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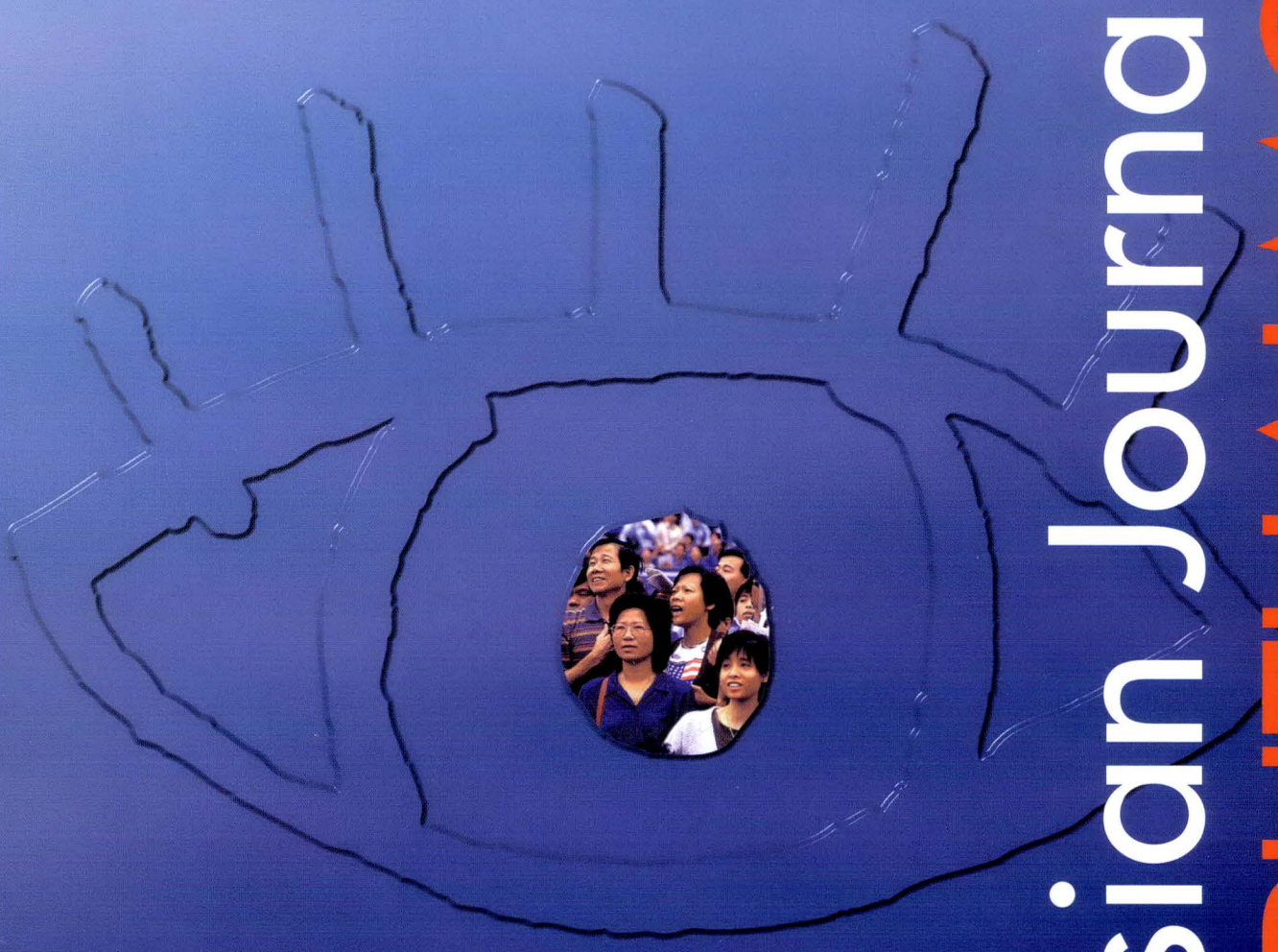

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The Effect of Latanoprost *vs* Timolol on Intraocular Pressure in Patients with Glaucoma and Ocular Hypertension

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The objective of this study was to compare the effect on intraocular pressure (IOP) of latanoprost 0.005% once daily with timolol 0.5% twice daily in patients with open angle glaucoma or ocular hypertension. The study was designed as a single-centre, randomised, double-masked parallel-group comparison of latanoprost with timolol after 12 weeks of treatment.

