Latanoprost Treatment for Glaucoma: Effects of Treating for 1 Year and of Switching From Timolol

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• PURPOSE: To determine the efficacy and safety of latanoprost treatment for 1 year in glaucoma patients, and to evaluate the effects of switching from timolol to latanoprost therapy.

• METHODS: Latanoprost 0.005% was topically applied once daily without masking for 6 months in 223 patients with elevated intraocular pressure after previous treatment with latanoprost once daily or 0.5% timolol twice daily for 6 months in a multicenter, randomized, double-masked, parallel group study.

• RESULTS: Compared with baseline values before treatment, a significant ($P < .0001$) diurnal reduction in intraocular pressure of 6 to 8 mm Hg was maintained with minimal fluctuation for the duration of treatment. When treatment was switched from timolol to latanoprost, intraocular pressure was reduced by 1.5 ± 0.3 mm Hg (mean ± SEM; 8% change in intraocular pressure; 31% of the intraocular pressure reduction produced by timolol; $P < .001$) compared with the change in intraocular pressure in patients remaining on latanoprost therapy. Of

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Dr Camras and others in the Latanoprost Study Group are consultants to Pharmacia & Upjohn Company, Uppsala, Sweden, which manufactures latanoprost. Others in the Latanoprost Study Group are consultants to the manufacturer of timolol, and to other companies that manufacture competing products. Dr Stjernschantz was an employee of the Pharmacia & Upjohn Company. None of the authors has a proprietary interest in the development or marketing of any drug used in this study or any competing drug.

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the patients initially enrolled, 95% successfully completed treatment. There was a slight overall increase in conjunctival hyperemia in patients who switched from timolol to latanoprost, but no change in those who continued latanoprost. The timolol-induced reduction of resting heart rate returned to baseline levels after switching to latanoprost. Of the 247 patients treated with latanoprost during the masked and/or open-label studies, 12 (5%) demonstrated a definite (n = 4) or possible (n = 8) increase in iris pigmentation.

• CONCLUSIONS: Latanoprost is a well-tolerated ocular hypotensive agent that appears to be more effective than timolol in reducing intraocular pressure. The increase in iris pigmentation appears to be harmless but requires further investigation. (Am J Ophthalmol 1998;126:390–399. © 1998 by Elsevier Science Inc. All rights reserved.)

LATANOPROST IS A PRODRUG OF A 17-PHENYL-substituted prostaglandin $F_{2\alpha}$ analogue[1–3] that was approved for the treatment of glaucoma by the Food and Drug Administration in June 1996. In multicenter, randomized, double-masked trials carried out for 3 to 6 months involving over 1,000 patients with ocular hypertension or glaucoma, 0.005% latanoprost applied once daily was found to be more effective than and as well tolerated an ocular hypotensive agent as 0.5% timolol applied twice daily.[4–7] Another study evaluated the effect of latanoprost therapy in the first 198 patients who completed 1 year of therapy, which included 50 patients from the United States.[8] No previous study, to our knowledge, has evaluated the effect of switching from timolol to latanoprost therapy.

The present multicenter study evaluates the safety and ocular hypotensive efficacy of latanoprost therapy in 104 patients in the United States who continued treatment for up to 1 year. It also provides information on the effect of switching from timolol to latanoprost therapy in 119 patients.

PATIENTS AND METHODS

THE PRESENT STUDY IS A 6-MONTH EXTENSION OF A previous report[5] involving 268 patients with ocular hypertension or early chronic open-angle glaucoma treated with 0.005% latanoprost (group A) applied topically once daily or 0.5% timolol (group B) applied twice daily for 6 months in a randomized, double-masked trial involving 17 centers in the United States. Selection criteria, detailed protocol, and results of the first 6-month masked trial have been reported previously.[5] Patients completing 6 months of therapy included 118 of the 128 in group A and 130 of the 140 in group B (Table 1). These patients were given the option of continuing therapy without masking with latanoprost applied once daily for an additional 6 months.

