were assigned a patient number and sequentially randomly assigned to one of three treatment groups in an equal (1:1:1) ratio by means of a computer-generated randomization schedule prepared by the Alcon Biostatistics Department. Randomization was stratified by site to ensure balanced treatment within each site. Medication description was concealed from the patient, investigator, and clinical study staff. Masked medication was packaged in identical Drop-Tainers and provided to the investigators along with sealed envelopes containing the medication description for each patient. The treatment code was not broken at any time during this study. Masked study medication, travoprost 0.0015% or travoprost 0.004% or timolol 0.5%, was dispensed in sequence to the patients according to patient number. To maintain masking, patients received bottles labeled "morning" and "evening." Patients randomly assigned to travoprost (0.0015% or 0.004%) received travoprost vehicle (placebo) in the morning and active medication in the evening. The vehicle formulation contained the same ingredients as the active test articles without the active component and was indistinguishable from the active drugs. The preservative for vehicle and active drug was benzalkonium chloride 0.015%. Patients randomly assigned to timolol received active medication in the morning and evening. Patients were instructed to dose with masked medication, 1 drop in each eye with the bottle labeled "morning" once daily at 8 AM and with the bottle labeled "evening" once daily at 8 PM. Patients were instructed not to instill the morning dose of medication on study visit days.

Safety and efficacy evaluations were conducted during the treatment phase of the study at week 2 and months 1.5, 3, 4.5, and 6. All patient examinations at week 2 and months 3 and 6 were conducted at 8 AM, 10 AM, and 4 PM (± 30 minutes). Patient examinations at months 1.5 and 4.5 were conducted at 8 AM and 10 AM (± 30 minutes). IOP measurements were taken at each examination at 8 AM, and "morning dose" study medications were instilled approximately 15 minutes after the IOP measurement. Examinations for the follow-up visits were performed and documented as follows: *week 2*—pulse and blood pressure, visual acuity

(logMAR scale), ocular hyperemia and flare/cell assessment, biomicroscopy, and IOP; *month 1.5*—pulse and blood pressure, visual acuity (logMAR scale), ocular hyperemia, and flare/cell assessment, biomicroscopy, iris/eyelash photographs, and IOP; *month 3*—pulse and blood pressure, visual acuity (logMAR scale), ocular hyperemia, flare/cell assessment, biomicroscopy, iris/eyelash photographs, and IOP; *month 4.5*—pulse and blood pressure, visual acuity (logMAR scale), ocular hyperemia, and flare/cell assessment, biomicroscopy, iris/eyelash photographs, and IOP; *month 6* (exit examination)—pulse and blood pressure, visual acuity (logMAR scale), ocular hyperemia, and flare/cell assessment, biomicroscopy, iris/eyelash photographs, IOP, hematology/blood chemistry, urinalysis, dilated fundus examination, cup/disc ratio, and visual field.

All statistical analyses were conducted as set forth in the signed and archived biostatistics analysis plan for this study. The analysis plan was reviewed before database lock. The International Conference on Harmonization established breaking the mask for randomized treatment assignment to ensure compliance with the Principles for Statistical Analysis of Clinical Trials. Clarifications to the plan were made at the time of review to address recent understanding of the regulatory interpretation for this study,^{19,20} but the primary efficacy and safety analyses developed in the original analysis plan remained unchanged.

A mixed-effects repeated measures analysis of variance model was used in the analysis of the efficacy parameter to make treatment group comparisons and to estimate confidence limits. Treatment group, visit day, and visit time of day were analyzed as fixed effects, and patient within treatment group was analyzed as a random effect to take into account the repeated measurements on a patient. Unless otherwise noted, all estimates presented in this report are based on least squares means from the repeated measures analysis of variance. All tests were conducted with a 5% chance of a type I error. A sequential testing strategy²¹ was used to control the type I error associated with multiple comparisons and was planned only for the primary comparisons of mean IOP between travoprost and timolol. No adjustments were made for the secondary analyses of IOP responder rates or for any of the safety analyses. Analysis of the safety parameters was conducted using analysis of variance models, Mantel-Haenszel chi-square tests, Pearson chi-square tests, or Fisher's exact tests, as appropriate, depending on the variable being analyzed. All analyses were performed using SAS for Windows, version 6.12 (SAS Institute, Inc., Cary, NC).