60 patients with open angle glaucoma or ocular hypertension with IOP of at least 22 mm Hg were included. Administration of previous ocular hypotensive medication necessitated a wash-out period of 5 to 21 days before the start of the study treatment. The patients were randomised to treatment with latanoprost 0.005% once daily or timolol 0.5% twice daily. Mean diurnal IOP was measured at baseline and after 6 and 12 weeks of treatment.

After 6 weeks of treatment, the diurnal IOP reduction (mean ± standard error of the mean [SEM]) in the latanoprost group was 12.1 ± 1.1 mm Hg (41%; $p < 0.001$; analysis of covariance [ANCOVA]) and 8.7 ± 1.1 mm Hg (30%; $p < 0.001$; ANCOVA) in the timolol group. The difference of 3.4 ± 1.6 mm Hg was statistically significant in favour of latanoprost ($p = 0.034$; ANCOVA). A 30% reduction or more in mean diurnal IOP was achieved by 71% of patients in the latanoprost group and by 34% of patients in the timolol group. After 12 weeks of treatment, the diurnal IOP reduction (mean ± SEM) in the latanoprost group was 11.1 ± 1.2 mm Hg (39%; $p < 0.001$; ANCOVA) and 9.1 ± 1.1 mm Hg (32%; $p < 0.001$; ANCOVA) in the timolol group.

Most side effects observed were mild and transient and no serious adverse events were reported. Latanoprost 0.005% administered once daily in the evening was at least as effective as timolol 0.5% twice daily in reducing the mean diurnal IOP after 6 and 12 weeks of treatment. Both medications were well tolerated during the study period.

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Key Words: Glaucoma; Ocular hypertension; Diurnal intraocular pressure; Latanoprost; Timolol.

Latanoprost (13,14-dihydro-17-phenyl-18,19,20-trinor-prostaglandin $F_{2\alpha}$-isopropylester, previously PhXA41) has proven to be an effective ocular hypotensive drug.[1-7] The mechanism of action is an increase in aqueous humour outflow, with little or no effect on aqueous humour production.[8,9] Latanoprost administered to monkey eyes increased uveoscleral outflow with no effect on conventional outflow,[10] and a corresponding effect has indirectly been demonstrated in humans.[8] In long-term studies, latanoprost 0.005% applied once daily reduced intraocular pressure (IOP) at least as effectively as β-adrenergic antagonists.[2-5] After 1 to 2 years of treatment, the IOP reduction is maintained with no evidence of major drift of IOP over time.[6,7] Latanoprost is well tolerated both locally and systemically. Apart from mild conjunctival hyperaemia and some other transient ocular symptoms, the only adverse reaction of clinical importance noted in long-term studies was increased pigmentation of the iris,[2-4,6,7] most probably due to increased melanin production in the melanocytes. The purpose of this study was to compare the effect of latanoprost administered once daily with timolol administered twice daily for 12 weeks in patients with open angle glaucoma or ocular hypertension in a Philippine population. In addition, ocular and systemic safety variables were monitored and reported throughout the study.

Patients and Methods

The study was a single-centre, randomised, double-masked parallel-group comparison of latanoprost 0.005% administered once daily with timolol 0.5% administered twice daily. After obtaining approval from the Medicine Control Council and the Ethics Committee of the

University of the Philippines, a signed informed consent was obtained from all patients before enrolment in the study. The study followed the guidelines of the Declaration of Helsinki.