Of the patients completing 6 months of therapy in the masked study, 104 in group A and 119 in group B elected to participate in the open-label extension (Table 1). Demographic and ocular characteristics of patients enrolled in the 6-month, open-label extension study with latanoprost did not differ between the two groups (Tables 2 and 3). The patients chose to apply their daily dose at either 8:00 AM or 8:00 PM consistently throughout the second 6-month, open-label trial. Those taking latanoprost in the morning were instructed not to take their drops in the morning of an examination day until just after their morning evaluation.

Patients returned for visits at 6.5, 8, 10, and 12 months of treatment. Subjective side effects, visual acuity, refraction (if a change in visual acuity occurred), conjunctival hyperemia, slit-lamp biomicroscopy, intraocular pressure (IOP), and color photographs of the iris were assessed or performed on each visit in the morning. In addition, at the 12-month visit, the examination included automated visual field using the same perimeter as at baseline (Humphrey 24-2 or 30-2, or Octopus G1), dilated ophthalmoscopy and optic disk assessment, blood pressure, heart rate, and diurnal (8:00 AM, 12:00 noon, and 4:00 PM) assessments of subjective side effects, conjunctival hyperemia, slit-lamp biomicroscopy, and IOP.

Because of prior concerns about changes in iris color,[4–6] the iris photographs were reviewed by an independent panel of two or three ophthalmologists and scientists who were not investigators or examiners of any of the patients. The panel usually decided as a group whether a definite or suspected darkening of iris color occurred. The slightest suggestion of a change in pigmentation, including

TABLE 1. Patient Withdrawals From Study

Treatment Group*	Enrolled (No.)	Completed (No. [%])	Withdrawals† (No. [%])			
			Inadequate IOP Control	Ocular Reasons‡	Systemic Medical Reasons	Nonmedical Reasons
Masked study§						
Group A	128	118 (92)	0	2 (2)	4 (3)	4 (3)
Group B	140	130 (93)	4 (3)	2 (1)	3 (2)	1 (1)
Open-label						
Group A	104	98 (94)	1 (1)	2 (2)	1 (1)	2 (2)
Group B	119	113 (95)	0	2 (2)	3 (3)	1 (1)

IOP = intraocular pressure.

*Group A: latanoprost 0.005% once daily for 6 months in the masked study, then continued for 6 months in the open-label study. Group B: timolol 0.5% twice daily for 6 months in the masked study, then latanoprost 0.005% once daily for 6 months in the open-label study.

†Not necessarily related to treatment.

‡Includes allergic blepharoconjunctivitis, allergic conjunctivitis, swelling of eyelids, and iris color darkening.

§Modified from Camras et al,[5] with permission.

TABLE 2. Demographics

	Group A* (n = 104)	Group B* (n = 119)
Sex (no. [%])		
Male	46 (44)	51 (43)
Female	58 (56)	68 (57)
Age (yrs)		
Mean ± SD	61 ± 12	64 ± 11
Range	30–89	33–91
Race (no. [%])		
White	78 (75)	77 (65)
African-American	20 (19)	35 (29)
Hispanic	6 (6)	7 (6)

*Group A: latanoprost 0.005% once daily for 12 months. Group B: timolol 0.5% twice daily for 6 months, then latanoprost 0.005% once daily for 6 months.

TABLE 3. Baseline Characteristics of Pairs of Eyes

	Group A* (n = 104)	Group B* (n = 119)
Diagnosis (no. [%])		
Ocular hypertension	61 (59)	78 (66)
Primary open-angle glaucoma	35 (34)	37 (31)
Exfoliation glaucoma	2 (2)	1 (1)
Pigmentary glaucoma	3 (3)	1 (1)
Mixed types	3 (3)	2 (2)
Eyes receiving treatment per patient (no. [%])		
One eye	14 (13)	17 (14)
Both eyes	90 (87)	102 (86)
Prior glaucoma therapy (no. [%])		
β-Adrenergic blocker	63 (61)	75 (63)
Adrenergic agonist	6 (6)	5 (4)
Cholinergic agonist	6 (6)	5 (4)
Carbonic anhydrase inhibitor	5 (5)	5 (4)

*Group A: latanoprost 0.005% once daily for 12 months. Group B: timolol 0.5% twice daily for 6 months, then latanoprost 0.005% once daily for 6 months.

slight darkening or enlargement of a preexisting brown area, was considered a change. When possible, differences in lighting exposure were considered during the evaluation by comparing the relative appearance between photographs of the periocular skin color.