The sample size was chosen based on a greater than 90% probability that with 150 patients per group a 95% two-sided confidence interval would fall within ± 1.5 mmHg for a test of noninferiority. In this study, noninferiority was declared if the 95% confidence interval about the treatment difference lay entirely below +1.5 mmHg, which is considered smaller than a clinically meaningful change from baseline in IOP. This criterion is less than one half of the difference between timolol and placebo (based on data from the Timoptic Summary Basis of Approval), indicating that the noninferiority region is sufficient to exclude clinically insignificant differences from placebo. For a test of superiority, there was more than 90% power to detect a difference of 1.5 mmHg between treatments. The sample sizes were based on a standard deviation for IOP of 3.5 mmHg and a two-sample *t* test conducted at a 5% chance of a type I error.

The primary efficacy parameter was mean IOP at 8 AM, 10 AM, and 4 PM for the patient's worse eye defined as follows:

- The eye with the higher IOP at 8 AM averaged across both eligibility visits. If both eyes were equal, then,
- The eye with the higher IOP at 10 AM averaged across both eligibility visits. If both eyes were equal, then,

Table 1. Demographic Statistics of Each Treatment Group

Treatment	Age		N	Minimum	Maximum
	Mean*	Std			
Travoprost 0.0015%	62.9	12.4	198	21	87
Travoprost 0.004%	64.4	10.2	197	37	87
Timolol 0.5%	63.9	11.2	199	30	91

*P = 0.368 for test of mean age differences among groups.

	Treatment						P Value
	Travoprost 0.0015%		Travoprost 0.004%		Timolol 0.5%		
	N	%	N	%	N	%	
Age group							
<65	91	46.0	89	45.2	94	47.2	0.918
≥65	107	54.0	108	54.8	105	52.8	
<65	91	46.0	89	45.2	94	47.2	0.967
≥65–<75	71	35.9	76	38.6	68	34.2	
≥75–<85	34	17.2	29	14.7	34	17.1	
≥85–<95	2	1.0	3	1.5	3	1.5	
Gender							
Male	105	53.0	94	47.7	94	47.2	0.441
Female	93	47.0	103	52.3	105	52.8	
Race							
Caucasian	161	81.3	166	84.3	161	80.9	0.942
Black	23	11.6	17	8.6	23	11.6	
Asian	1	0.5	1	0.5	2	1.0	
Other	13	6.6	13	6.6	13	6.5	
Iris color							
Brown	80	40.4	88	44.7	91	45.7	0.401
Hazel	22	11.1	29	14.7	28	14.1	
Green	9	4.5	5	2.5	12	6.0	
Blue	81	40.9	67	34.0	64	32.2	
Grey	6	3.0	8	4.1	4	2.0	
Diagnosis (ICD9)							
Ocular hypertension	64	32.3	61	31.0	71	35.7	0.789
Open-angle glaucoma	131	66.2	129	65.5	122	61.3	
Pigmentary glaucoma	3	1.5	6	3.0	5	2.5	
Pseudoexfoliating glaucoma	—	—	1	0.5	1	0.5	

- The eye with the higher IOP at 4 PM averaged across both eligibility visits. If both eyes were equal, then the right eye was selected for analysis.