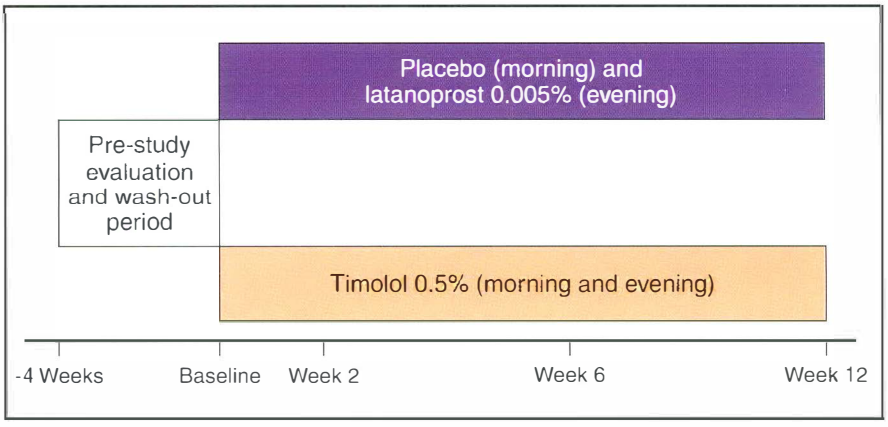
Patients with unilateral or bilateral open angle glaucoma, capsular glaucoma, pigmentary glaucoma, or ocular hypertension were included in the study. If both eyes fulfilled the eligibility criteria they were both regarded as study eyes and the mean IOP was used for the analysis. Inclusion criteria also comprised a minimum age of 18 years, no prior glaucoma treatment or only single-drug treatment for elevated IOP and IOP of at least 22 mm Hg at the pre-study visit with or without medication. If the patients were receiving single-drug glaucoma treatment, they were eligible after a wash-out period of at least 21 days for β-adrenergic antagonists, 14 days for adrenergic agonists and 5 days for cholinergic agonists and carbonic anhydrase inhibitors.

Exclusion criteria included use of any medications other than glaucoma drugs, closed or barely open anterior chamber angle, ocular surgery or argon laser trabeculoplasty within the last 3 months, current use of contact lenses, ocular inflammation within the last 3 months, any condition preventing reliable applanation tonometry, current pregnancy or lactation, pregnancy consideration, or inability to adhere to the protocol design.

After inclusion in the study, the patients were randomly assigned to either latanoprost treatment, in which placebo eye drops were given in the morning and latanoprost 0.005% eye drops in the evening, or timolol treatment, in which timolol 0.5% eye drops were given twice daily (figure 1).

At the pre-study visit, both medical and ocular histories were taken. Gonioscopy and perimetry were carried out unless recently performed. Also, visual acuity and refraction, slit-lamp examination, ophthalmoscopy, and IOP measurement were performed. This pre-study visit took place 1 month before the study started and the patients were included after these eligibility assessments. If the patients were taking a single-drug glaucoma treatment, an appropriate wash-out period was allowed for before the start of the study, as outlined above. During the study period of 12 weeks there were 4 scheduled follow-up visits: at baseline and after 2, 6, and 12 weeks.

Figure 1. **Study outline.**



The IOP was measured with a calibrated Goldmann applanation tonometer. Three measurements were performed in each eye. The mean of the 3 measurements was used in the statistical analyses. The IOP was measured at 9.00 am, 1.00 pm and 5.00 pm at the baseline visit, and at weeks 6 and 12, whereas IOP was measured only at 9.00 am at the week 2 visit. Best corrected Snellen visual acuity and refractive error were determined at each visit and a slit-lamp examination was performed. Flare was graded as none, mild, moderate, or severe and cells present in a slit width of 2 mm were graded as none (1 cell), mild (3-5 cells), moderate (6-20 cells) or severe (>20 cells). At the prestudy visit and at the week 12 visit ophthalmoscopy was performed through dilated pupils. Iris and en face photographs were taken at the baseline visit and at the week 12 visit.

An analysis of covariance (ANCOVA) was performed with diurnal IOP change as a response variable, baseline diurnal IOP as a covariate and the group as a study effect. The difference between the latanoprost group and the timolol group was estimated from the ANCOVA. The mean diurnal IOP was defined as the mean of the measurements at 9.00 am, 1.00 pm and 5.00 pm.

Table 1. **Patients' characteristics.**

Characteristics	Latanoprost (n = 30)	Timolol (n = 30)
Sex (male/female)	17/13	21/9
Mean age (range)	58 (21-92)	56 (20-86)
Asian race	30	30
Eye colour homogeneously brown	30	30
Primary open angle glaucoma	26	29
Exfoliation glaucoma	1	0
Ocular hypertension	3	1

Results

60 patients were included in the study with 30 patients randomised to each of the latanoprost and timolol groups, respectively. The patients' characteristics are presented in table 1. There was no significant difference between the 2 treatment groups with respect to age, sex distribution, or diagnosis. Of the 60 patients included, 53 completed the study. Of the 7 patients withdrawn, 4 participated in the week 6 visit and the IOP measurements from this visit could be incorporated in the week 6 analysis. Patients were withdrawn for the following reasons: lost to follow-up (3 patients), systemic hypertension (2 patients) and increased IOP (2 patients).

