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A 5-year, randomized, open-label safety study of latanoprost and usual care in patients with open-angle glaucoma or ocular hypertension

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PURPOSE. *To investigate the incidence of latanoprost-related adverse events of the cornea, iris, and retina and the occurrence of hyperpigmentation.*
METHODS. *An open-label safety surveillance study was conducted in 14 countries. Patients on intraocular pressure (IOP)-reducing therapy other than latanoprost were eligible if they required a change in therapy. Patients were randomly assigned (2:1) to latanoprost administered once daily or to usual care (any other commercially available medication). Patients were examined at baseline and every 6 months for 5 years.*
RESULTS. *In all, 5854 patients were included (latanoprost, 3936; usual care, 1918). Of those initially randomized to latanoprost, 2707 (68.8%) completed the study, and 4638 (79.2%) patients received at least one dose of latanoprost. Five-year risks were ≤3.17% for new occurrences of corneal erosions, iritis/uveitis, or macular edema in both randomization groups. Serious adverse drug reactions were reported in 17/3936 (0.43%) latanoprost and 9/1918 (0.47%) usual care patients. In all, 87.6% of patients ever treated with latanoprost had no increased iris pigmentation; no serious adverse drug reactions were reported in patients with increased iris pigmentation.*
CONCLUSIONS. *This 5-year study suggests that latanoprost as prescribed in 14 countries is a safe long-term treatment for patients with glaucoma and ocular hypertension. (Eur J Ophthalmol 2008; 18: 408-16)*

KEY WORDS. *Adverse events, Glaucoma, Iris pigmentation, Latanoprost, Ocular hypertension*

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INTRODUCTION

Latanoprost is a prostaglandin F_{2a} analogue that lowers intraocular pressure (IOP) levels in patients with glaucoma or ocular hypertension. Since 1996, latanoprost has been approved for clinical use in the United States and Europe and currently is approved in 120 countries.

Although long-term studies have shown once-daily latanoprost monotherapy to be effective and well tolerated locally and systemically (1-3), questions remain about possible adverse effects on the retina, iris, and cornea. The putative side effects of cystoid macular edema and iritis/uveitis were not noted during the trial clinical use of latanoprost, but case reports after commercial release have been published (4-15). Corneal erosions occurred at an increased rate compared with timolol in phase 3 trials of latanoprost (16, 17).

Long-term studies conducted in clinical practice settings are required to monitor adverse events and confirm safety after an agent has received marketing approval. The pre-

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sent study was initiated after market introduction of latanoprost to investigate the incidence and seriousness of putative prostaglandin-related adverse effects on the retina, iris, and cornea. The specific purposes of the study were to determine the frequency of occurrence of macular edema, iritis/uveitis, and corneal erosions during treatment with latanoprost as compared with their frequency during treatment with usual care; to follow any serious adverse drug reactions occurring throughout the study period; and to identify any possible long-term adverse consequences of increased iris pigmentation by comparing the type and frequency of serious adverse drug reactions in patients who developed iris pigmentation and those who did not.

METHODS

This 5-year, randomized, open-label safety study compared once-daily latanoprost with usual care, defined as any commercially available IOP-reducing medication except latanoprost. The study was conducted at 406 centers in 14 countries (Tab. I). The protocol was reviewed and approved by the Institutional Review Boards and Independent Ethics Committees at each investigational center, and the study complied with the ethical principles maintained in the 1964 Declaration of Helsinki.

