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Latanoprost, a Prostaglandin Analog, for Glaucoma Therapy

Efficacy and Safety after 1 Year of Treatment in 198 Patients

*Carl B. Camras, MD,[1] Albert Alm, MD,[2] Peter Watson, MD,[3] Johan Stjernschantz, MD,[4] the Latanoprost Study Groups**

Purpose: To determine efficacy and safety of latanoprost, a prostaglandin analog for glaucoma, during 1 year of treatment.

Methods: After baseline measurements, 0.005% latanoprost was topically applied once daily for 12 months in patients from Scandinavia, the United Kingdom, and the United States who had elevated intraocular pressure (IOP). Diagnoses included ocular hypertension, chronic open-angle glaucoma, exfoliation syndrome, and pigment dispersion syndrome. Treatment was masked for the first 6 months and open-label during the second 6 months.

Results: Of the 272 patients initially enrolled, withdrawals were due to inadequate IOP control (1%), increased iris pigmentation (5%), other ocular problems (3%), systemic medical problems (3%), and nonmedical reasons (14%). Latanoprost significantly ($P < 0.0001$) reduced diurnal IOP from 25.3 ± 3.0 mmHg (mean ± standard deviation) at baseline to 17.4 ± 2.7 mmHg (32% reduction) at 12 months in the 198 patients who completed 1 year of treatment. The IOP reduction was maintained at a consistent level throughout the 12 months without evidence of drift, and was not affected by sex, age, race, or eye color. Overall, latanoprost caused a possible or definite increase in iris pigmentation in 12% of the 272 patients, all of whom had multicolored irides at baseline. One half of these patients with increased pigmentation withdrew before completing 1 year of therapy. Visual field, optic disc cupping, visual acuity, refractive error, conjunctival hyperemia, aqueous flare, anterior chamber cellular response, lens examination, blood pressure, heart rate, blood tests, and urinalysis were not appreciably altered.

Conclusion: Latanoprost safely and effectively reduces IOP for 1 year in patients of diverse nationalities, providing further evidence for its usefulness in chronic glaucoma therapy. *Ophthalmology 1996;103:1916–1924*

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Latanoprost, a prodrug of a 17-phenyl–substituted prostaglandin (PG)$F_{2\alpha}$ analog, when topically applied once daily at a concentration of 0.005%, is as effective and well tolerated as 0.5% timolol applied twice daily for 6 months in randomized, double-masked studies evaluating more than 800 patients with ocular hypertension or glaucoma.[1–6] However, to effectively treat chronic glaucoma, efficacy and safety must be demonstrated for more prolonged periods of time.

To provide this important longer-term information, this report describes the safety and efficacy of the first 198 patients who completed 1 year of treatment with 0.005% latanoprost topically applied once daily. These patients were recruited from three different parts of the world, enabling an international comparison of the relative efficacy and side effects of latanoprost.

Methods

Patients were recruited from 10 centers in Scandinavia, 14 centers in the United Kingdom (UK), and 13 centers in the United States (US). To be eligible for the study, at least one eye of each patient had to meet the following criteria: (1) intraocular pressure (IOP) of at least 22 mmHg during treatment with no more than a single ocular hypotensive medication during the screening examination; (2) diagnosis of primary open-angle glaucoma, ocular hypertension, exfoliation syndrome, or pigment dispersion syndrome. If treated for their elevated IOP, patients discontinued their medication for a minimum of the following intervals before the baseline day: 3 weeks for beta-adrenergic antagonists, 2 weeks for adrenergic agonists, and 5 days for cholinergic agonists or carbonic anhydrase inhibitors. Patients previously treated with beta-adrenergic antagonists were not eligible to participate in the studies in Scandinavia or the UK, but were still eligible for the study in the US. Patients were ineligible for any of the following reasons: (1) younger than 40 years of age; (2) use of any ocular medications other than for glaucoma; (3) advanced glaucoma that would be at risk for progression during the washout period or during treatment with a single ocular hypotensive medication; (4) ocular conditions, including a history of acute angle-closure glaucoma, severe eye trauma, intraocular surgery or argon laser trabeculoplasty within 6 months, severe dry eye syndrome, or ocular inflammation/infection within 3 months; and/or (5) any unstable medical condition.

The first 6 months of the study were carried out in a randomized, double-masked fashion, with either 0.005% latanoprost applied once daily or 0.5% timolol applied twice daily to one or both eyes (depending on eligibility) for each patient. The latanoprost-assigned patients received active latanoprost at 8:00 PM and the vehicle at 8:00 AM each day for 6 months in the UK and US. In Scandinavia, the patients taking latanoprost were divided randomly into two groups. One group received the active latanoprost at 8:00 AM for the first 3 months, and at 8:00 PM for the second 3 months. The other group received latanoprost at 8:00 PM for the first 3 months and at 8:00 AM for the second 3 months. Each center used standard procedures to assess the parameters that were evaluated.[1–3] Details of the 6-month, masked trial are described further in previous publications.[1–5]

After completion of 6 months of treatment, all centers were encouraged to give their subjects the option of continuing treatment with latanoprost in an open-label fashion for an additional 6 months. Each patient was given the option of applying 0.005% latanoprost once daily either in the morning (at approximately 8:00 AM) or the evening (at approximately 8:00 PM), with their choice of treatment time remaining unaltered during the course of the second 6-month, open-label trial. The patients receiving latanoprost in the morning were instructed not to take their drops in the morning of an examination day. Instead, the latanoprost was administered after their examination.