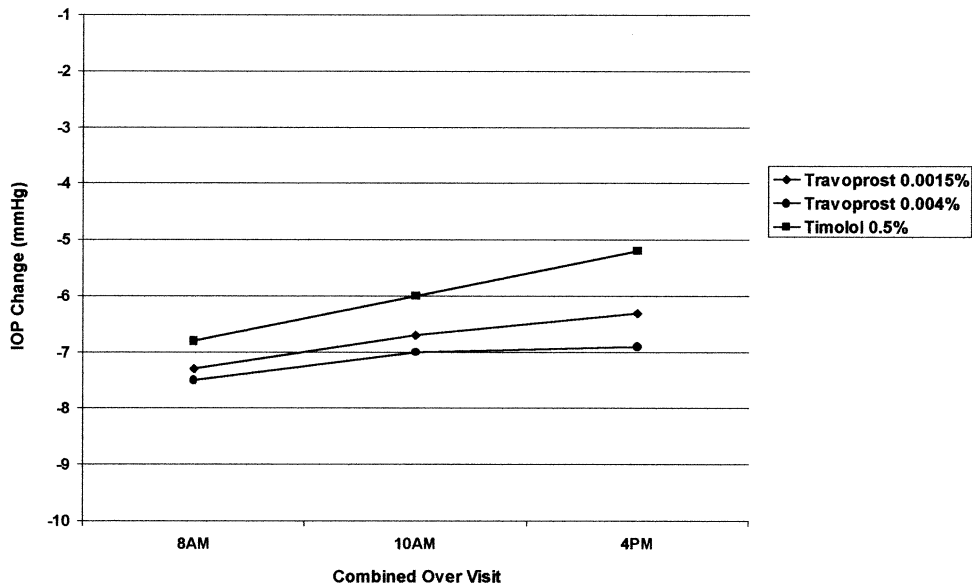
Three analysis data sets—safety, intent-to-treat (ITT), and per protocol—were used, and all patients received their assigned medication. The safety data set included all patients who received study medication; the ITT data set included all patients who received study medication and completed at least one on-therapy scheduled visit; and the per protocol data set included all patients who received study medication, completed at least one on-therapy scheduled visit, and satisfied protocol inclusion/exclusion criteria. The last observation-carried-forward was used to impute missing data in the ITT data set caused by missed visits or discontinued patients. Only those data points that satisfied protocol criteria (inclusion/exclusion criteria, proper dosing, etc.) were included in the per protocol data set. No imputation for missing data was done for the per protocol data set.

The primary hypothesis for this study was to show that travoprost (0.0015% and 0.004%) was equal to or better than (i.e., noninferior to) timolol. In accordance with established definitions,¹⁹ the per protocol data were used first to establish noninferiority, then the ITT data set was used to establish superiority. Because of the superiority findings in this study and the agreement

of the results between the ITT and per protocol analyses, the findings presented in this report are based on the ITT data except the responder analysis, which was based on per protocol data.

Results

Six hundred five patients were enrolled at 44 investigational sites: 202 patients in the travoprost 0.0015% group; 201 patients in the travoprost 0.004% group; and 202 patients in the timolol group. All 605 patients were included in the safety analysis. Eleven patients had no on-therapy study visit data and were therefore excluded from the ITT and per protocol analyses. Forty-eight patients were excluded from the per protocol analysis (12 in 0.0015%, 22 in 0.004%, and 14 in timolol group) because of protocol deviations that included nonqualifying IOP, inadequate time interval from dosing to IOP measurement, improper dosing of or noncompliance to study medication, and contraindicated concomitant medication. There were no significant differences among treatment groups for age, gender, race, iris color, or diagnosis (see Table 1 for demographics). From 4% to 6% of patients in each treatment group (4% in 0.0015%, 5% in 0.004%, and 6% in timolol 0.5%) were on a stable dosing regimen of oral β-blockers



No significant difference in baseline IOP between groups.

IOP reduction with travoprost 0.0015% and 0.004% was significantly greater than timolol at all three time points ($p \leq 0.0130$). There was no significant difference between travoprost groups.

Figure 1. Mean intraocular pressure (IOP) change from baseline for patients treated with evening-dosed travoprost 0.0015%, travoprost 0.004%, and timolol 0.5%, twice daily. The data are combined over the 6-month visits of the study. Travoprost 0.0015% significantly lowered IOP better than timolol 0.5% at 8 AM ($P \leq 0.0130$), 10 AM ($P \leq 0.0020$), and 4 PM ($P \leq 0.0001$). Travoprost 0.004% significantly lowered IOP better than timolol at 8 AM ($P \leq 0.0044$), and 10 AM and 4 PM ($P \leq 0.0001$).

before beginning the study and continued concomitant dosing during the study. When we excluded these patients from the analysis, there was no change in the statistical significance of the results. There were 161 patients who had not previously been on glaucoma medication (62 in the timolol group, 51 in travoprost 0.0015%, and 48 in travoprost 0.004% groups). Although there were differences in numbers of patients not previously on glaucoma medication, these differences were not significantly different between groups.