TABLE I - PATIENT RECRUITMENT BY COUNTRY (total safety population)

Country	Latanoprost, n=3936	Usual care, n=1918	Total, n=5854
Argentina	64 (1.6)	31 (1.6)	95 (1.6)
Australia	149 (3.8)	68 (3.5)	217 (3.7)
Brazil	90 (2.3)	40 (2.1)	130 (2.2)
Canada	593 (15.1)	291 (15.2)	884 (15.1)
Chile	60 (1.5)	30 (1.6)	90 (1.5)
Colombia	32 (0.8)	19 (1.0)	51 (0.9)
France	679 (17.3)	328 (17.1)	1007 (17.2)
Ireland	59 (1.5)	26 (1.4)	85 (1.5)
Mexico	26 (0.7)	13 (0.7)	39 (0.7)
New Zealand	48 (1.2)	23 (1.2)	71 (1.2)
Peru	51 (1.3)	24 (1.3)	75 (1.3)
United Kingdom	585 (14.9)	279 (14.5)	864 (14.8)
United States	1480 (37.6)	736 (38.4)	2216 (37.9)
Venezuela	20 (0.5)	10 (0.5)	30 (0.5)

Any patient eligible, in the investigator's opinion, for treatment with latanoprost and another IOP-reducing agent in accordance with approved labeling could be included. Patients were excluded if they had previously been or currently were being treated with latanoprost or another prostaglandin, had any contraindication to the use of latanoprost, or were sufficiently responsive to their current IOP-reducing therapy.

At baseline, eligible patients provided written informed consent and underwent a screening examination including a review of their ocular and medical history, Snellen visual acuity, slit-lamp examination, ophthalmoscopy, and IOP measurement once in both eyes with a Goldmann applanation tonometer. Patients were assigned to latanoprost or usual care 2:1 according to a computer-generated randomization list with patient numbers assigned consecutively by a central treatment allocation center. Full frontal photographs of the face and each iris were taken of patients assigned to receive latanoprost.

Those randomized to latanoprost administered latanoprost once daily as monotherapy or in combination with other IOP-reducing medications. For patients randomized to usual care, investigators prescribed a commercially available IOP-reducing therapy; prostaglandins other than latanoprost were allowed if approved in the study site country. Either one or both eyes could be treated with assigned therapy. Investigators could modify the therapy of any patient; the reason for change was recorded.

Patient follow-up continued for 5 years regardless of IOP treatment postenrollment, with scheduled follow-up every 6 months. At each scheduled visit, the examination for both eyes included IOP measurement, ophthalmoscopy and slit-lamp examination of the conjunctiva, cornea, anterior chamber, iris, and lens. Visual acuity was measured yearly. Patient deaths were recorded throughout the study. Macular edema, iritis/uveitis, and corneal erosions were recorded at each visit by investigators. Serious adverse drug reactions, defined as serious adverse events considered by an investigator to be possibly related to either latanoprost or usual care, were recorded at each visit and followed until they resolved or the investigator deemed them to be chronic or stable. At each visit, patients randomized or changed to latanoprost had full face and iris photographs; investigator assessment of whether any change had occurred in pigmentation of the iris, eyelashes (lengthening, darkening, and/or thickening), and/or periorbital skin using baseline photographs and his or her own judgment; and patient reports of whether he or she

had noticed any change in iris pigmentation, eyelashes, and/or periorbital skin in or around either eye.

Endpoints and analyses

Endpoints for the study were the number of patients with macular edema, iritis/uveitis, corneal erosions, and serious adverse drug reactions (overall and by type). Analyses were conducted in the following populations:

1. The total safety population (intention-to-treat population) included all randomized patients who received at least one dose of IOP-reducing medication during the study. Frequencies and proportions of patients in each randomization group with macular edema, iritis/uveitis, corneal erosions, or serious adverse drug reactions were compared. Incidences over time of occurrences of macular edema, iritis/uveitis, and corneal erosions were analyzed with Kaplan-Meier survival analysis techniques.
2. The total latanoprost population consisted of all randomized patients who received at least one dose of latanoprost regardless of randomization group. The frequency and proportion of patients with serious adverse drug reactions were calculated, and the relationship between serious adverse drug reactions and the occurrence of increased iris pigmentation was evaluated.
3. The initial treatment population included all patients randomized to latanoprost for the time on study that they continued to receive latanoprost and all patients randomized to usual care for the time on study that they continued to receive ocular hypotensive therapy other than latanoprost.

