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Response to Travoprost in Black and Nonblack Patients With Open-Angle Glaucoma or Ocular Hypertension

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ABSTRACT

Two prospective, controlled, multicenter, double-masked studies—one lasting 6 months (n=594) and the other, 12 months (n=787)—examined the intraocular pressure (IOP)–lowering efficacy of travoprost in 1381 black and nonblack patients with open-angle glaucoma or ocular hypertension. Investigated regimens were travoprost 0.004% once daily, latanoprost 0.005% once daily, and timolol 0.5% twice daily. In both studies, mean IOP was significantly lower in blacks treated with travoprost. The IOP reduction was also significantly greater in blacks after adjustments for age, sex, iris color, diagnosis, and corneal thickness. Timolol lowered mean IOP to a greater extent in nonblack patients. The significantly larger IOP reduction with travoprost compared with timolol in both racial groups was more pronounced in blacks. Travoprost also was superior to latanoprost in blacks. Mean changes from baseline generally were greater for black than for nonblack patients, although the differences did not achieve statistical significance. The response rate to travoprost was higher in blacks. The most common adverse effect was hyperemia.

Keywords: open-angle glaucoma; ocular hypertension; black; nonblack; travoprost; latanoprost; timolol

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INTRODUCTION

Glaucoma is a leading cause of visual impairment and blindness in black populations,[1,2] and at diagnosis, glaucomatous damage is more advanced in black than in nonblack patients.[3,4] In the Barbados Eye Study,[5] which enrolled a majority black population, risk factors for open-angle glaucoma included age, male sex, elevated intraocular pressure (IOP), family history, lean body mass, and history of cataract. Only IOP and perhaps body mass are amenable to change.

Patients with elevated IOP are often treated with one or more topical medications. In the laser-induced ocular hypertensive monkey model,[6] dose-related IOP reductions of 17% to 30% were obtained following twice-daily administration of 0.00033% to 0.001% concentrations of travoprost (0.1- and 0.3-µg doses).

Two dose-response and three phase III pivotal clinical trials of travoprost monotherapy have been conducted. As required by the US Food and Drug Administration, subgroup analyses (age, sex, iris color, race, and diagnosis) were included and showed no significant differences in IOP lowering except for race. One of the pivotal studies, a 9-month international trial,[7] enrolled only seven black patients, however, and its race subgroup results are not part of this report.

Pooled data from the dose-response studies demonstrated that mean IOP lowering increased significantly with increasing travoprost concentration in both racial groups, although the concentration–IOP response relationship was more pronounced in black than in nonblack patients.[8]

This report used data from two pivotal studies, one lasting 6 months, the other, 12 months, to examine differences in response to travoprost among black and nonblack patients and to compare these responses with those to latanoprost and timolol.

PATIENTS AND METHODS

These randomized, controlled, multicenter, double-masked, prospective, parallel-group studies were conducted in accordance with the principles articulated in the Declaration of Helsinki, the US Code of Federal Regulations, and the guidelines of the International Conference on Harmonization, under an Investigational New Drug exemption. Institutional review board approval was obtained at each site, and all patients or their legal representatives signed a consent form prior to participation. The designs of these studies have been published.[9,10]

Procedures

In both studies, an initial screening visit and two eligibility visits were followed by evaluations at week 2 and at months 1.5, 3, 4.5, and 6, with additional visits at months 9 and 12 in the 1-year study. Patients were seen at 8 AM and 10 AM at the eligibility and all on-therapy visits; 4 PM assessments were performed at eligibility, at week 2, and at months 3, 6, and 12.

Safety assessments concerned parameters believed to be affected by topical beta-adrenergic–blocking agents, such as pulse and blood pressure, or by topical prostaglandin analogues, such as ocular hyperemia, inflammatory cells, and flare and iris pigmentation or eyelash changes. Visual acuity was also measured and slit-lamp biomicroscopy performed. Dilated-fundus and visual-field examinations were included

to monitor the normal progression of glaucoma. Any clinically relevant change from baseline on any of these parameters was reported as an adverse event. In general, the eye with the worse outcome was selected for analysis of ocular safety.