There was no significant difference among the groups in pre-treatment diurnal or baseline IOP. The mean IOP at 8 AM, 10 AM, and 4 PM, pooled across visit days, was significantly lower ($P < 0.0130$) (Fig 1) for both concentrations of travoprost compared with timolol. When treatment comparisons were considered individually at each visit day and time of day, travoprost 0.0015% was superior to timolol at 9 of 13 visits, with differences in IOP reductions ranging from 0.9 to 1.8 mmHg. Travoprost 0.004% was superior to timolol at 10 of 13 visits (and equal to timolol at the other 3 visits), with differences in IOP reductions ranging from 0.9 to 2.4 mmHg (Table 2). The pooled data also demonstrate that the IOP-lowering efficacy of travoprost, relative to timolol, improves over the course of the day, with the greatest treatment differences favoring travoprost at the 4 PM time point.

Significant IOP reductions from baseline were achieved with travoprost (0.0015% and 0.004%) and timolol 0.5% ($P < 0.0001$) (Table 3). Mean IOP changes observed for travoprost combined over visits ranged from -6.3 to -7.3 mmHg for the 0.0015% concentration and from -6.9 to -7.5 mmHg for the 0.004% concentration. For timolol, mean IOP changes ranged from -5.2 to -6.8 mmHg.

Reductions in IOP were greater in the travoprost 0.004% group

compared with the travoprost 0.0015% group. The by-visit analysis demonstrated that the mean IOP produced by travoprost 0.004% was lower than that produced by travoprost 0.0015% at 8 of 13 treatment visits by up to 0.7 mmHg in favor of the 0.004% concentration. In addition, the combined analysis collapsed across all visits demonstrated that travoprost 0.004% had better IOP control over the course of the day by up to 0.4 mmHg (Table 4).

In a posthoc analysis, patients were considered to have achieved a favorable response to therapy if they had a $\geq 25\%$ reduction in IOP from the diurnal baseline. Data were combined for all visits and time points to give an overall view of how patients responded to treatment from the beginning to the end of the study. Using these criteria, 62% to 65% of patients receiving 0.004% travoprost achieved greater than a 25% reduction in IOP at the 8 AM, 10 AM, and 4 PM time points. This compares with 38% to 48% of timolol patients (Table 5). Few patients discontinued therapy because of lack of IOP control: 2 of 202 (0.9%) in travoprost 0.0015%, 2 of 201 (0.9%) in travoprost 0.004%, and 4 of 202 (1.9%) in the timolol 0.5% group. The most prevalent ocular adverse events included hyperemia, pruritus, discomfort, and ocular pain. No serious, related, unexpected adverse events were reported for either travoprost (0.0015% or 0.004%) or timolol. Table 6 identifies combined related and unrelated ocular adverse events that occurred at an incidence of greater than 2% in any study group.

Fourteen patients were discontinued from the study because of treatment-related adverse events. Three of the 202 patients (1.5%) from the travoprost 0.0015% study group were discontinued: 1 patient experienced moderate, intermittent ocular discomfort; 1 patient experienced moderate ocular hyperemia and pruritus; and 1 patient experienced moderate headache and abdominal pain. Nine

Table 2. Mean Intraocular Pressure Comparison of Travoprost (0.0015% and 0.004%) and Timolol 0.5%

Treatment	Baseline*		
	8 AM	10 AM	4 PM
Travoprost 0.0015%	27.1	25.5	24.8
Travoprost 0.004%	27.2	25.5	25.0
Timolol 0.5%	27.4	25.8	25.3

*No significant differences were observed among treatment groups (P = 0.4302).

Treatment	Combined			Week 2			Month 1.5			Month 3			Month 4.5		Month 6		
	8 AM	10 AM	4 PM	8 AM	10 AM	4 PM	8 AM	10 AM	4 PM	8 AM	10 AM	4 PM	8 AM	10 AM	8 AM	10 AM	4 PM
Travoprost 0.0015%	19.80	18.80	18.50	19.90	18.80	18.30	19.80	18.60	19.50	18.80	18.20	19.90	18.70	19.90	18.90	18.80	
Timolol 0.500%	20.60	19.80	20.10	20.80	20.00	20.00	20.30	19.70	20.70	19.80	19.60	20.70	20.00	20.50	19.50	20.10	
0.0015%-TIM	-0.80	-1.00	-1.60	-0.90	-1.20	-1.80	-0.60	-1.10	-1.20	-1.00	-1.40	-0.80	-1.30	-0.60	-0.60	-1.30	
P value	0.013	0.002	0.000	0.020	0.003	0.000	0.153	0.006	0.008	0.014	0.000	0.032	0.001	0.099	0.107	0.008	
Upper 95% CI	-0.17	-0.37	-0.91	-0.15	-0.41	-1.00	0.21	-0.30	-0.40	-0.20	-0.62	-0.07	-0.52	0.12	0.14	-0.54	
Lower 95% CI	-1.46	-1.66	-2.34	-1.66	-1.93	-2.52	-1.31	-1.82	-1.92	-1.72	-2.14	-1.59	-2.04	-1.40	-1.38	-2.06	