If the investigators believed that the IOP of patients was inadequately controlled with latanoprost, they had the option of adding either 0.25% or 0.5% timolol once or twice daily to their patients' regimen. If the addition of timolol did not adequately control the IOP, the patients were discontinued from the study and treated in a standard fashion without latanoprost at the discretion of their ophthalmologist.

An adverse event was defined as any undesirable event that occurred to a subject, whether or not it was considered related to the investigational drug. A serious adverse event was defined as potentially fatal, life-threatening, sight-threatening, perma-

nently disabling, requiring hospitalization, cancer, or a drug overdose.

Blood samples collected at baseline and after 6 and 12 months of treatment were analyzed for the following: hematocrit, hemoglobin, mean corpuscular volume, mean corpuscular hemoglobin level, mean corpuscular hemoglobin concentration, red blood cell count, white blood cell count, differential count, platelet count, prothrombin, partial thromboplastin time, cholesterol (total, high-density lipoprotein, low-density lipoprotein), triglycerides, protein, glucose, creatinine, urea, bilirubin, alkaline phosphatase, serum glutamic oxaloacetic transaminase, serum glutamic pyruvate transaminase, sodium, potassium, calcium, and chloride. Urinalysis included assessment of protein and glucose.

RESULTS

OF THE 223 ENROLLED PATIENTS IN THIS OPEN-LABEL extension, 95% successfully completed 6 months of therapy with latanoprost (Table 1). Withdrawals secondary to inadequate IOP control and adverse ocular side effects (not necessarily related to treatment) included 0.4% and 2% of patients, respectively (Table 1). The ocular adverse events resulting in discontinuation of therapy included two patients (1%) who developed darkening of eye color, and two patients (1%) with tearing, burning, itching, and/or eye pain. Withdrawal rates and reasons for dropouts did not differ between groups A and B (Table 1).

Compared with baseline measurements before treatment (mean ± SEM of 24.4 ± 0.3 and 24.1 ± 0.3 mm Hg for groups A and B, respectively), the significant ($P < .0001$) 6- to 8-mm Hg (25% to 30%) diurnal IOP reduction achieved after 6 months of masked treatment with latanoprost was maintained during the subsequent 6 months of therapy in the open-label extension in group A without appreciable fluctuation (Figure 1). Those patients switched from timolol to latanoprost at 6 months (group B) demonstrated an additional 1.5 ± 0.3 mm Hg (8% change from 6-month IOP values; 31% of the IOP reduction produced by timolol at 6 months; $P < .001$) reduction of IOP at 12 months compared with patients who remained on latanoprost (group A) for 12 months (Figure 1, A, B, and C). Once-daily administration of latanoprost was chosen in the morning or evening in 62% or 38% of patients, respectively. The mean diurnal IOP reduction was not affected by the time of day latanoprost was taken (Figure 1, D). In 9% of patients, timolol was added to the latanoprost therapy in an attempt to further reduce IOP to target levels. Even if the "inadequately controlled" IOP of these patients before the addition of timolol were carried forward through the 12 months of therapy, the latanoprost-induced IOP reduction would not be significantly altered. In the 14% of patients receiving unilateral therapy, the IOPs in the contralateral, untreated eyes were not significantly altered. Sex, age, race, diagnosis (ocular hypertension vs glaucoma), previous glaucoma therapy, and eye color did not affect the IOP reduction.

TABLE 4. Incidence of Possible Iris Color Darkening Relative to Baseline Iris Color

Iris Color	n	Darkening (no. [%])
Blue/gray	21	0
Blue/gray with slight brown	36	0
Blue/gray-brown	34	3 (9)
Green with slight brown	4	0
Green-brown	49	6 (12)
Brown (white patients)	19	0
Yellow-brown (white patients)	23	3 (13)
Brown (African-American patients)	61	0
Total	247	12 (5)

The small increase in conjunctival hyperemia noted at 6 months in group A did not change at 12 months (Figure 2). This mean change in conjunctival hyperemia was graded at 0.1 to 0.2 on a scale of 0 to 3 as follows: 0 = none, 1 = mild, 2 = moderate, 3 = severe. The conjunctival hyperemia showed a small increase to trace levels in those patients switched from timolol to latanoprost (Figure 2). Eight percent of patients showed at least a mild increase in hyperemia when switched from timolol to latanoprost.