Best-corrected baseline visual acuity was measured as logMAR values at 8 AM during the second eligibility visit. The eye with the greater decrease from baseline to the final visit was selected, and the change in logMAR lines (0.1=1 logMAR line) was analyzed. Any clinically relevant decrease (three or more logMAR lines) from baseline was reported as an adverse event.

Two trained individuals (operator and reader) measured IOP with a recently calibrated Goldmann applanation tonometer (Haag-Streit, Bern, Switzerland). Throughout the study, the same masked observer used a standard set of photographs to assess hyperemia in ambient light prior to IOP measurements and instillation of fluorescein. The hyperemia scale (0=none/trace; 1=mild; 2=moderate; 3=severe) could be reported in 0.5-unit increments. A clinically relevant change from baseline was defined as an increase of one or more units from the maximum hyperemia score recorded at any timepoint during the second eligibility visit. A pachymeter was used to measure central corneal thickness in patients participating in the 12-month study.

Photographs (Polaroid® Macro 5 SLR Camera, Polaroid® 990 film; Polaroid Corp, Cambridge, Mass) of each eye tracked potential changes from baseline in iris pigmentation or eyelash characteristics. The photographs were evaluated by a group of ophthalmologists and scientists who were masked to treatment and were not study investigators. All changes had to be confirmed at the last visit.

Visual fields were evaluated with either a Humphrey Field Analyzer (24-2 or 30-2; Humphrey Instruments, Inc, San Leandro, Calif), equipped with STATPAC or FASTPAC, or an Octopus perimeter (program G1 or G1X; Interzeag AG, Schlierien, Switzerland). Results were analyzed as change from baseline to exit; separate analyses were performed for each device.

Blood chemistry and hematologic values and urinalysis were determined in both studies to evaluate potential systemic effects. SmithKline Beecham Clinical Laboratories analyzed all specimens; each study site received common training on collection, processing, and shipping of specimens. Out-of-range laboratory values were followed up with the patient.

Adverse events—any change from baseline in a patient's ophthalmic or medical health during the study—were obtained as solicited complaints or investigator observations and recorded at each visit. Discontinuation from the study occurred if the investigator considered the patient to be at risk or if the patient chose to withdraw for any reason.

Inclusion Criteria

Both studies enrolled patients of either sex and any race with a diagnosis of open-angle glaucoma (with or without pigment dispersion or pseudoexfoliation) or ocular hypertension. The patients identified themselves as black or nonblack (white, Asian, other). An IOP of 24 to 36 mm Hg was required in at least one eye (same eye) at 8 AM on two eligibility visits at least 7 days apart. (Patients who met this criterion in only one eye were eligible.) IOP also had to be 21 to 36 mm Hg, inclusive, in the same eye(s) at the 10 AM and 4 PM examinations on both eligibility visits. IOP in both eyes had to be 36 mm Hg or lower at all times.

In the 6-month study, patients removed contact lenses before instilling study medication and waited at least 15 minutes afterward before replacing them. Contact lenses were not allowed on study visit days. Patients who met inclusion criteria at screening underwent a washout of appropriate length, during which all glaucoma medications were discontinued (3 weeks for beta-antagonists and prostaglandin analogues, 2 weeks for alpha- and alpha-beta-agonists, 5 days for miotics and oral or topical carbonic anhydrase inhibitors; 3 days if no ocular hypotensive medications were used).

Exclusion Criteria

Exclusion criteria were chosen primarily for reasons of safety and to further characterize the study population. Women of childbearing potential were excluded, and all female participants were either postmenopausal for 1 year or had been surgically sterilized at least 3 months prior to enrollment. Patients with IOP exceeding 36 mm Hg in either eye during the eligibility phase were excluded, as were those with a best-corrected visual acuity worse than 0.60 logMAR (approximately 20/80 Snellen equivalent) in either eye.

Other reasons for exclusion were chronic or recurrent severe inflammatory eye disease; ocular trauma within the past 6 months; ocular infection or inflammation within the past 3 months; progressive retinal disease or severe ocular disease in either eye that would preclude administration of a topical beta-blocker or prostaglandin; cup:disc ratio greater than .80 in either eye; intraocular surgery within the past 6 months; history of severe or serious hypersensitivity to prostaglandin analogues or systemic beta-blockers; history of severe, unstable, or uncontrolled cardiovascular, hepatic, or renal disease; and bronchial asthma or severe chronic obstructive pulmonary disease that would preclude the safe administration of a topical beta-blocker.