Least squares means and confidence intervals from the repeated measures analysis of variance.

CI = confidence interval.

Treatment	Combined			Week 2			Month 1.5			Month 3			Month 4.5		Month 6		
	8 AM	10 AM	4 PM	8 AM	10 AM	4 PM	8 AM	10 AM	4 PM	8 AM	10 AM	4 PM	8 AM	10 AM	8 AM	10 AM	4 PM
Travoprost 0.004%	19.70	18.50	18.10	19.20	18.20	17.60	19.40	18.10	19.70	18.50	18.10	19.90	18.80	20.10	18.90	18.50	
Timolol 0.500%	20.60	19.80	20.10	20.80	20.00	20.00	20.30	19.70	20.70	19.80	19.60	20.70	20.00	20.50	19.50	20.10	
0.004%-TIM	-0.90	-1.30	-2.00	-1.50	-1.80	-2.40	-0.90	-1.60	-1.00	-1.20	-1.50	-0.80	-1.20	-0.40	-0.60	-1.50	
P value	0.004	0.000	0.000	0.000	0.000	0.000	0.023	0.000	0.008	0.001	0.000	0.030	0.002	0.284	0.154	0.000	
Upper 95% CI	-0.29	-0.63	-1.32	-0.76	-1.08	-1.63	-0.12	-0.80	-0.27	-0.48	-0.78	-0.08	-0.42	0.34	0.21	-0.77	
Lower 95% CI	-1.58	-1.92	-2.75	-2.28	-2.60	-3.16	-1.65	-2.32	-1.79	-2.00	-2.30	-1.60	-1.94	-1.18	-1.31	-2.29	

CI = confidence interval

Table 3. Mean Intraocular Pressure Change from Baseline (Intent-to-treat Data)

Treatment	Change from Baseline																				
	Baseline			Combined			Week 2			Month 1.5			Month 3			Month 4.5		Month 6			
	8 AM	10 AM	4 PM	8 AM	10 AM	4 PM	8 AM	10 AM	4 PM	8 AM	10 AM	4 PM	8 AM	10 AM	4 PM	8 AM	10 AM	8 AM	10 AM	4 PM	
AL-6221 0.0015%																					
Mean	27.10	25.5	24.8	-7.3	-6.7	-6.3	-7.2	-6.7	-6.5	-7.3	-6.9	-7.5	-6.7	-6.5	-7.2	-6.8	-7.2	-6.6	-6.0		
P value*	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
AL-6221 0.004%																					
Mean	27.2	25.5	25.0	-7.5	-7.0	-6.9	-8.0	-7.4	-7.3	-7.8	-7.4	-7.5	-7.0	-6.9	-7.4	-6.8	-7.1	-6.6	-6.5		
P value*	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Timoptic 0.5%																					
Mean	27.4	25.8	25.3	-6.8	-6.0	-5.2	-6.6	-5.8	-5.3	-7.0	-6.1	-6.7	-6.0	-5.7	-6.7	-5.8	-6.8	-6.3	-5.2		
P value*	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—

Least squares means (intraocular pressure change) from repeated measures analysis of variance.