Of the 247 patients treated with latanoprost in either the masked or open-label phase of the study, darkening of iris color was suspected or definite in eight (3%) or four (2%) patients, respectively (Table 4). All cases of suspect or definite iris color

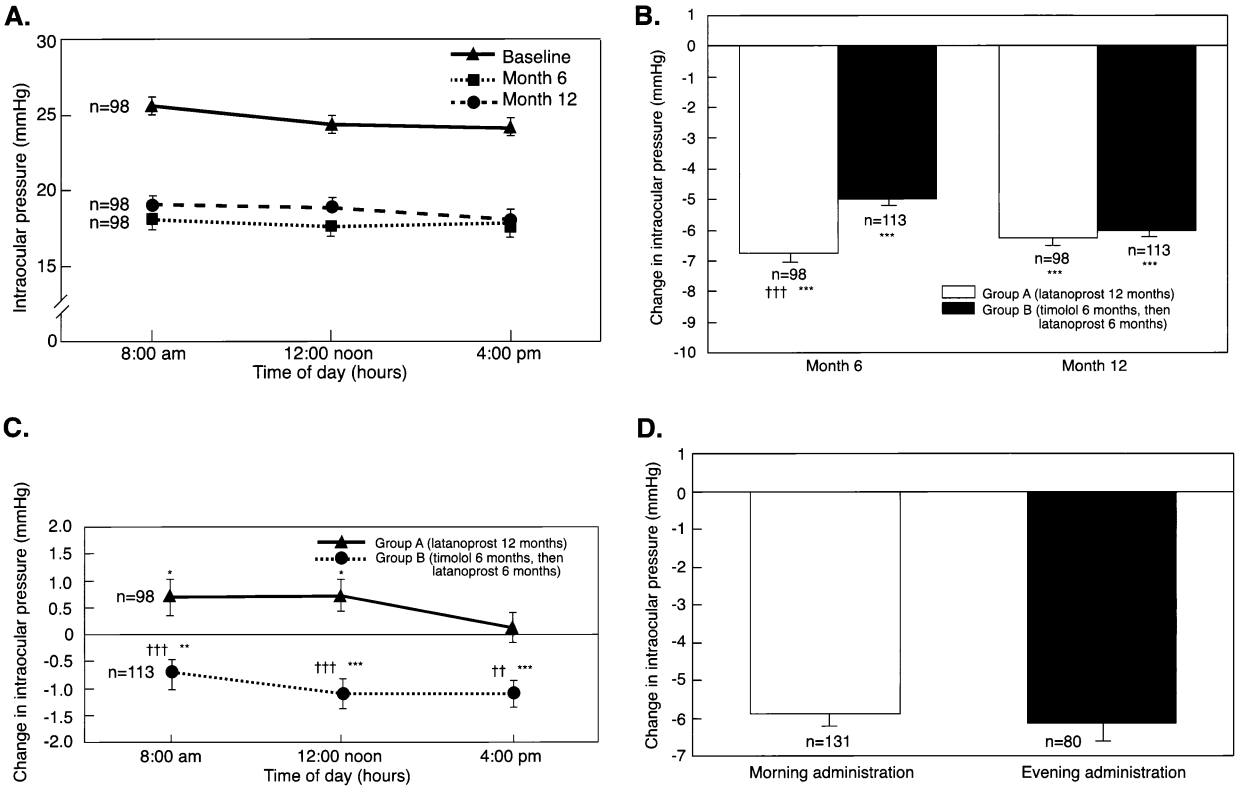

FIGURE 1. Effect of 0.005% latanoprost applied once daily or 0.5% timolol applied twice daily on intraocular pressure (IOP) in patients with ocular hypertension or glaucoma. Each value represents a mean ± SEM. Significant differences using two-tailed, unpaired comparisons between groups A and B, or paired comparisons at 6 and 12 months are indicated by daggers (one dagger, $P < .05$; two daggers, $P < .01$; three daggers, $P < .001$) or asterisks (one asterisk, $P < .05$; two asterisks, $P < .01$; three asterisks, $P < .001$), respectively. A, Mean diurnal IOP at baseline, 6 months, and 12 months of treatment in those 98 patients in group A who completed 1 year of treatment with latanoprost. B, Mean diurnal reduction of IOP at 6 and 12 months of treatment compared with baseline in those 98 patients who completed 1 year of treatment with latanoprost (group A) and in those 113 patients completing 6 months of treatment with latanoprost after 6 previous months of treatment with timolol (group B). C, The mean difference in diurnal IOP after 12 months compared with 6 months of treatment in groups A and B. D, Mean diurnal IOP reduction at 12 months compared with baseline in those patients taking latanoprost once daily at 8 AM vs 8 PM.