After 6 weeks of treatment, latanoprost reduced the diurnal IOP from 29.9 ± 1.8 mm Hg (mean ± SEM) to 17.3 ± 1.2 mm Hg. Timolol treatment reduced the diurnal IOP from 28.7 ± 1.5 mm Hg (mean ± SEM) to 20.5 ± 1.2 mm Hg. The diurnal IOP reduction in the latanoprost group was 12.1 ± 1.1 mm Hg (41%; $p < 0.001$; ANCOVA) and 8.7 ± 1.1 mm Hg (30%; $p < 0.001$; ANCOVA) in the timolol group

Figure 2. Change in diurnal intraocular pressure (IOP)[mean ± SEM] from baseline to week 6.

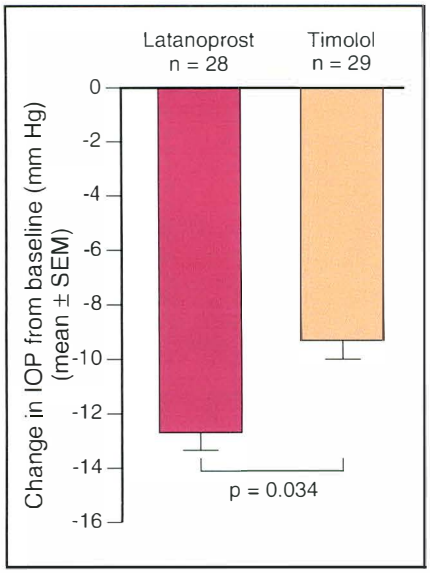
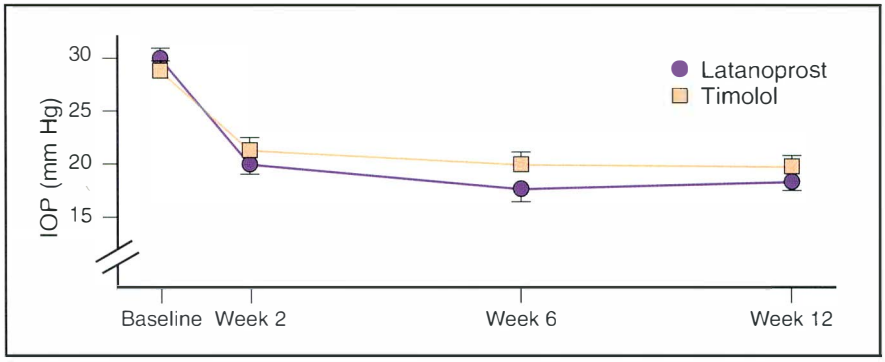


Figure 3. Diurnal intraocular pressure (IOP)[mean ± SEM] at baseline, week 6 and week 12 for the latanoprost and timolol groups. At week 2, IOP was measured in the morning.



from the overall baseline of 29.3 mm Hg. The difference of 3.4 ± 1.6 mm Hg was statistically significant in favour of latanoprost ($p = 0.034$; ANCOVA) [figure 2]. A 30% reduction or more in mean diurnal IOP at week 6 compared with baseline was achieved by 71% of the patients in the latanoprost group and by 34% of the patients in the timolol group.

After 12 weeks of treatment, the diurnal IOP was reduced to 17.7 ± 1.3 mm Hg (mean ± SEM) in the latanoprost group and to 19.4 ± 1.2 mm Hg (mean ± SEM) in the timolol group. The diurnal IOP reduction in the latanoprost group was 11.1 ± 1.2 mm Hg (39%; $p < 0.001$; ANCOVA) and 9.1 ± 1.1 mm Hg (32%; $p < 0.001$; ANCOVA) in the timolol group. The difference of 2.1 ± 1.6 mm Hg in diurnal IOP reduction between the 2 groups from the overall baseline of 28.7 mm Hg, was in favour of latanoprost but not statistically significant ($p = 0.21$; ANCOVA). The mean diurnal IOP at each measurement for the two treatment groups is shown in figure 3.

Table 2 shows the percentage of patients reaching a specific target IOP of between 15 mm Hg and 20 mm Hg at the week 6 visit. A mean diurnal IOP of ± 15 mm Hg was reached by 46% of the patients in the latanoprost group compared with 10% of timolol patients.