*P = 0.0001 for all time points

Table 4. Comparison of Mean Intraocular Pressure for Travoprost 0.004% and 0.0015% (Intent-to-Treat Data)

Treatment	Combined			Week 2			Month 1.5		Month 3			Month 4.5		Month 6		
	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
AL-6221 0.004%	19.70	18.50	18.10	19.20	18.20	17.60	19.40	18.10	19.70	18.50	18.10	19.90	18.80	20.10	18.90	18.50
AL-6221 0.002%	19.80	18.50	18.50	19.90	18.80	18.30	19.80	18.60	19.50	18.80	18.20	19.90	18.70	19.90	18.90	18.80
0.004%–0.002%	–0.10	–0.30	–0.40	–0.60	–0.70	–0.60	–0.30	–0.50	0.10	–0.30	–0.20	–0.00	0.10	0.20	0.10	–0.20
P value	0.712	0.436	0.264	0.114	0.082	0.101	0.394	0.203	0.749	0.463	0.669	0.978	0.797	0.567	0.8564	0.546
Upper 95% CI	0.52	0.39	0.31	0.15	0.09	0.12	0.43	0.27	0.89	0.48	0.60	0.75	0.86	0.98	0.83	0.53
Lower 95% CI	–0.77	–0.90	–1.13	–1.38	–1.44	–1.40	–1.09	–1.26	–0.64	–1.05	–0.93	–0.77	–0.66	–0.54	–0.69	–1.00

Least squares means and confidence intervals from the repeated measures analysis of variance.

CI = confidence interval

Table 5. Percent Intraocular Pressure Change from Baseline (mmHg)

Percent Intraocular Pressure Change (mmHg)	Travoprost 0.0015%		Travoprost 0.004%		Timolol 0.5%	
	N	%	N	%	N	%
8 AM						
≥ 25%	103	54.2	111	62.0	90	47.9
≥ 15% to <25%	68	35.8	52	29.1	74	39.4
< 15%	19	10.0	16	8.9	24	12.8
10 AM						
≥ 25%	103	54.2	112	62.9	76	40.6
≥ 15% to <25%	69	36.3	47	26.4	69	36.9
< 15%	18	9.5	19	10.7	42	22.5
4 PM						
≥ 25%	87	45.8	115	64.6	70	37.6
≥ 15% to <25%	75	39.5	41	23.0	57	30.6
< 15%	28	14.7	22	12.4	59	31.7

Table 6. Frequency and Incidence of Ocular Adverse Events*

Ocular	Travoprost 0.0015% (n = 202)		Travoprost 0.004% (n = 201)		Timolol 0.5% (n = 202)	
	N	%	N	%	N	%
Hyperemia	60	29.7	87	43.3	18	8.9
Pruritus	7	3.5	12	6.0	5	2.5
Pain	3	1.5	12	6.0	1	0.5
Visual acuity Decrease	9	4.5	10	5.0	9	4.5
Keratitis	6	3.0	9	4.5	4	2.0
Foreign body Sensation	4	2.0	6	3.0	2	1.0
Dry eye	3	1.5	6	3.0	4	2.0
Blurred vision	6	3.0	5	2.5	6	3.0
Discomfort	5	2.5	5	2.5	9	4.5

Includes all ocular adverse events (related and nonrelated combined) occurring with a frequency >2.0%