Assuming a true incidence of 1% for macular edema, iritis/uveitis, and corneal erosions, a sample of 6000 patients would detect an additional incidence of 1% in the latanoprost group with a significance level of a=0.05 and a power of 80% with an allocation of 2:1 for latanoprost to usual care. It was not possible to calculate unbiased estimates of the direct treatment effect of latanoprost versus usual care for the total safety population because patients were allowed to change their initial assigned treatment as many times as needed. Moreover, comparisons between latanoprost and usual care in the initial treatment population were confounded by differential exposure to medication in the two treatment arms. Thus, 5-year risks and 95% confidence intervals of serious adverse events were calculated using Kaplan-Meier estimates, but tests of the statistical significance of differences between groups were not performed.

RESULTS

Study populations and patient disposition

In all, 5893 patients were randomized (Fig. 1), and 5854 (99.3%) received at least one dose of study medication. The first subject visit occurred January 26, 1999, and the last was on May 1, 2005. In the total safety population, 3936 (67.2%) patients were randomized to latanoprost, and 2707/3936 (68.8%) completed the study; 1918 patients were initially randomized to usual care, and 1285/1918 (67.0%) completed the study. During the 5 years, 4638 (79.2%) patients received at least one dose of latanoprost regardless of their initial randomization group (total latanoprost population). The number of patients in the initial treatment population varied according to the measurement time point; at baseline, there were 3687 patients in the latanoprost group and 1635 in the usual care group.

Baseline characteristics

Patient groups were balanced with respect to age, sex, race, eye color, and baseline diagnosis (Tab. II). In both groups, the mean age was approximately 68 years, there were somewhat more females than males, and primary open-angle glaucoma was the most frequent diagnosis. At baseline, approximately 95% of patients were receiving IOP-reducing medications, with 78% being treated with ß-adrenergic antagonists and 20% receiving topical carbonic anhydrase inhibitors.

Safety

In the total safety population, the 5-year incidence of macular edema, iritis/uveitis, or corneal erosions was low (≤2.72%) and comparable for patients randomized to latanoprost or usual care (Tab. III). Kaplan-Meier estimates indicated a low risk (≤3.17%) for each of the three events at 5 years. Rates of these events in the total latanoprost and initial treatment populations were consistent with those for the total safety population. Patients with and without macular edema, iritis/uveitis, and corneal erosions had similar rates of baseline risk factors (history of diabetes mellitus, dry eye, corneal erosions, contact lens usage).

Medication discontinuations over 5 years due to macular edema, iritis/uveitis, corneal erosions, iris pigmentation,