changes occurred in eyes classified at baseline as blue/gray-brown, green-brown, or yellow-brown. No change was documented in the more uniformly blue or brown irides. In each case, the relatively hypopigmented periphery (compared with the more central sphincter region) of the iris became darker, resulting in a more uniform color. This darkening was first observed after 2 to 12 months of latanoprost therapy. Patients demonstrating a possible or definite change in color were asked to discontinue latanoprost treatment and to enter a follow-up study in which iris color has been carefully monitored with periodic photographs. No obvious further change (either increase or decrease of the darkening) in iris color has occurred in these patients. Iris nevi and freckles, documented photographically at baseline and followed up carefully, did not change with latanoprost treatment.

Ocular symptoms and signs were graded as mild with few exceptions. In general, they were reported more frequently during the first 6 months of therapy with either latanoprost or timolol than during the second 6 months of treatment with latanoprost. No appreciable changes were observed in either group A or B during the second 6 months of treatment, compared with the first 6 months, for any of the

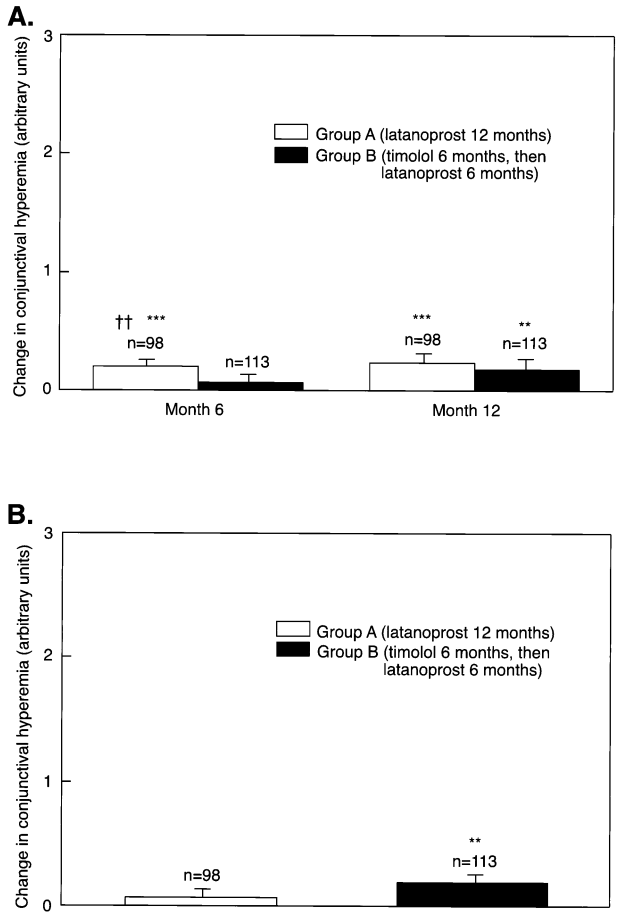

FIGURE 2. Effect of latanoprost and timolol on conjunctival hyperemia. A, Change in relative conjunctival hyperemia after 6 and 12 months of treatment compared with baseline in groups A and B. B, Change in conjunctival hyperemia at 6 months vs 12 months in groups A and B. See text for relative grading scale of conjunctival hyperemia. Also, see legend of Figure 1.