Ocular and systemic adverse events reported during the study are presented in table 3. In this table, the withdrawn patients are included. However, for the patients remaining in the study most events were reported as mild. No cells or flare in the anterior chamber were reported for any patient during the study. Iris photograph and slit-lamp examinations did not reveal any changes in the pigmentation of the iris. No serious adverse events were reported.

Discussion

This study demonstrates that latanoprost 0.005%, given once daily, safely and effectively reduces the IOP during the study period of 12 weeks in patients with

Table 2. Percentage (%) of patients who reached a specific target intraocular pressure (IOP) at week 6.

Diurnal IOP	Latanoprost (n = 28)	Timolol (n = 29)
≤ 15 mm Hg	46	10
≤ 16 mm Hg	46	21
≤ 17 mm Hg	54	41
≤ 18 mm Hg	54	45
≤ 19 mm Hg	71	45
≤ 20 mm Hg	79	48

Table 3. **Number of ocular and systemic adverse events reported during the study (withdrawn patients included).**

Adverse event	Latanoprost	Timolol
Ocular	n = 12	n = 11
Change in refractive power	7	7
Increased intraocular pressure	3	1
Blepharitis/lid swelling	2	1
Hypersensitivity/stinging	2	1
Blurred vision	1	0
Conjunctivitis	0	1
Systemic	n = 2	n = 5
Increased blood pressure	1	1
Dizziness	1	0
Upper respiratory tract infection	0	1
Fever/influenza	0	3

open angle glaucoma or ocular hypertension. Compared with timolol 0.5% given twice daily, latanoprost once daily was significantly more effective in reducing mean diurnal IOP after 6 weeks and at least as effective after 12 weeks. This is in agreement with long-term phase III studies lasting for 3 to 6 months in which latanoprost was found to be more effective than,[2,3,5] or at least as effective as,[4] timolol in lowering the IOP in patients with similar diagnosis. The IOP reduction in the latanoprost group of 39 to 41% was higher than the 30 to 35% reduction seen in previously reported randomised, double-masked studies;[2-5] the IOP reduction of 30 to 32% in the timolol group was also higher,[2,3,5] or comparable to,[4] these earlier results.

The design of the present study included IOP measurements at 1, 5 and 9 hours after the last dose of timolol and at 13, 17, and 21 hours after the last dose of latanoprost. There is no noticeable peak or trough effect after each dose of timolol or latanoprost since they both have a long duration. Comparing the effect on mean diurnal IOP thus seems to be a reasonable evaluation of the clinical effect.

Another way to evaluate the clinical efficacy of different ocular hypotensive drugs is to analyse the number of patients that reached a target IOP. In this study the patients in the latanoprost group were more successful in reaching a specific target IOP compared with the timolol group. A total of 46% of all latanoprost-treated patients succeeded in reaching a mean diurnal IOP of 15 mm Hg or lower, whereas 10% of all timolol-treated patients succeeded in reaching that target. This finding is in agreement with the results from the three 6-month phase III clinical trials[2-4] where 27% of the latanoprost-treated patients reached the target IOP of 15 mm Hg or less compared with 14% of the timolol-treated patients (Katarina Hedman, unpublished observations).

Most side effects observed were mild and transient and no serious adverse events were reported. Slit-lamp examinations were performed regularly to detect any cells or flare in the anterior chamber as a sign of increased permeability of the blood-aqueous barrier. In several clinical studies,[9,11-14] no signs of breakdown of the blood-aqueous barrier were observed. In the three 6-month phase III clinical studies,[2-4] there was no difference between latanoprost and timolol in the incidence of cells or flare. During 1 year of treatment with latanoprost, slight aqueous flare and a few cells have been reported in a small number of patients, however 2 of these patients had cells present at baseline.[6] In this 12-week study, no signs of flare or cells in the anterior chamber were found, indicating an intact blood-aqueous barrier in patients receiving latanoprost treatment as well as for those receiving timolol treatment.

Iris pigmentation has been reported following latanoprost treatment.[2-4,6,7] After 1 year of treatment this was reported in approximately 16% of patients.[15] The increased pigmentation predominantly occurred in patients with mixed coloured iris, ie blue/grey-brown, green-brown or yellow-brown eyes. Between 3 and 17 months of latanoprost treatment preceded the first sign of increased brown pigment in these irides.[7,15] Melanogenesis is considered the underlying mechanism of increased iris pigmentation and no signs of a proliferative effect have been found.[15] In our study, all participating patients had homogeneously brown iris colour and there were no signs of increased iris pigmentation in any of the patients in the 2 treatment groups.