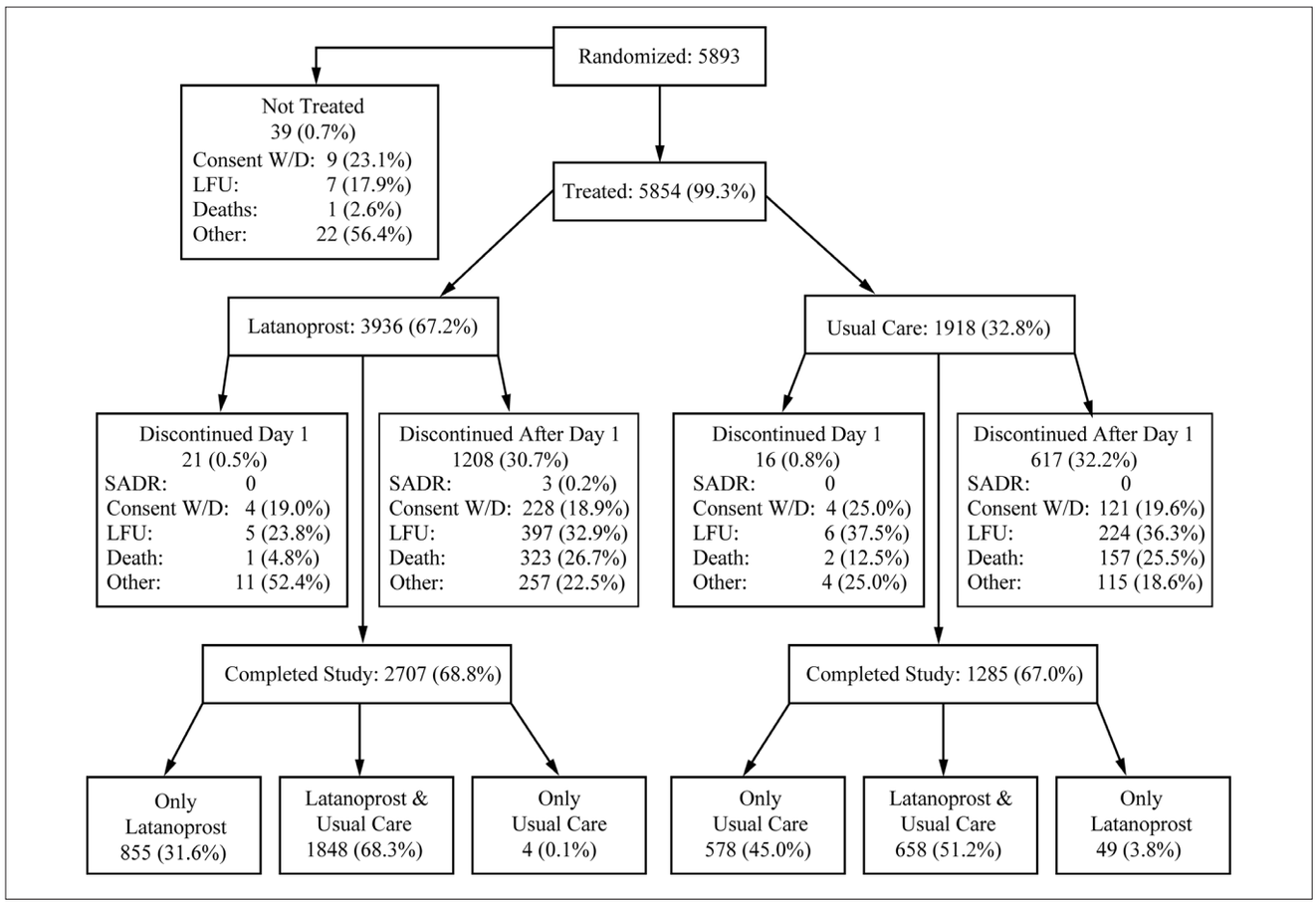

Fig. 1 - *Patient disposition. LFU = lost to follow-up; SADR = serious adverse drug reaction; W/D = withdrawn.*

and asthma/chronic obstructive pulmonary disease occurred in 197/5854 (0.3%) patients in the total safety population (Tab. IV). Overall discontinuation rates were similar among patients receiving their randomized medication (2.46%, latanoprost; 2.24%, usual care). Discontinuation of latanoprost, although infrequent, occurred in 27 patients due to macular edema and in 30 patients due to iritis/uveitis; in the usual care group, three and six patients discontinued due to macular edema or iritis/uveitis, respectively. In contrast, a greater number of patients discontinued usual care compared to latanoprost due to asthma/chronic obstructive pulmonary disease (60 vs 16 patients, respectively).

Only 26/5854 (0.44%) patients in the total safety population reported a serious adverse drug reaction. Patients randomized to latanoprost and usual care had similar rates of occurrence (17/3936 [0.43%] and 9/1918 [0.47%], respectively). Serious adverse drug reaction resulted in 14 discontinuations from latanoprost and 13 from another IOP-reducing therapy (2 patients discontinued both latanoprost and another therapy). The 14 discontinuations in the latanoprost group were attributed to cystoid macular edema (n=4), uveitis (n=3), chest pain, eye irritation, headache, dermatitis due to eye drop allergy, conjunctivitis, dyspnea, and macula lutea degeneration (n=1 each).