MEAN HYPEREMIA SCORE AT 8 AM

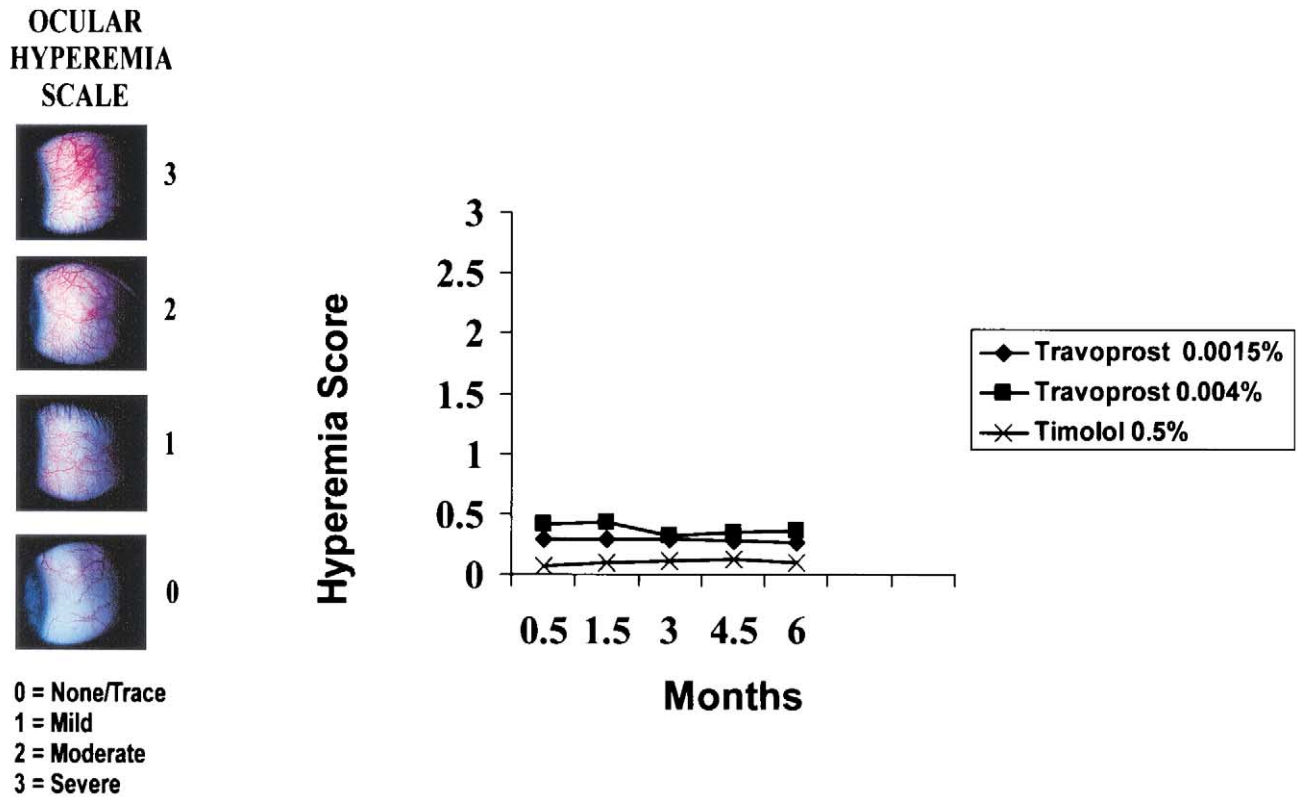


Figure 2. Average hyperemia scores for travoprost and timolol. Using the scale included in this figure, hyperemia was assessed at the 8 AM, 10 AM, and 4 PM visits with 0 = none to trace, 1 = mild, 2 = moderate, and 3 = severe. The mean hyperemia score was less than 1 for travoprost and timolol, with most patients experiencing none/trace to mild hyperemia.

of the 201 patients (4.5%) from the travoprost 0.004% group discontinued the study for reasons including, malaise, ocular hyperemia and ocular pain, moderate allergic conjunctivitis, foreign body sensation, moderate arrhythmia, hypotension, and asthenia. Two of the 202 patients (1.0%) from the timolol study group were discontinued: 1 patient experienced dizziness, asthenia, and ocular discomfort, and 1 patient experienced moderate bradycardia, hypotension, and dizziness.

Clinically significant increases from baseline in ocular hyperemia (defined as an increase of 1 or more units from the maximum hyperemia score recorded at any one time point at the baseline visits) were reported as an adverse event. Twenty-nine percent (59 of 202) of the patients receiving travoprost 0.0015%, 43% (86 of 201) of patients receiving travoprost 0.004%, and 9% (18 of 202) of the patients receiving timolol experienced a clinically significant increase in ocular hyperemia. One percent (2 of 202) of the patients receiving travoprost 0.0015% and 3.0% (6 of 201) of the patients receiving travoprost 0.004% were discontinued from the study because of ocular hyperemia (Fig 2). No patients receiving timolol were discontinued from the study because of OH.

Iris pigmentation changes were observed in 1.0% (2 of 200) of patients receiving travoprost 0.004%. The iris color of these two patients at the beginning of the study was blue/gray-brown and yellow brown. No change in iris pigment was noted in the travoprost 0.0015% group or the timolol group. Changes in eyelash characteristics, including length, thickness, density, and color, were reported in 36% (73 of 201) of the patients receiving

travoprost 0.0015%, 51% (102 of 200) of the patients receiving travoprost 0.004%, and 2.0% (4 of 201) of the patients receiving timolol. No patients were discontinued from the study because of eyelash changes or changes in iris pigmentation.

