

SCIENTIFIC REPORT

A 12 week study comparing the fixed combination of latanoprost and timolol with the concomitant use of the individual components in patients with open angle glaucoma and ocular hypertension

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Background: To compare the intraocular pressure (IOP) lowering effect and safety of the fixed combination of latanoprost and timolol with that of the concomitant use of the individual components.

Methods: A 12 week, double masked, randomised, crossover, multicentre study of patients with open angle glaucoma or ocular hypertension and IOP controlled on ocular hypotensive treatment (mean ≤ 21 mmHg). Patients received either a once daily morning dose of the fixed combination of latanoprost 0.005% and timolol 0.5% or once daily evening latanoprost 0.005% and twice daily timolol 0.5% for six weeks and then switched to the other combination. The primary efficacy endpoint was the within-patient difference in diurnal IOP between fixed and unfixed treatment combinations after six weeks of treatment; a one sided 97.5% confidence interval (CI) for the mean difference in IOP < 1.0 mmHg indicated the fixed combination was not inferior to the unfixed combination. Adverse events were recorded at each visit.

Results: In all, 190 patients were included in observed cases analyses (93 fixed to unfixed combination; 97 unfixed to fixed combination). Mean IOP at baseline was 16.9 mmHg in both groups. The mean diurnal IOP was 17.0 mmHg after fixed combination treatment and 15.9 mmHg after unfixed combination therapy ($p < 0.0001$). The difference in mean within-patient diurnal IOP was 1.1 mmHg favouring the unfixed combination (95% CI 0.8 to 1.4 mmHg). Both treatments were tolerated well.

Conclusions: Although the primary efficacy endpoint was not met, once daily administration of the fixed combination of latanoprost and timolol was found to be safe and effective. The fixed combination provides a convenient alternative to the three instillations required with the individual components.

potential adjunctive treatment options.³ Clearly, identifying treatments that best maximise considerations of safety, efficacy, and patient compliance remains a substantial challenge.

The β -adrenergic receptor antagonist timolol has been shown to provide excellent additivity with other ocular hypotensives.^{4–7} Approved for use in 1977, timolol given once or twice daily lowers IOP in POAG and OH by reducing the production of aqueous humour.^{8–10} Latanoprost, the first prostaglandin $F_{2\alpha}$ analogue to be commercially available in Europe and the US, has been shown to lower IOP more effectively than timolol when administered once daily.^{11–13} Prostaglandin $F_{2\alpha}$ analogues lower IOP by facilitating uveoscleral outflow of aqueous humour,¹⁴ a mechanism distinct from that of timolol. The additivity of the IOP-lowering effect of latanoprost and timolol has been shown.^{9, 7, 15} In the case of combination treatments including timolol, a single fixed formulation may improve patient compliance by reducing both the number of medication containers and, when feasible, the number of doses administered each day.^{16, 17}

The efficacy of a fixed formulation of latanoprost 0.005% and timolol 0.5% given once daily has been evaluated in trials in Europe and the US, and the fixed combination provided greater IOP lowering than either monotherapy.^{18–20} A single dose of the fixed combination administered in the morning has been shown to provide maximal IOP reduction after 6.4 hours with a pronounced reduction in IOP levels still evident 48 hours post dose.²¹ No direct comparison, however, of the efficacy and safety of the fixed and unfixed combinations of latanoprost and timolol has been reported. This randomised, 12 week, double masked, crossover study compared the IOP lowering effect and safety of the fixed combination of latanoprost and timolol with that of the concomitant use of the individual components.

MATERIALS AND METHODS

Study design

In this 12 week, randomised, double masked, multicentre study, patients with primary open angle glaucoma or ocular hypertension were treated with either a once daily morning dose of the fixed combination of latanoprost 0.005% and timolol 0.5%, or with once daily latanoprost 0.005% administered in the evening and twice daily timolol 0.5% for six weeks and then switched to the other drug combination. An independent ethics committee reviewed the protocol before initiating the study, and the research was conducted in accordance with the ethical standards maintained in the Declaration of Helsinki. All patients were fully informed and gave their written consent prior to enrolment.

Heterogeneity among patients with primary open angle glaucoma (POAG) and ocular hypertension (OH) ensures the need for multiple approaches to the management of elevated intraocular pressure (IOP). Topical application of a single hypotensive medication remains the preferred treatment for new patients.¹ When the targeted IOP reduction cannot be reached with monotherapy, however, combining drugs is often indicated, and as many as 40% of glaucoma patients are treated with a combination of medications.² Currently available ocular hypotensive treatments comprise roughly 20 distinct agents in five different drug classes thus providing physicians with over 2500