In conclusion, the results of this study show that latanoprost 0.005% administered once daily in the evening is statistically significantly more effective than timolol 0.5% administered twice daily in reducing the mean diurnal IOP after 6 weeks of treatment and at least as effective as timolol after 12 weeks of treatment. Systemic and ocular side effects were mild and transient for both medications. Latanoprost can be considered to be a safe and effective agent for treating ocular hypertension and open angle glaucoma.

References

1. Alm A, Widengard I, Kjellgren D, *et al.* Latanoprost administered once daily caused a maintained reduction of intraocular pressure in glaucoma patients treated concomitantly with

timolol. *Br J Ophthalmol* 1995;**79**:12-16.
2. Alm A, Stjernschantz J, the Scandinavian Latanoprost Study Group. Effects on intraocular pressure and side effects of 0.005% latanoprost applied once daily, evening or morning. A comparison with timolol. *Ophthalmology* 1995;**102**: 1743-1752.
3. Camras CB, the United States Latanoprost Study Group. Comparison of latanoprost and timolol in patients with ocular hypertension and glaucoma. A six-month, masked, multicenter trial in the United States. *Ophthalmology* 1996; **103**:138-147.
4. Watson P, Stjernschantz J, the Latanoprost Study Group. A six-month, randomized, double-masked study comparing latanoprost with timolol in open-angle glaucoma and ocular hypertension. *Ophthalmology* 1996; **103**:126-137.
5. Mishima HK, Masuda K, Kitazawa Y, *et al.* A comparison of latanoprost and timolol in primary open-angle glaucoma and ocular hypertension. A 12-week study. *Arch Ophthalmol* 1996;**114**: 929-932.
6. Camras CB, Alm A, Watson P, Stjernschantz J, the Latanoprost Study Groups. Latanoprost, a prostaglandin analog, for glaucoma therapy. Efficacy and safety after 1 year of treatment in 198 patients. *Ophthalmology* 1996;**103**: 1916-1924.
7. Watson PG, the Latanoprost Study Group. Latanoprost two years' experience of its use in the United Kingdom. *Ophthalmology* 1998;**105**:82-87.
8. Toris CB, Camras CB, Yablonski ME. Effects of PhXA41, a new prostaglandin $F_{2\alpha}$ analog, on aqueous humor dynamics in human eyes. *Ophthalmology* 1993; **100**:1297-1304.
9. Ziai N, Dolan JW, Kacere RD, Brubaker RF. The effects on aqueous dynamics of PhXA41, a new prostaglandin $F_{2\alpha}$ analogue, after topical application in normal and ocular hypertensive human eyes. *Arch Ophthalmol* 1993;**111**: 1351-1358.
10. Stjernschantz J, Selen G, Sjoquist B, Resul B. Preclinical pharmacology of latanoprost, a phenyl-substituted $PGF_{2\alpha}$ analogue. *Adv Prostaglandin Thromboxane Leukot Res* 1995;**23**:513-518.
11. Hotehama Y, Mishima HK. Clinical efficacy of PhXA34 and PhXA41, two novel prostaglandin $F_{2\alpha}$-isopropyl ester analogues for glaucoma treatment. *Jpn J Ophthalmol* 1993;**37**:259-269.
12. Linden C, Nuija E, Alm A. Effects on IOP restoration and blood-aqueous barrier after long term treatment with latanoprost in open angle glaucoma and ocular hypertension. *Br J Ophthalmol* 1997;**81**:370-372.
13. Widengard I, Maepea O, Alm A. Effects of latanoprost and dipivefrin, alone or combined, on intraocular pressure and on blood-aqueous barrier permeability. *Br J Ophthalmol* 1998;**82**:404-406.
14. Diestelhorst M, Roters S, Krieglstein GK. The effect of latanoprost 0.005% once daily versus 0.015% twice daily on intraocular pressure and aqueous humour protein concentration in glaucoma patients. A randomized, double-masked comparison with timolol 0.5%. *Graefes Arch Clin Exp Ophthalmol* 1997;**235**:20-26.
15. Wistrand PJ, Stjernschantz J, Olsson K. The incidence and time-course of latanoprost-induced iridial pigmentation as a function of eye color. *Surv Ophthalmol* 1997;**41** (Suppl 2): S129-S138.

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