Use of any glucocorticoid during the eligibility phase or use during the study of topical ocular nonsteroidal anti-inflammatory agents that inhibit cyclooxygenase and prostaglandin synthesis was another reason for exclusion. Prior to the first eligibility visit, long-term glucocorticoid therapy was discontinued for at least 4 weeks. Patients who used any ocular hypotensive therapy except for study medications during the study or who had received hypotensive therapy with another investigational agent within 30 days prior to screening were also excluded.

12-Month Study

Patients from 44 sites were assigned to one of four treatment groups: travoprost 0.0015%; travoprost 0.004%; latanoprost 0.005%; timolol 0.5%. The results presented herein are for travoprost 0.004%, the commercially available concentration. Travoprost and latanoprost were administered at 8 PM; timolol was administered at 8 AM and 8 PM. Patients receiving travoprost or latanoprost instilled vehicle at 8 AM to maintain masking. The primary efficacy variable was diurnal IOP at 8 AM, 10 AM, and 4 PM in the eye with the higher IOP at baseline.

6-Month Study

Patients from 39 sites were assigned to one of three treatments: travoprost 0.0015%, travoprost 0.004%, timolol 0.5%. The dosage schedule and the primary efficacy variable were as in the 12-month study.

Statistical Analysis

Repeated-measures analysis of variance (ANOVA) was used to make treatment-group comparisons of IOP and to estimate confidence limits, and unless otherwise noted, all estimates in this report are based on least-squares means from this ANOVA. Safety was analyzed by means of ANOVA models, Mantel-Haenszel ^{2} tests, Pearson ^{2} tests, or Fisher's exact tests, as appropriate. SAS® for Windows (SAS Institute, Inc, Cary, NC) was used for all analyses.

Sample sizes were based on a greater than 90% probability that a 95% two-sided confidence interval would fall within ±1.5 mm Hg for tests of noninferiority. For tests of superiority, the power to detect a 1.5-mm Hg difference between treatments was more than 90%. The sample sizes were based on a standard deviation for IOP of 3.5 mm Hg and a two-sample *t* test conducted at a 5% chance of a type I error.

Prospective subgroup analyses by race, age, sex, iris color, and diagnosis were conducted as planned.

RESULTS

Demographics (Table 1)

In the 12-month study, 801 patients were randomized to treatment, and 14 were excluded from the intention-to-treat analysis because of no on-therapy visits; the resulting data set contained 177 black and 610 nonblack patients.

In the 6-month study, 605 patients were randomized to treatment, and 11 were excluded from the intention-to-treat analysis because of no on-therapy visits; the resulting data set contained 63 black and 531 nonblack patients.

Table 1. Demographic Data

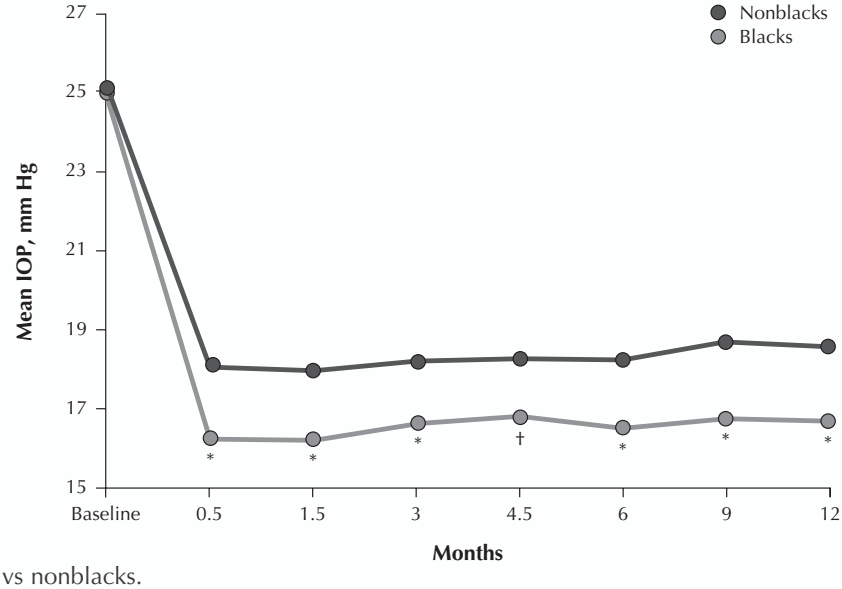
	Clinical Trial, no. (%)	
	6 Months	12 Months
ITT, no.	594	787
Age, y		
11–64	274 (46.1)	350 (44.5)
65–94	320 (53.9)	437 (55.5)
Sex		
Male	293 (49.3)	392 (49.8)
Female	301 (50.7)	395 (50.2)
Race		
Black	63 (10.6)	177 (22.5)
Nonblack	531 (89.4)	610 (77.5)
Diagnosis		
OH	196 (33.0)	247 (31.4)
OAG	398 (67.0)	540 (68.6)