There were no clinically relevant or statistically significant differences observed between the three treatment groups for visual acuity, inflammatory cells and aqueous flare, ocular signs, fundus parameters, and cup/disk ratio. For visual fields, the mean standard deviation at the exit visit was compared with the baseline visit (for either Humphrey or Octopus) for the treatment groups, and there were no significant differences between the treatment groups for changes in visual fields. In addition, there were no clinically significant treatment-related changes from baseline in laboratory values (hematology, blood chemistry, urinalysis). CME was not reported in any of the treatment groups.

Cardiovascular effects of travoprost (0.0015% and 0.004%) and timolol were evaluated at screening, baseline, and all subsequent visits. No clinically or statistically significant difference in pulse or blood pressure was noted with either concentration of travoprost. Patients in the timolol group had a statistically significant decrease in pulse measurements ($P = 0.0001$) and systolic blood pressure ($P = 0.0022$) compared with patients in the travoprost groups when pulse and systolic blood pressure were averaged for patients in these groups. No serious, related, unexpected adverse events were reported for either travoprost (0.0015% or 0.004%) or timolol.

Discussion

The reduction and control of elevated IOP in OAG and ocular hypertension is classically managed by chronic, long-term topical ocular therapy using β -adrenergic blocking drugs. Analogues of prostaglandin PGF 2α represent a class of drugs capable of effectively reducing IOP better than timolol in some patients with OAG and ocular hypertension without the systemic side effects of nonselective β -blocking drugs.

This 6-month pivotal study evaluated the safety and efficacy of two concentrations of travoprost (0.0015% and 0.004%) compared with timolol for the treatment of OAG or ocular hypertension. The results demonstrate that both concentrations of travoprost are statistically superior to timolol, with IOP lowering up to 2.0 mmHg greater for travoprost 0.004% than timolol. In addition, more patients responded to treatment in the travoprost groups than in the timolol group. Although response rates are by necessity arbitrary, they are often used as an indication of how patients, in general, respond to a particular therapy.²²

A difference of as much as 2.0 mmHg (mean change of 7.3 mmHg for travoprost 0.004% and 5.3 mmHg for timolol) was observed between the travoprost 0.004% and timolol groups at 4 PM. Because this does not represent the peak or trough for either of these two medicines, a comparison at this time point is more valid than at 8 AM, which represents the trough for timolol and the likely peak for travoprost.¹⁷

In this 6-month study, iris pigmentation changes were observed in 1.0% of patients receiving travoprost 0.004% and none receiving travoprost 0.0015%. The iris color of these two patients was already a mixture of brown as has been reported to be the case with those who experienced iris color changes with ocular PG analogues.²²⁻²⁴ Although eyelash changes were reported, these are common effects also observed with ocular PG analogues and did not seem to pose any safety issues to the patient or interfere with daily activities.

Hyperemia was the most common adverse event reported. However, most patients experienced between none and trace to mild hyperemia, and most continued in the study. Notably, there were no other clinically or statistically significant increases in the safety parameters tested.

Topical administration of nonselective β -blockers such as timolol is known to precipitate respiratory and/or other cardiovascular complications. On average, there was a significant decrease in pulse and systolic blood pressure with timolol. In contrast, one patient discontinued travoprost because of a drop in systemic blood pressure. On average, there was no significant decrease in pulse and systolic blood pressure with either concentration of travoprost.

CME has been reported in some patients using PG analogues,^{12,13} but was not seen in any patient in this study. The absence of CME might be expected in this group of patients who were selected using stringent inclusion and exclusion criteria so that the efficacy and safety results could be interpreted without the introduction of other variables. It remains to be seen whether some susceptible patients (pseudophakic or aphakic) develop CME with widespread use of this medication.

This study indicates that travoprost (0.0015% and 0.004%), dosed once daily in the evening, is statistically superior or equal to timolol 0.5%, dosed twice daily at all treatment visits, with IOP reductions up to 2.0 mmHg greater than timolol in the 0.004% pooled data group. Travoprost was associated with significantly more hyperemia and eyelash growth than timolol and was safe and well tolerated when used as primary therapy in patients with OAG or ocular hypertension.

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