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Efficacy and Safety of Latanoprost Eye Drops for Glaucoma Treatment: A 1-Year Study in Japan

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Purpose: To evaluate the intraocular pressure (IOP)-lowering effect and safety of latanoprost, a prostaglandin analogue, in patients with primary open-angle glaucoma or ocular hypertension.

Method: One hundred and twenty-four Japanese patients with primary open-angle glaucoma or ocular hypertension were enrolled in this open-labeled study and were treated with 0.005% latanoprost once daily for 1 year.

Results: At all follow-up visits there was a significant ($P < .001$) reduction in IOP compared with the baseline value. After 1 year, the IOP was reduced by 5.4 ± 2.9 (mean ± SD) mm Hg from a baseline value of 23.5 ± 2.2 mm Hg. No evidence of an upward drift in the IOP was observed during the treatment period. The most frequently reported adverse ocular events were mild conjunctival hyperemia and iris pigmentation. Very few adverse systemic events were observed.

Conclusions: Latanoprost eye drops showed a marked and stable IOP-lowering effect during the 1-year treatment period. Furthermore, latanoprost was well-tolerated and should be a valuable contribution to the management of glaucoma. **Jpn J Ophthalmol 2000;44: 33–38** © 2000 Japanese Ophthalmological Society

Key Words: Clinical study, glaucoma, latanoprost, prostaglandin $F_{2\alpha}$.

Introduction

Latanoprost (Xalatan™) and isopropyl unoprostone (Rescula™) are prostaglandin $F_{2\alpha}$ analogues that act on prostaglandin $F_{2\alpha}$ receptors.[1,2] Both drugs have shown ocular hypotensive effect in topical application for primary open-angle glaucoma (POAG) and ocular hypertension (OH). In phase II clinical studies of latanoprost eye drops performed in Japan, the optimal clinical dose regimen was confirmed to be 0.005% (50 μg/mL) administered once daily.[3,4] Latanoprost has been shown to have an intraocular pressure (IOP)-lowering effect of long duration when administered once daily.[5]

The mechanism of action of prostaglandins is believed to be an increase of uveoscleral outflow with no effect on aqueous humor production.[6,7] A morphological background of the mechanism of action was obtained from in vitro studies that showed an alteration of the extracellular matrix (ECM) around the ciliary smooth muscle cells.[8–10] In a study by Lindén and Alm,[11] the IOP slowly returned to baseline after discontinuation of latanoprost, suggesting that the morphological changes in the extracellular matrix induced by prostaglandins are reversible.

In double-masked, randomized clinical studies performed in Japan, the United States, Scandinavia, and the United Kingdom, it was shown that once-daily application of 0.005% latanoprost was more effective, or at least as effective, as timolol 0.5% twice daily in IOP-lowering effect.[12–15] Camras et al[16] reported on the excellent safety and efficacy of latano-

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prost after 1-year treatment. Recently Watson[17] reported the results of long-term experience with latanoprost treatment in patients with POAG or OH, in which latanoprost provided a stable IOP reduction with no sign of upward drift for up to 2 years of treatment of patients in the United Kingdom.

A new and true side effect in some patients is a darkening of the iris color after latanoprost[13–15] and unoprostone[18] treatment. The darkening is caused by an increase of melanin synthesis without cell proliferation and is more apparent in patients with mixed-colored irides.[19] This effect seems to be a classic effect of prostoglandins.[20]

The purpose of this multicenter, 1-year clinical study was to investigate the efficacy and safety of latanoprost 0.005% eye drops in Japanese patients.

Materials and Methods

This open-labeled study was performed at 25 centers throughout Japan between September 1993 and March 1995. The protocol was approved by the institutional review board (Ethics Committee) at each participating center, and all patients gave their written informed consent before the start of the study.

A total of 124 patients with primary open-angle glaucoma or OH were enrolled in the study. Patients who were 20–80 years of age with either POAG or OH and who had a baseline IOP in both eyes above 20 mm Hg and below 34 mm Hg were included. Patients who were excluded had undergone intraocular or laser surgery within the preceding year, had a history of serious ophthalmic trauma, wore contact lenses, or had infectious keratitis or uveitis within the 6 months prior to the start of the study. Patients were also excluded if they suffered from or had a history of serious cardiac disease or serious hepatic, renal, or metabolic disorders, or if they, in the opinion of the physician-in-charge, were otherwise ineligible. Women who were breastfeeding, pregnant, or likely to become pregnant were not included in the study.