ITT = intention to treat; OH = ocular hypertension; OAG = open-angle glaucoma.

12-Month Study

Baseline IOP was not significantly different in black and nonblack patients treated with travoprost 0.004% (P>1.0), which lowered IOP in both groups (P .0001).

Fig 1. Mean IOP in black and nonblack patients treated with travoprost 0.004% in a 12-month study (data from the 10 AM visit, 14 hours postdose).



*P<.01 vs nonblacks.
†P<.05 vs nonblacks.

At all visits, however, mean IOP was significantly lower for black than for nonblack patients at the 10 AM timepoint (Fig 1).

Central corneal thickness, measured in 782 patients (175 black, 607 nonblack), was less for blacks than nonblacks (mean ± standard deviations 550 ± 50 µm and 566 ± 44 µm; P<.01). Measurements in the group treated with travoprost were 553 ± 45 µm for blacks (n=48) and 567 ± 45 µm for nonblacks (n=147) (P=.06).

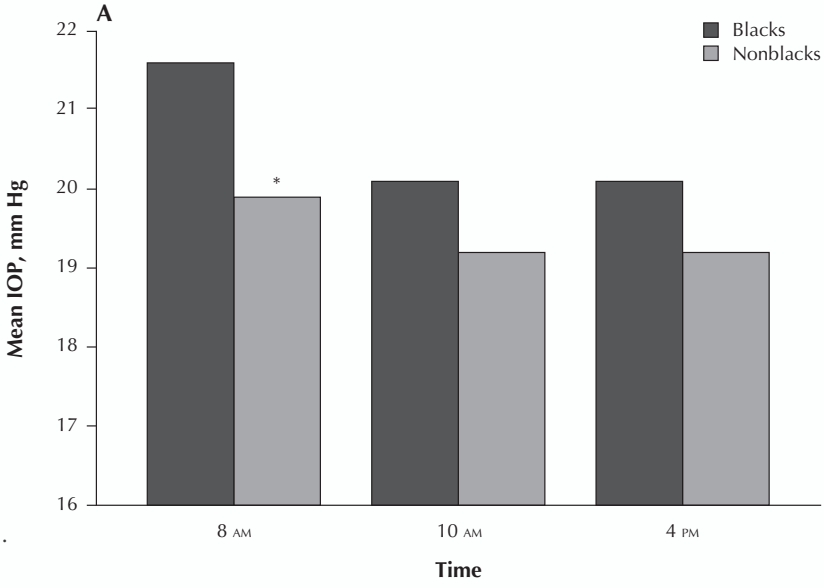
The difference between black and nonblack patients in IOP reduction with travoprost was significant both with (P=.005) and without (P=.004) adjustments for age, sex, iris color, diagnosis, and corneal thickness.

Following treatment with timolol, mean IOP was higher in black than in nonblack patients (Fig 2A), with the difference achieving significance at 8 AM (P=.0012) but not at 10 AM (P=.082) or 4 PM (P=.1689). Following latanoprost treatment, mean IOP did not differ significantly between blacks and nonblacks at any timepoint (Fig 2B).