A total of 21/4638 (0.45%) patients in the total latanoprost population reported at least one serious adverse drug reaction (Tab. V); 19 were on latanoprost treatment at the time of the reaction. Vision disorders were the most prevalent type of serious adverse drug reaction (11 events). In the total safety population, 17/3936 (0.43%) patients randomized to latanoprost and 9/1918 (0.47%) patients had at least one serious adverse drug reaction

TABLE II - DEMOGRAPHIC AND BASELINE CHARACTERISTICS (total safety population)

Characteristics	Latanoprost, n=3936	Usual care, n=1918
Sex		
Female	2158 (54.8)	1079 (56.3)
Male	1778 (45.2)	839 (43.7)
Race		
Caucasian	2673 (67.9)	1295 (67.5)
African American	325 (8.3)	172 (9.0)
Other	259 (6.6)	123 (6.4)
Not allowed to ask*	679 (17.2)	328 (17.1)
Age, yr		
Mean ± SD	67.6 ± 12.4	67.8 ± 12,2
Range	12–98	20–94
Diagnosis		
Primary open-angle glaucoma	3123 (79.3)	1566 (81.6)
Ocular hypertension	401 (10.2)	167 (8.7)
Exfoliation glaucoma	143 (3.6)	69 (3.6)
Different in right and left eye	119 (3.0)	56 (2.9)
Other (<3% per category)	150 (3.8)	60 (3.1)
Eye color		
Homogeneously brown	1459 (37.1)	738 (38.5)
Homogeneously blue, grey, or green	1111 (28.2) 791 (20.1)	637 (33.2) 288 (15.0)
Blue-brown/grey-brown	456 (11.6)	190 (9.9)
Green-brown	94 (2.4)	50 (2.6)
Yellow-brown	25 (0.6)	7 (0.4)
Different in right and left eye	0	8 (0.4)
Missing data		

Values are n (%) unless otherwise specified.
*Investigators in France were not permitted to ask about race

TABLE III - 5-YEAR INCIDENCE OF MACULAR EDEMA, IRITIS/UVEITIS, AND CORNEAL EROSIONS (total safety population)

Outcome	Latanoprost, n=3936	Usual care, n=1918
Incidence of macular edema	95 (2.41); 2.95 (2.35, 3.54)	36 (1.88); 2.27 (1.51, 3.03)
Incidence of iritis/uveitis	98 (2.49); 2.99 (2.40, 3.58)	43 (2.24); 2.72 (1.92, 3.53)
Incidence of corneal erosions	107 (2.72); 3.17 (2.57, 3.77)	42 (2.19); 2.62 (1.82, 3.42)

Values are n (%); Kaplan-Meier estimate of 5-year risk, % (95% CI)

(Tab. V). Fourteen such events were recorded in the latanoprost group of the initial treatment population (14/3687; 0.38%).

Among patients ever treated with latanoprost, investigators judged that 577/4638 (12.4%) had increased iris pigmentation, 1871/4638 (40.3%) experienced eyelash changes, and 363/4638 (7.8%) had increased pigmentation of the periorbital skin (Tab. VI). When patient assessments were considered, the incidence of each of these side effects was reduced. None of the 21 patients in the total latanoprost population who had serious adverse drug reactions had increased iris, eyelash, or periocular pigmentation.

TABLE IV - MEDICATION DISCONTINUATIONS OVER 5 YEARS (total safety population)

	Latanoprost, n=3936		Usual care, n=1918	
	Medication discontinued			
Event	**Latanoprost**	**Other**	**Latanoprost**	**Other**
Macular edema	25 (0.64)	1 (0.03)	2 (0.10)	2 (0.10)
Iritis/uveitis	24 (0.61)	4 (0.10)	6 (0.31)	2 (0.10)
Corneal erosions	32 (0.81)	7 (0.18)	2 (0.10)	11 (0.57)
Iris pigmentation	2 (0.05)	0	1 (0.05)	0
Asthma/COPD	14 (0.36)	32 (0.81)	2 (0.10)	28 (1.46)
Total	97 (2.46)	44 (1.11)	13 (0.68)	43 (2.24)