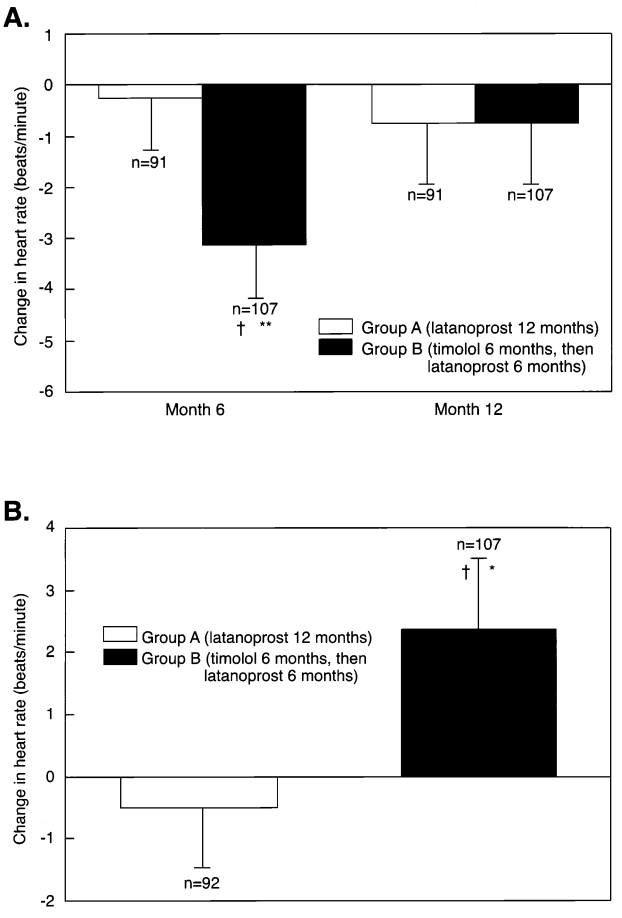

FIGURE 3. Effect of latanoprost and timolol on heart rate. A, Change in heart rate after 6 months and 12 months of treatment compared with baseline in groups A and B. B, Change in heart rate at 6 months vs 12 months in groups A and B. Also, see legend of Figure 1.

following: visual acuity, refractive error, aqueous flare, anterior chamber cellular response, cup/disk ratio, visual fields, eyelids, conjunctiva (except for hyperemia), cornea, iris (except for pigmentation), lens, vitreous, or retina.

The significant ($P < .01$) timolol-induced reduction in heart rate at 6 months returned to baseline levels in those patients switched from timolol to latanoprost (Figure 3). Those remaining on latanoprost for 12 months had no change in heart rate. Latanoprost treatment did not affect blood pressure, blood test results, or urinalysis.

Of the 247 patients treated with latanoprost in either the 6-month, masked study and/or the subsequent 6-month, open-label extension, none experienced serious ocular adverse events in latanoprost-treated eyes (Table 5). Sixteen percent of patients experienced ocular adverse events (none serious) in latanoprost-treated eyes. Serious systemic adverse events, none of which was felt to be related to treatment, occurred infrequently (Table 5).

DISCUSSION

THIS STUDY DEMONSTRATES THAT LATANOPROST APplied once daily reduces IOP safely and effectively

TABLE 5. Number of Patients Reporting Adverse Events (Not Necessarily Related to Treatment)

	Group A* (n = 128)	Group B* (n = 119)
Serious†		
Ocular‡	0	0
Systemic§	10	4
Not serious		
Ocular‡	15	17
Systemic	32	27

*Group A: latanoprost 0.005% once daily for 12 months. Group B: timolol 0.5% twice daily for 6 months, then latanoprost 0.005% once daily for 6 months.

†Defined as potentially fatal, life-threatening, sight-threatening, permanently disabling, requiring hospitalization, cancer, or overdose.

‡Ocular adverse events are reported only for latanoprost-treated eyes. They include posterior vitreous detachment, increased iridial pigmentation, blurring of vision, conjunctival chemosis, burning, tearing, conjunctival hyperemia, eyelid edema, branch retinal vein occlusion, iritis, hemorrhage, ophthalmic migraine, foreign body sensation, diplopia, visual field defect, hordeolum, ecchymosis of lid, itching, chalazion, pain, floaters, blepharitis, vitreous condensation, and photopsia.