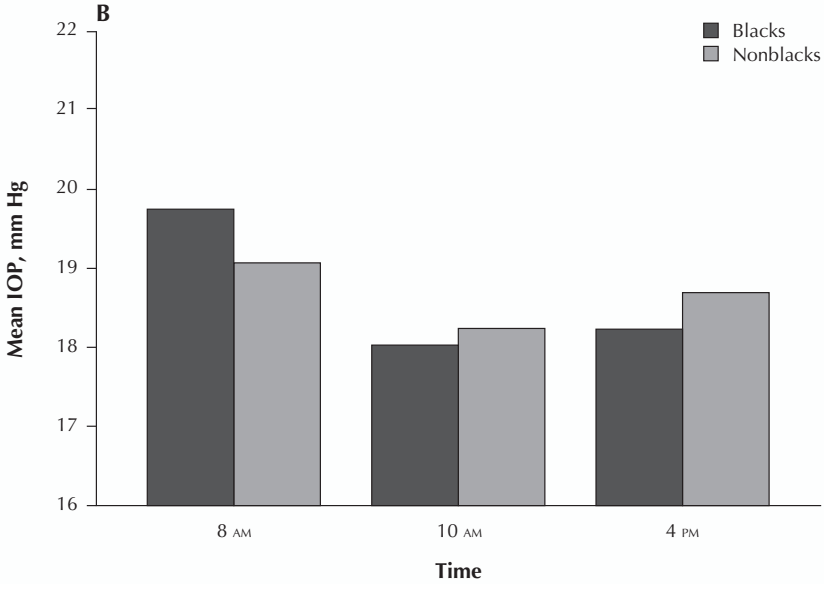
In black patients, mean IOP was 18.4 mm Hg at 8 AM, 16.5 mm Hg at 10 AM, and 16.7 mm Hg at 4 PM after travoprost 0.004%; respective values were 21.6, 20.1, and 20.1 mm Hg after timolol 0.5% (pooled data; P<.0001 for all three timepoints in favor

of travoprost). In nonblack patients, mean IOP was 19.3, 18.3, and 18.1 mm Hg after travoprost, and 19.9, 19.2, and 19.2 mm Hg after timolol at 8 AM, 10 AM, and 4 PM (*P*=.080, .0037, and .0030 in favor of travoprost).

Fig 2. Effect of timolol (A) and latanoprost (B) on mean IOP in black and nonblack patients across all visits in a 12-month study.



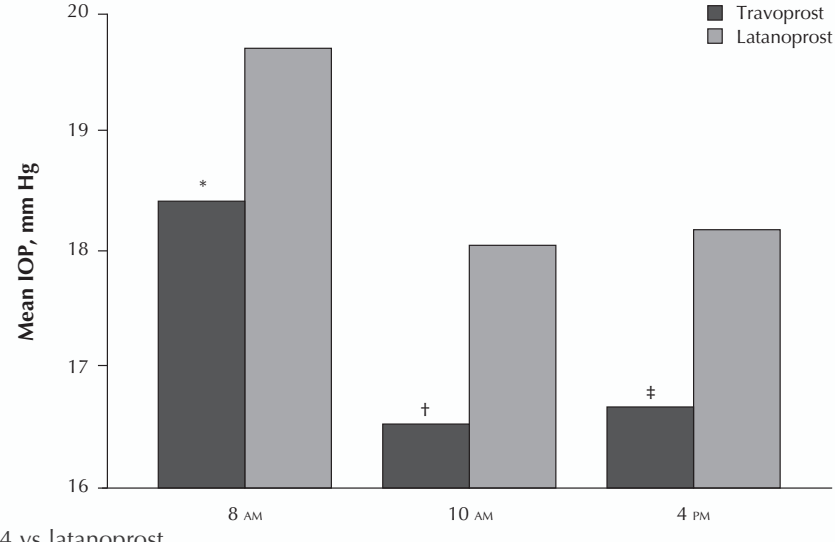
*P=.0012.



Pooled data across visits showed that mean IOP in black patients decreased from baseline by 8.4, 8.5, and 7.3 mm Hg with travoprost 0.004% at the three timepoints and by 5.7, 5.3, and 4.7 mm Hg with timolol 0.5%. Corresponding decreases in nonblack patients were 7.5, 6.9, and 6.6 mm Hg with travoprost and 7.0, 6.2, and 5.3 mm Hg with timolol.