Values are n (%).
COPD=Chronic obstructive pulmonary disease

TABLE V - SERIOUS ADVERSE DRUG REACTIONS OVER 5 YEARS IN PATIENTS RECEIVING LATANOPROST

		Total latanoprost population, n=4638	Total safety population latanoprost, n=3936	Usual care, n=1918
Patients with ³1 serious adverse drug reaction		21 (0.45)	17 (0.43)	9 (0.47)
WHO body system and preferred term				
Body as a whole	Allergy	1 (0.02)	1 (0.03)	2 (0.10)
	Chest pain	2 (0.04)	1 (0.03)	1 (0.05)
Cardiovascular disorders	Cardiac failure	1 (0.02)	1 (0.03)	0
Central and peripheral nervous system disorders	Headache	1 (0.02)	1 (0.03)	0
Heart rate and rhythm disorders	Arrhythmia	0	0	1 (0.05)
Myo-, endo-, pericardial and valve disorders	Angina pectoris	0	0	1 (0.05)
Psychiatric disorders	Insomnia	1 (0.02)	1 (0.03)	0
	Somnolence	0	0	1 (0.05)
Resistance mechanism disorders	Chest infection	1 (0.02)	1 (0.03)	0
Respiratory system disorders	Bronchitis	1 (0.02)	0	1 (0.05)
	Dyspnea	1 (0.02)	1 (0.03)	0
Skin and appendages disorders	Dermatitis	1 (0.02)	1 (0.03)	0
Vision-related reactions	Conjunctivitis	2 (0.04)	1 (0.03)	1 (0.05)
	Cystoid macular edema	4 (0.09)	3 (0.08)	1 (0.05)
	Eye irritation	1 (0.02)	1 (0.03)	0
	Macula lutea degeneration	1 (0.02)	1 (0.03)	0
	Uveitis	3 (0.06)	3 (0.08)	0

Values are n (%). A serious adverse drug reaction could be attributed to an ocular hypotensive agent other than that to which the patient was assigned at randomization

TABLE VI - CHANGES IN IRIS PIGMENTATION, EYELASHES, OR PERIORBITAL SKIN OVER 5 YEARS (total latanoprost population; N=4638)

Outcome	Investigator assessment	Patient assessment
Increased iris pigmentation	577 (12.4)	382 (8.2)
Eyelash changes*	1871 (40.3)	1329 (28.7)
Increased pigmentation of periorbital skin	363 (7.8)	355 (7.7)

Values are n (%).
*Darkening, lengthening, or thickening of the eyelashes

More than 70% of eyes had best-corrected visual acuity of 0.6 (Snellen chart equivalent, 20/80) or more at baseline. Corrected visual acuity remained essentially unchanged in all populations at the conclusion of the 5-year study.

DISCUSSION

Results of this 5-year, open-label, randomized, postmarketing safety study demonstrated that latanoprost is a safe long-term treatment for patients with glaucoma and ocular hypertension.

Across analysis populations, the 5-year incidence of macular edema was low and comparable between latanoprost and usual care groups. The ocular pharmacokinetics of latanoprost suggest an insufficient concentration of drug expected in the posterior segment of the eye to cause a pharmacologic effect, and latanoprost has not been shown to have either inflammatory or vasoactive properties (18, 19). Although clinical case reports have described the occurrence of macular edema in eyes treated with latanoprost (4-15), a review of putative cases of cystoid macular edema in 113 latanoprost-treated eyes found that nearly all affected eyes had known risk factors predisposing them to the condition (18). Moreover, macular

edema is rare even in high-risk eyes treated with latanoprost (18).

Rates of iritis/uveitis over the 5-year study period also were similar in patients randomized to receive latanoprost or usual care. As Schumer et al (18) note, four phase 3, multicenter, double-masked comparative trials (16, 17, 20, 21) including more than 1000 patients did not demonstrate a causal relationship between latanoprost and either aqueous flare or a cellular response in the anterior chamber in eyes. However, administration of excessive doses of latanoprost (four times daily) has been associated with transient cells, flare, and photophobia, which resolved spontaneously (22).