Twelve patients were withdrawn from the study. Of two withdrawn for medical reasons, 1 patient had aggravated preexisting pulmonary cancer, which was not known when the patient was enrolled. The other had a cerebral hemorrhage due to a brain tumor that was undetected until the occurrence of the hemorrhage. Two other patients were withdrawn; 1 because of an adverse event diagnosed as severe headache and nausea, and the other with conjunctival hyperemia. Five patients were lost to follow-up and 3 patients withdrew consent. Therefore, 112 patients were included in the efficacy analysis. Patient demographics are shown in Table 1.

Table 1. Patient Demographics

	Initial No. of Patients
Age (y)	55.8 ± 13.3 (mean ± SD)
Maximum	80
Minimum	25
Gender	
Female	55
Male	69
Diagnosis	
Primary open-angle glaucoma	51*
Right eye	47
Left eye	49
Ocular hypertension	79*
Right eye	76
Left eye	75
Previous IOP medication	
β-adrenergic antagonist	71
Adrenergic agonist	23
Cholinergic agonist	24
Oral carbonic anhydrase inhibitor	4
Other antiglaucoma drugs	11

IOP: intraocular pressure.
*Six patients had different diagnoses in left and right eyes.

For patients with ongoing medical antiglaucoma treatment, a wash-out period of 2 (α-adrenergic agonists or cholinergic agonists) to 4 weeks (β-adrenergic antagonists, systemic carbonic anhydrase inhibitors) was used prior to study start. After determining eligibility, patients were given 0.005% latanoprost eye drops with instruction to use one drop once daily in the morning in both eyes.

The IOP was measured with a Goldmann applanation tonometer in the morning before administration of latanoprost, ie, 24 hours post-dose at the trough. The schedule of examinations and procedures is presented in Table 2. These included the following: systemic subjective symptoms, ocular subjective and objective findings (slit-lamp examinations), pupillary diameter, visual acuity and refraction, visual field, anterior chamber angle and ocular fundus (measurement of cup/disc [C/D] ratio, retinal findings). Clinical laboratory tests (hematology, serum biochemistry, and urine analysis) were also performed. In a small group of patients (26 patients at 5 centers), iris photographs were obtained at baseline, week 24, and at week 52.

Adverse events were defined as any undesirable event occurring to a patient whether or not it was considered related to the treatment with latanoprost.

Table 2. Schedule of Examinations and Procedures

Examinations	Prestudy −4 weeks	Baseline	Week 2	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 28	Week 32	Week 36	Week 40	Week 44	Week 48	Week 52
Systemic subjective symptoms		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Ocular subjective symptoms	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Ocular objective findings (slit-lamp examination)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
IOP	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pupillary diameter	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Visual acuity/refraction	X	X				X			X			X				X
Ocular fundus	X	X				X			X			X				X
Visual field/anterior chamber angle		X							X							X
Clinical laboratory tests (hematology, serum biochemistry, and urine analysis)		X														X

IOP: intraocular pressure.

Statistical Analysis

The mean IOP value of both eyes was calculated and used in the analyses. The results were analyzed by the Wilcoxon test, *t*-test, or analysis of variance. The level of significance was $P < .05$ (two-tailed test).

Results

Compared with the baseline IOP of 23.5 ± 2.2 mm Hg (mean ± SD), the IOP at week 2 had decreased significantly to 18.1 ± 2.4 mm Hg ($P < .001$). Latanoprost consistently reduced IOP between 5.4 mm Hg and 6.3 mm Hg throughout the remaining 50-week treatment period (Table 3). At the end of 52 weeks of treatment, 12.5% of the 112 patients attained an IOP reduction of 10 mm Hg or more.

The IOP reduction reached a maximum at week 28, which for most patients occurred in the summer, when the IOP response to hypotensive agents has been shown to be greater than in the winter.[21] This also coincided with the time when the majority of our patients terminated the study. This could, perhaps, explain the very slight seasonal variation of the IOP reduction during the study period.

Sixty-four adverse events were reported in 49 patients, of which 60 were ocular events (Table 4). The most common of these ocular events were 27 cases of conjunctival hyperemia (3 moderate and 24 mild), 10 of iris pigmentation, and 8 of ocular itching. Almost all the adverse events were mild and transient.

Ten patients developed a suspected increase in iris pigmentation as observed by slit-lamp microscopy. The darkening appeared 6 months after the start of latanoprost treatment and was seen as a diffuse darkening of the uniformly brown irides. However, the suspected increase could not be noticed by the naked eye.

The visual acuity and the diameter of the pupils did not change significantly during the study. In 8 eyes of 8 patients, a deterioration of the visual field was reported. However, the changes were small and were not considered to be clinically relevant. Flare or cells in the anterior chamber were not found.