In black patients, travoprost 0.004% lowered mean IOP significantly more at all timepoints than did latanoprost 0.005% (Fig 3). Pooled data from all visits for nonblack patients showed no significant reduction in IOP with either treatment. In the analysis of individual visits by nonblack patients, the mean IOP was significantly lower with travoprost than with latanoprost at 4 PM during the week 2 visit (P=.039). Although IOP was not significantly decreased from baseline with travoprost compared with latanoprost, the change from baseline was greater with travoprost at 15 of 18 timepoints.

Fig 3. Mean IOP after treatment with travoprost or latanoprost in black patients across all visits in a 12-month study.



*P=.0354 vs latanoprost.
†P=.0143 vs latanoprost.
‡P=.0356 vs latanoprost.

The responder analysis (patients who achieved target IOP levels) was based on mean IOP in pooled data from all visits at 4 PM, 20 hours after drug instillation. Higher (but not significantly so) responder rates were observed at different IOP cutoffs (from <22 to <18 mm Hg) in black compared with nonblack patients treated with travoprost (Fig 4); there was also a greater response in blacks to travoprost than to timolol and latanoprost (Fig 5). Responder rates did not differ significantly by IOP (<22, <20, and <18 mm Hg) except at less than 16 mm Hg, at which level travoprost produced significantly more responders than did latanoprost (P<.004) and timolol (P<.001).

Fig 4. Responder rates in black and nonblack patients treated with travoprost (data from all visits at 4 PM in a 12-month study).

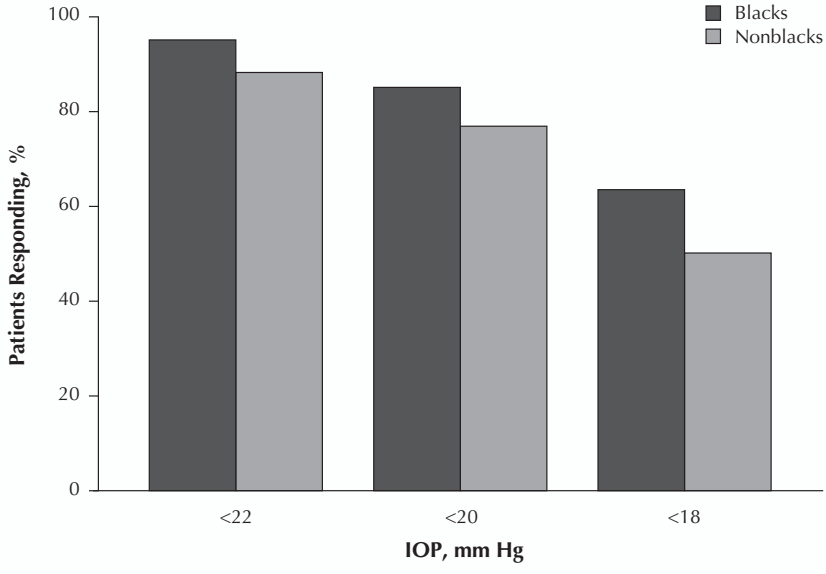
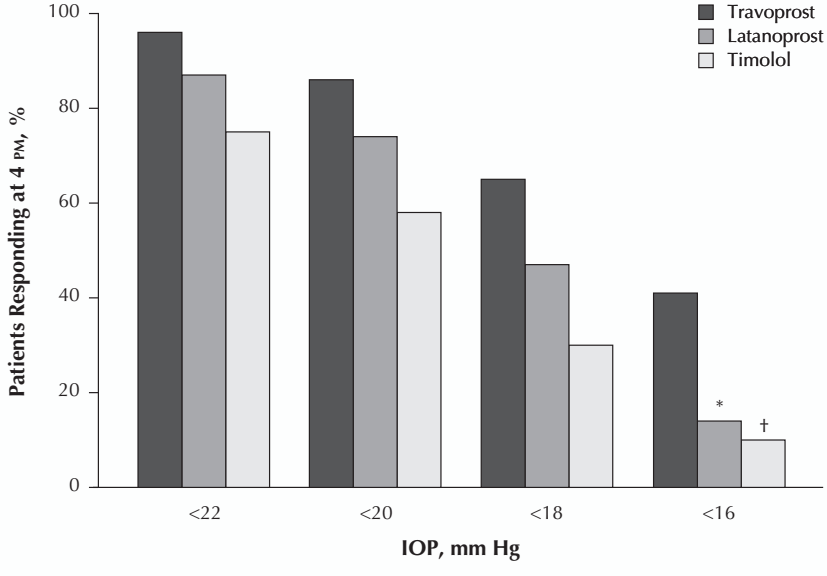