The 5-year incidence of corneal erosions was 2.72% in those randomized to latanoprost and 2.19% in patients randomized to usual care. Two phase 3, 6-month, randomized, double-masked, placebo-controlled trials found such erosions occurred more frequently in latanoprost- than timolol-treated patients (16, 17). In those studies, however, patients randomized to once-daily latanoprost received twice as much preservative as those treated with twice-daily timolol (200 mg/mL vs 100 mg/mL) because the vehicle used as placebo in the latanoprost groups also contained the preservative. It is notable that the incidence of corneal erosions decreased during an 18-month open-label follow-up period during which latanoprost was administered once daily and placebo drops were withdrawn (3).

Although macular edema and iritis/uveitis seemed to occur at the same rate in the latanoprost and usual care groups in the total safety population, a greater number of patients receiving latanoprost were discontinued for these conditions. The reasons for this inconsistency are not clear, but two explanations are plausible. First, uveitis that was ranked as "severe" occurred in 3 of 3963 patients in the latanoprost group versus in 0 of 1918 patients in the usual care group. Although the number of patients with severe drug reactions was very small, discontinuation rates may reflect a level of severity in latanoprost-treated patients that, in at least some cases, was somewhat greater when compared with patients under usual care. Another potential explanation is methodologic in nature. Because macular edema and iris/uveitis were initially considered putative effects of prostaglandin agonists, it is conceivable that in this open-label study in which the study treatment administered to individual patients was unmasked by design at least some participating clinicians may have been biased towards attributing a causal relationship with latanoprost more frequently than with other comparative treatments in the usual care group.

The presence of increased iris pigmentation did not affect the safety profile of latanoprost, confirming results of a previous 5-year, multicenter, open-label, safety study (23). Serious adverse drug reactions were rare among those in the total latanoprost population, reported in 21/4638 (0.45%) patients of whom 19 were receiving latanoprost at the time of the reaction. Differences in distributions of eye color or in assessment methods may explain, in part, the fact that 12.4% of our patients demonstrated increased iris pigmentation (investigator assessment) compared with 33.4% in the 5-year study (23).

Medication discontinuations due to exacerbation of asthma/chronic obstructive pulmonary disease occurred more frequently among patients receiving usual care than latanoprost (60 vs 16 patients, respectively). Population surveys have demonstrated that as many as 40% of elderly patients have obstructive airway disease suggesting an overlap with glaucoma in a significant number of patients (24). Studies have shown that latanoprost has no effect on pulmonary function in patients with asthma (25, 26). Although some systemic absorption occurs, there are no proven systemic side effects with latanoprost therapy, and none would be expected given its pharmacokinetics (27, 28).

The primary strength of the present study was its long-term follow-up of a wide spectrum of patients worldwide. However, as a postmarketing surveillance study, patients were treated according to routine medical practice, and investigators could modify the therapy of any patient in either randomization group. Because a large proportion of patients received both latanoprost and usual care over the 5-year study period, no meaningful statistical comparisons could be made between treatments. Despite this limitation, the overall conclusion is that latanoprost does not carry a significant safety risk over the long term compared to all other agents, prostaglandins and non-prostaglandins, used in clinical practice in this study.

Results of this 5-year study indicate that latanoprost as prescribed in clinical practice in 14 countries worldwide is a safe long-term treatment for patients with glaucoma and ocular hypertension. The incidence of serious adverse drug reactions was low and did not raise any new safety concerns. Reassuringly for patients and physicians, there was no evidence of possible long-term consequences associated with increased iris pigmentation.

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The protocol was reviewed and approved by the Institutional Review Boards and Independent Ethics Committees at each investigational center, and the study complied with the ethical principles maintained in the 1964 Declaration of Helsinki.

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