Patients returned for visits at 6 ½, 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, IOP, and magnified color photography 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 (Humphrey 24-2 or 30-2 [Allergan Humphrey, San Leandro, CA], Octopus G1 [Interzeag, Schlieren, Switzerland], or Competer [Bara Elektronik AB, Lund, Sweden]); dilated ophthalmoscopy, including assessment of the cup:disc ratio; 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.

The iris photographs were reviewed by an independent panel of two or three ophthalmologists or scientists who were not investigators or examiners of any of the patients. The panel usually decided as a group whether a definite or suspect darkening of iris color occurred. The slightest suggestion of a change in pigmentation, including slight darkening or enlargement of a pre-existing brown area, was considered a change.

If the investigators believed that the latanoprost inadequately controlled the IOP, they were given the option of adding 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 at the discretion of their ophthalmologist.

Adverse events were monitored carefully throughout the study. An adverse event was defined as any undesirable event occurring 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, permanently 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 level, hemoglobin level, mean corpuscular volume, mean corpuscular hemoglobin level, mean corpuscular hemoglobin concentration, erythrocyte count, leukocyte count, differential count, platelets, prothrombin, partial thromboplastin time, serum cholesterol level

Table 1. International Distribution and Reasons for Withdrawal from the Group of 272 Patients Who Began Therapy with Latanoprost by April 30, 1993*

		Reason for Withdrawal								
	Completed	*Inadequate IOP Control*	*Increased Iris Pigment*	*Other Ocular Reasons†*	*Systemic Medical Reasons*	*Option of Withdrawing at 6 Mos*	*Knowledge about Increased Iris Pigment§*	*Other Nonmedical Reasons*	Total	% Withdrawal
Scandinavia	88	1	5	5	3	6‡	14‡	0	122 (45%)	28
United Kingdom	60	2	6	3	3	10	0	1	85 (31%)	29
United States	50	0	3	1	3	3	0	5	65 (24%)	24
Total	198 (73%)	3 (1%)	14 (5%)	9 (3%)	9 (3%)	19 (7%)	14 (5%)	6 (2%)	272 (100%)	27

IOP = intraocular pressure.

* Values are number of patients.

† Includes blurred vision, photophobia, tearing, eye pain, punctate epithelial erosions, conjunctival hyperemia, chemosis, stinging, embolus in retinal artery, central retinal vein occlusion, branch retinal vein occlusion, and diabetic retinopathy.

‡ One of these patients was later found to show increased iris pigmentation.

§ Patients decided to withdraw after being informed that other patients in the study developed increased iris pigmentation.

(total, high-density lipoprotein, low-density lipoprotein), serum triglycerides, serum proteins, glucose value, creatinine level, urea level, bilirubin level, alkaline phosphatase, SGOT, SGPT, sodium, potassium, calcium, and chloride. Urinalysis included assessment of protein and glucose.

Results

One hundred ninety-eight patients successfully completed 1 year of therapy with latanoprost by April 30, 1994. These 198 patients represent a subset of a total of 272 patients who began treatment with latanoprost in the randomized, masked study by April 30, 1993, and therefore had the potential of completing 1 year of treatment by April 30, 1994. Overall, the withdrawal rate was slightly less in the US compared with the other geographic areas (Table 1). Of the 272 patients, 3 (1%) were withdrawn because of inadequate IOP control, all within the first 3 months of therapy (Tables 1 and 2). Excluding iris pigmentation, nine patients (3%) dropped out because of the development of adverse ocular side effects. Of these nine patients, six (67%) withdrew within the first 3 months, and 8 (89%) within the first 6 months of therapy (Tables 1 and 2). Symptoms or signs that may have represented an allergic or toxic reaction developed in only three of these nine patients (1% overall incidence). Of the 74 patients who withdrew from the study, 39 (53%) dropped out for nonmedical reasons, which included center deciding not to participate in the second 6-month, open-label trial; patients electing the option not to continue treatment during the second 6 months; information that an increase in iris pigmentation occurred in other patients; and lost to follow-up because of moving or traveling.

Table 2. Timing of and Reasons for Withdrawal of the 74 Patients Who Began Therapy with Latanoprost by April 30, 1993 but Did Not Complete 1 Year of Treatment*

	Reason for Withdrawal							
Time of Withdrawal (mos)	*Inadequate IOP Control*	*Increased Iris Pigment*	*Other Ocular Reasons†*	*Systemic Medical Reasons*	*Option of Withdrawing at 6 Mos*	*Knowledge about Increased Iris Pigment*	*Other Nonmedical Reasons*	Total
≤3	3	0	6	6	0	0	3	18 (24%)
>3 and ≤6	0	2	2	3	19‡	3	3	32 (43%)
>6 and ≤9	0	10	1	0	0	10‡	0	21 (28%)
>9	0	2	0	0	0	1	0	3 (4%)
Total	3 (4%)	14 (19%)	9 (12%)	9 (12%)	19 (26%)	14 (19%)	6 (8%)	74 (100%)

IOP = intraocular pressure.

* Values are number of patients. These 74 patients are a subset of the total 272 patients who began treatment by April 30, 1993.

† Includes blurred vision, photophobia, tearing, eye pain, punctate epithelial erosions, conjunctival hyperemia, chemosis, stinging, embolus in retinal artery, central retinal vein occlusion, branch retinal vein occlusion, and diabetic retinopathy.

‡ One of these patients was later found to show increased iris pigmentation.

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