Fig 5. Responder rates in black patients treated with travoprost, latanoprost, and timolol (data from all visits at 4 PM in a 12-month study).



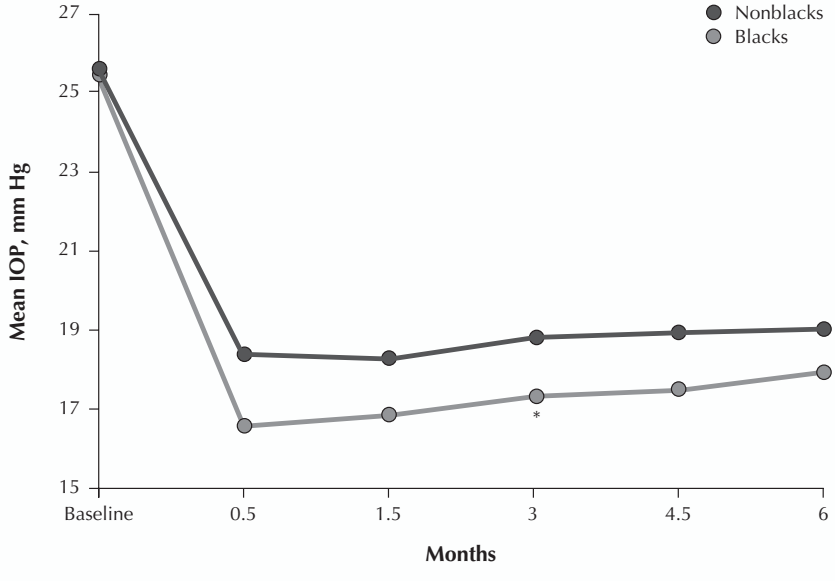
*P<.004 travoprost vs latanoprost.
†P<.001 travoprost vs timolol.

No serious treatment-related adverse events were reported. The most frequent ocular adverse events (related and unrelated to treatment) were hyperemia, decrease in visual acuity, pain, discomfort, and pruritus. Hyperemia scores were higher at baseline and at all visits in nonblacks, but analysis of change from baseline showed no significant differences in overall hyperemia scores between racial groups. In each study, one black patient treated with travoprost withdrew because of hyperemia. No iris pigment changes occurred in black patients in these studies, but dark brown irides made this determination difficult.

6-Month Study

Baseline IOP did not differ significantly in patients from either racial group treated with travoprost, although the reduction from baseline was significant in both blacks ($P<.0001$) and nonblacks (P .0001). Following therapy with travoprost, the mean IOP was lower for blacks at 10 AM during all visits; this difference was significant at month 3 (Fig 6).

Fig 6. Effect of travoprost on IOP in black and nonblack patients in a 6-month study (data from the 10 AM visit, 14 hours postdose).



*$P<.05$ vs nonblacks.

Combined Analysis

Data from travoprost-treated patients were pooled from both studies. At 16 of 18 visits, as well as for results averaged across study visits at each diurnal assessment, mean IOP was significantly lower for blacks (Table 2).