§Includes basal cell carcinoma on leg, suspected myocardial infarction, cholelithiasis, liver biopsy for abnormal liver function tests, hospitalization for renal calculi, surgery for anterior cervical disk problem, painful swelling of breast nodule, chest pain (diagnosed as peptic ulcer disease), exacerbation of manic phase, foot and oral surgery (in same patient), hospitalization for dehydration, colon resection for abscess, myocardial infarction, and coronary artery bypass surgery.

for 1 year in patients with ocular hypertension and open-angle glaucoma. These results are consistent with the findings evaluating latanoprost treatment for 1 year in an international study.[8] In addition, switching patients from twice-daily timolol to once-daily latanoprost therapy resulted in a further reduction in IOP which was maintained during the next 6 months of latanoprost therapy. The greater efficacy of latanoprost compared with timolol observed in the current study is consistent with greater efficacy demonstrated in some previous studies.[4,5,7]

The latanoprost-induced reduction of IOP (25% to 30%) showed little evidence of drift or diurnal fluctuation during the 1 year of treatment, regardless of whether latanoprost was applied in the morning or evening. On the other hand, in a previous study, latanoprost was significantly more effective when given once daily in the evening compared with the morning.[4] It is unclear whether differences in patient population (for example, Scandinavian vs American), patient selection, glaucoma types (more exfoliation in Scandinavia), or study design (masked vs open-label) may account for these contrasting results.

The present study with latanoprost may be compared with similar studies performed with other medications frequently used in glaucoma therapy. Comparing the present study with a 1-year, open-label trial with dorzolamide in 333 patients, the magnitude of the IOP reduction was less, the drop-out rate because of inadequate IOP control was greater, and the proportion of patients requiring adjunctive therapy with timolol was greater in the dorzolamide trial.[9] Overall withdrawal rates, especially those resulting from the development of adverse side effects, were greater for dorzolamide,[9] apraclonidine,[10–12] brimonidine,[13] epinephrine,[14,15] miotics,[16] and oral carbonic anhydrase inhibitors.[16]

Systemic adverse events resulting in discontinuation of timolol treatment occur in 15% to 25% of patients.[17–19] Of 80 patients without a known history of airway disease who were treated with timolol for glaucoma, more than one fourth demonstrated at least a 15% improvement in pulmonary function tests (forced expiratory volume in 1 second) after discontinuing timolol.[20] Of 482 respiratory or cardiovascular adverse events associated with topical timolol therapy, 32 (8%) resulted in death of the patient.[21] Unlike timolol, latanoprost did not reduce resting heart rate in the current or previous studies.[4–7] In the current study, the timolol-induced decrease in heart rate reverted to baseline in those patients switching treatment from timolol to latanoprost. Latanoprost has not yet been demonstrated to produce systemic effects and is not expected to, based on pharmacokinetic considerations.[3,22]

Of all patients treated in the multicenter clinical trials in the United States, 5% (12 patients) demonstrated a possible or definite darkening of eye color. All of these patients had blue/gray-brown, green-brown, or yellow-brown irides at baseline. Although darkening of iris color in uniformly brown irides may be difficult to determine by the color photographic techniques that were used in this study, such techniques are sensitive in detecting

subtle pigmentary changes in uniformly blue irides. However, no such changes were detected in these blue irides in the present study. Eye color is determined by the amount of melanin (melanosomes) within iridial stromal melanocytes, not by the number of melanocytes.[23–25] Based on prolonged treatment with high doses of latanoprost and other prostaglandins in monkeys, the darkening of eye color is caused by an increase in melanogenesis (increase of melanin or melanosomes within melanocytes), but is not the result of proliferation of melanocytes.[26] Even large iris nevi observed at baseline do not change during the course of 1 year of treatment with latanoprost. Iris specimens obtained from patients who underwent intraocular surgery after many months of latanoprost therapy, including some demonstrating iris color darkening during treatment, have failed to demonstrate any pathologic changes as determined by light or electron microscopy.[27] This increase in iris pigmentation may be a result of prostaglandins substituting for deficient sympathetic tone.[28–31] Long-term follow-up studies are in progress to determine whether this darkening of eye color will have any adverse effect. Studies in progress have failed to demonstrate dispersion of the iridial stromal pigment to other ocular structures. Pigmentation in the trabecular meshwork that occurs normally and pathologically (in the case of pigment dispersion or exfoliation syndrome) originates from the pigment epithelium, not the stromal melanocytes, of the iris. Latanoprost has not been shown to affect the iridial pigment epithelium. Nevertheless, despite the failure to demonstrate adverse effects of the iris pigmentation during 1 year of follow up, more information is required after many years of treatment to guarantee long-term safety.