Four mild adverse systemic events were reported in three patients (Table 4). In one patient, the number of blood leukocytes increased but returned to normal during the latanoprost treatment. Otherwise, there were no clinically significant changes in hematology, blood chemistry, kidney, or liver functions. None of the events reported was considered to be related to latanoprost treatment. No cardiovascular or respiratory adverse events were reported during the study.

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Table 3. Differences in Intraocular Pressure (IOP) (mean ± SD), Baseline to Week 52

	Baseline	Week 2	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 28	Week 32	Week 36	Week 40	Week 44	Week 48	Week 52
IOP (mm Hg)	23.5 ± 2.2	18.1 ± 2.4	17.9 ± 2.4	18.0 ± 2.7	18.0 ± 2.6	17.6 ± 2.1	17.5 ± 2.4	17.6 ± 2.2	17.3 ± 2.4	17.4 ± 2.2	17.4 ± 2.3	17.6 ± 2.4	17.6 ± 2.4	18.1 ± 2.6	8.2 ± 2.6
IOP (Change from baseline)		5.4 ± 2.2	5.7 ± 2.4	5.6 ± 2.8	5.5 ± 2.7	5.9 ± 2.4	6.0 ± 2.8	6.0 ± 2.5	6.3 ± 2.6	6.1 ± 2.5	6.1 ± 2.7	5.9 ± 2.7	5.8 ± 2.6	5.4 ± 2.9	5.4 ± 2.9
No. of patients		110	110	111	110	108	110	108	100	101	108	104	103	101	106

Table 4. Ocular and Systemic Findings*

Findings	No. of Events Reported
Conjunctival hyperemia	27
Iris pigmentation	10
Itching	8
Smarting	5
Punctate epithelial keratitis	3
Allergic conjunctivitis	1
Eyelid pigmentation	1
Corneal erosion	1
Blepharitis	1
Filamentary keratitis	1
Heaviness	1
Pain	1
Increase in white blood cell count	1
Sore throat	1
Headache	1
Nausea	1

*Sixty-four adverse events were reported in 49 patients (47 patients had ocular adverse events and 3 patients had systemic adverse events). Twelve withdrawn patients are included.

Discussion

In this long-term study, the IOP reduction with latanoprost was of the same magnitude as reported earlier in the 3-month, double-masked, comparative study.[12] There was a small variation in the mean reduction of IOP during summer in the present study. Whether this was a coincidence or a true seasonal effect cannot be judged by this study design. More importantly, there was no tendency toward loss of efficacy during the 12-month treatment period. This stands in contrast to timolol, which is known to lose some of its initial IOP reducing capability.[22]

In preclinical[20] and clinical studies,[13–17] alteration of the iris pigmentation has been identified as a local side effect of latanoprost, and this phenomenon has been described as a classic effect of prostaglandins.[20] A well-known side effect of latanoprost on the ocular surface is conjunctival hyperemia.[13–15] Hyperemia was the most common adverse event in this study (42% of all events) and also occurred at a similar frequency in the 3-month, double-masked comparative study (39% of the events).[12] Hyperemia is a nonspecific, sporadic, and common ocular symptom. The severity of hyperemia was the only reason given for the withdrawal of 1 patient from this study. If the number of itching and smarting events are added together and a comparison is made in the present and the earlier 3-month study,[12] there is a tendency toward fewer superficial irritation symptoms during this long-term open study. This difference is most likely due to less irritative stimuli, such as preserva-

tives, because there were no placebo drops administered in the present open-labeled study.

A rare number of cases with iritis symptoms has been reported following latanoprost treatment.[13] However, the definite diagnosis of iritis in these cases remains unclear, as slight flare and cells are not equivalent to iritis/uveitis. In this study, there were no observations of flare or cells in the anterior chamber, and in the earlier 3-month study, only one case of flare was found. Furthermore, general support against a causality between latanoprost and iritis/uveitis has been published in studies using the Kowa laser flare cell meter.[3,11,23–25]

The main findings reported during this long-term study were conjunctival hyperemia, iris pigmentation, itching, smarting, and epithelial keratitis. These are all well-known events, which also have occurred in the phase III studies overseas.[13–17] All other events appeared only once during the study. No serious adverse events that could have been related to latanoprost occurred. There was thus no indication that Japanese patients tolerate latanoprost less well than patients in Scandinavia, the United Kingdom, and the United States.

The present results demonstrate that 0.005% latanoprost administered once daily reduces IOP in Japanese patients with POAG or OH for 1 year, without evidence of long-term drift. These results confirm the efficacy and safety of latanoprost treatment in Japanese patients as reported earlier from the double-masked, randomized comparative 3-month study with timolol as control.[12]

In conclusion, maintaining a marked and stable IOP-lowering effect during a 1-year treatment period and with an advantageous safety profile, latanoprost should be a valuable contribution to the management of glaucoma.

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