Table 2. Mean IOP With Travoprost 0.004% (Pooled Data From Two Studies)

	Blacks	Nonblacks	*P* Value
Baseline			
8 AM	27.0	27.0	
10 AM	25.2	25.4	
4 PM	24.3	24.9	
Pooled			
8 AM	18.5	19.6	<.01
10 AM	16.7	18.5	<.01
4 PM	16.8	18.3	<.01
Week 2			
8 AM	18.2	19.3	<.05
10 AM	16.3	18.2	<.01
4 PM	16.6	17.8	<.05
Month 1.5			
8 AM	18.1	19.4	<.01
10 AM	16.3	18.1	<.01
Month 3			
8 AM	18.1	19.4	<.05
10 AM	16.6	18.5	<.01
4 PM	17.0	18.1	<.05
Month 4.5			
8 AM	18.7	19.5	
10 AM	17.0	18.6	<.01
Month 6			
8 AM	18.9	19.8	
10 AM	16.9	18.6	<.01
4 PM	17.1	18.5	<.01
Month 9			
8 AM	18.4	19.8	<.05
10 AM	16.9	18.9	<.01
Month 12			
8 AM	18.9	20.2	<.05
10 AM	16.8	18.9	<.01
4 PM	16.7	18.6	<.01

DISCUSSION

Travoprost is a highly selective F prostaglandin receptor agonist with a potent ocular hypotensive effect.[9,10] In dose-response studies, reductions of IOP, which were greater in black than in nonblack patients, increased along with concentrations of travoprost.[8]

Our studies showed differences in mean IOP between black and nonblack patients with travoprost that may reflect differences in prostaglandin metabolism or prostaglandin receptors. Although little is known about racial or ethnic variation in prostaglandin metabolism, renal prostaglandin synthesis has differed between black Africans with hypertension and white Africans with hypertension.[11]

As did earlier studies,[12,13] our trials showed significantly less central corneal thickness in black than in nonblack patients with ocular hypertension and open-angle glaucoma. In eyes treated with travoprost, however, the difference between these racial groups was a nonsignificant 14 µm. Racial differences were significant on multivariate analysis, which included adjustment for corneal thickness. These differences, therefore, probably do not account for the variations in mean IOP observed after travoprost treatment in the black and nonblack patients.

The greater effect of travoprost in black than in nonblack patients, evident in dose-response studies, was confirmed in our clinical trials. Travoprost lowered the mean IOP in blacks significantly more than in nonblacks at all visits in the 12-month study and produced a lower mean IOP in blacks at all visits in the 6-month study (statistically significant difference at month 3). Given the similar IOP results in the two studies, the statistically significant difference at relatively more timepoints in the longer trial may be due to its larger number of black patients and consequent greater statistical power.

In the 12-month study, travoprost produced a greater reduction in black than in nonblack patients, whereas timolol had the opposite effect. Iris color has been correlated with response to topically administered timolol, perhaps as a result of drug binding to pigment-containing ocular structures.[14-16] With timolol treatment, a greater reduction of IOP may be observed in patients with light irides than in those with dark irides, perhaps explaining the differential responses in our studies. No correlation was apparent between iris color and IOP response with travoprost. Travoprost also was associated with a significantly lower mean IOP than latanoprost in black patients.

Glaucoma, advanced glaucomatous damage, and blindness due to glaucoma are more prevalent in blacks than in whites.[1-4,17,18] In the Baltimore Eye Study,[19] blacks were three to four times more likely than whites to have open-angle glaucoma, and in the general population, race is an important risk factor for this disease.[20] Race may also influence responses to laser and surgical therapy, as well as to medical interventions.[21-25] The superior IOP-lowering efficacy of travoprost in our studies has been described. Other differences associated with race have been documented following treatment with timolol[14-16] and pilocarpine[26] but have been attributed to melanin binding and not necessarily to other racial characteristics.

CONCLUSION

Travoprost ophthalmic solution 0.004% lowered mean IOP to a greater extent in black than in nonblack patients in 6- and 12-month pivotal trials. The differences in IOP reduction could not be accounted for by a multivariate analysis of age, sex, iris color, diagnosis, or corneal thickness. In both racial groups, travoprost was more effective than timolol, and this difference was significantly more pronounced in the black population. Travoprost also was superior to latanoprost in blacks, although the change from baseline was not significant. Response rates were higher in black patients treated with travoprost, although not significantly so, and a significantly greater proportion of blacks achieved an IOP below 16 mm Hg with travoprost than with latanoprost or timolol. Adverse effects were uncommon and were similar with travoprost in both black and nonblack patients.

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