In conclusion, latanoprost, when topically applied once daily for 1 year, is a safe and effective agent for the treatment of ocular hypertension and primary open-angle glaucoma. With the exception of the darkening of color in eyes with susceptible colors at baseline, no progressive ocular or systemic side effects occurred in patients treated with latanoprost for 12 months, compared with 6 months, in the current study, or in one reported previously.[8] When substituted for twice-daily timolol therapy, latanoprost results in a further reduction of IOP. In addition to greater efficacy and potency, latanoprost has several additional advantages compared with nonselective beta-blockers, including its safer systemic side-effect profile. It reduces IOP as effectively in the night as during the day[32] and effectively reduces IOP in patients with normal-tension glaucoma.[33,34] Because it reduces IOP by increasing outflow,[35–37] its hypotensive effect is additive to that produced by aqueous humor suppressants.[38,39] Excluding beta-blockers, its advantages over other agents used in glaucoma therapy include its efficacy, convenience of once-daily dosing, rare allergic reactions, tolerability, and systemic safety. Although the darkening of eye color appears to be harmless based on studies already reported, studies in large numbers of patients treated for many years are required to insure prolonged safety.

APPENDIX

CENTERS (OR AFFILIATIONS), OTHER INVESTIGATORS, and coordinators participating in the United States Latanoprost Study Group include the following.

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Medical University of South Carolina (Charleston, South Carolina): Study Coordinator: J. A. Stewart, RN.

Mount Sinai Medical Center (New York, New York): Co-investigator: S. M. Podos, MD; Study Coordinators: M. Arroyo, S. Nitzberg.

New York Eye and Ear Infirmary (New York, New York): Co-investigators: G. Abundo, MD, R. Caronia, MD, J. Liebmann, MD; Study Coordinator: D. Steinberger.

Northwestern University Medical School (Chicago, Illinois): Co-investigators: L. F. Rosenberg, MD, J. M. Ruderman, MD; Study Coordinator: K. Clarkson.

University of California, San Diego (La Jolla, California): Study Coordinator: R. Ochabski, MD.

University of Florida (Gainesville, Florida): Co-investigators: M. F. Smith, MD, D. W. Stokes, MD; Study Coordinator: Z. S. Zam.

University of Illinois (Chicago, Illinois): Co-inves-

tigators: D. Hillman, MD, B. Kaplan, MD; Study Coordinators: V. Gates, COT, C. Nail, COMT.

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University of Michigan (Ann Arbor, Michigan): Co-investigator: A. T. Johnson, MD, PhD; Study Coordinator: C. J. Pollack-Rundle.

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University of Southern California (Los Angeles, California): Co-investigators: D. Heuer, MD, P. Lee, MD; Study Coordinator: M. Padea.

University of Wisconsin (Madison, Wisconsin): Co-investigator: G. A. Heatley, MD; Study Coordinator: M. A. Vanderhof-Young.

Washington University School of Medicine (St Louis, Missouri): Study Coordinator: A. Jones.

Wills Eye Hospital (Philadelphia, Pennsylvania): Co-investigator: M. Moster, MD; Study Coordinator: B. Parker.

Wilmer Eye Institute at Johns Hopkins University (Baltimore, Maryland): Co-investigator: M. Juzych, MD; Study Coordinator: M. Brummett.

Sponsor: Pharmacia & Upjohn Company (Uppsala, Sweden): Study Director: U. Parkhede.

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