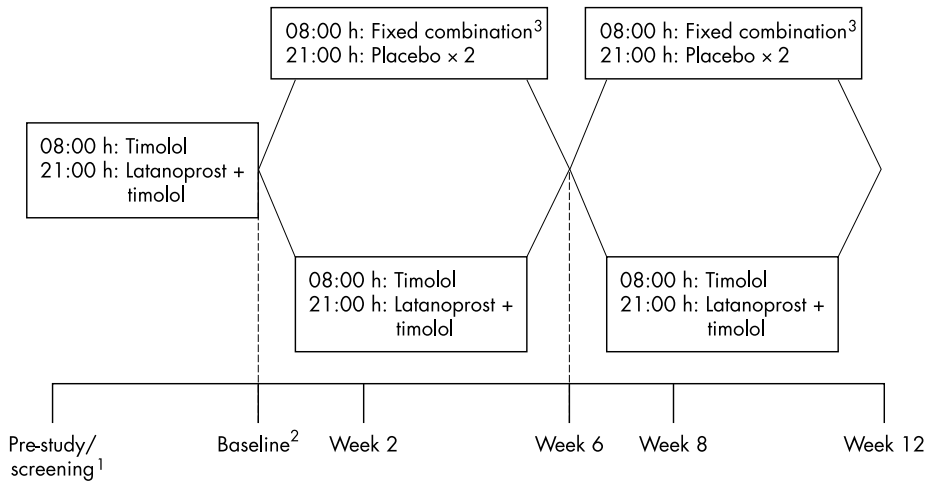


Figure 1 Study design. (1) Timing of screening visit 2–4 weeks before the baseline visit. (2) Baseline visit with randomisation and treatment initiation. (3) Fixed combination of latanoprost 0.005% and timolol 0.5%.

Patients

Patients ≥ 18 years of age with unilateral or bilateral open angle glaucoma (including also normal tension, pigmentary, or pseudoexfoliative glaucoma) or ocular hypertension were eligible for the study if they were receiving the unfixed combination of latanoprost 0.005% once daily and either timolol 0.5% once or twice daily, timolol 0.25% once or twice daily, or timolol 0.1% once daily. For inclusion in the study, patients had to have: (1) been using one of these therapeutic combinations for at least the preceding four weeks; (2) been satisfactorily controlled on current treatment in the opinion of the investigator; (3) had an IOP ≤ 21 mmHg as assessed by two determinations separated by at least one hour, and (4) had a best corrected visual acuity $>20/200$.

Patients were excluded from study if they had a history of acute angle closure, had a closed or barely open anterior chamber angle, or currently used contact lenses. In addition, patients were excluded if during the three months before the prestudy visit they had ocular surgery or argon laser trabeculoplasty in the study eye(s) or had an ocular inflammation or infection. Patients with a known sensitivity to benzalkonium chloride or to any other component of the study drug solutions were excluded, as were those with any condition preventing reliable applanation tonometry or any abnormal ocular condition or symptom preventing study eligibility as judged by the investigator. Patients with a medical condition in which treatment with β -blocking agents is contraindicated also were excluded. Women of child-bearing age not using adequate contraceptive methods in the three months before the study, and pregnant or nursing

women were ineligible, as was any patient deemed unable to adhere to the study protocol or who had participated in another clinical trial within the previous month.

Treatments and assessments

Potential patients were evaluated for eligibility at a prestudy visit two to four weeks before starting the study. At that visit, a medical history was taken, visual acuity and refraction were measured, and a lid and slit lamp examination and ophthalmoscopy were performed; a visual field examination and gonioscopy were performed unless previous findings were recorded in the patient’s record. IOP was measured with Goldmann applanation tonometry once on two occasions at least one hour apart. All ocular measurements were performed in both eyes.

At the prestudy visit, all patients were receiving latanoprost. In those receiving timolol once daily, the frequency of timolol administration was increased to twice daily (morning and evening); in those treated with a lower concentration of timolol (0.1% or 0.25%), the concentration was increased to 0.5% (fig 1). This medication regimen was continued in all patients for at least two weeks before the baseline visit.

A single blocked randomisation list was generated for the study and kept by Pharmacia, Nerviano, Italy. Study medications were shipped to individual sites in sets such that each set was a multiple of the block size of four used in generating the randomisation; this method provided for a stratified randomisation schedule with study site as the stratification factor. At the baseline visit, eligible patients were randomly assigned to one of two treatment sequences: (1) the fixed combination from baseline to week 6 and then the unfixed combination from week 6 to week 12, or (2) the unfixed combination from baseline to week 6 followed by the fixed combination from week 6 to week 12. The fixed combination (active ingredients: latanoprost 0.005%, timolol 0.5%) was administered once daily in the morning, and two drops of placebo, consisting of the timolol vehicle, were administered in the evening. The unfixed combination was given as latanoprost 0.005% administered once daily in the evening and timolol 0.5% administered both in the morning and evening. Following randomisation, a box of study medication for the first 6 week treatment period was dispensed. At week 6, patients received a new box of study medication for the second treatment period.

Study drugs were dispensed in 2.5 ml bottles, a size estimated to provide sufficient medication for 4 weeks’ use. Medications were packaged in boxes that each contained four

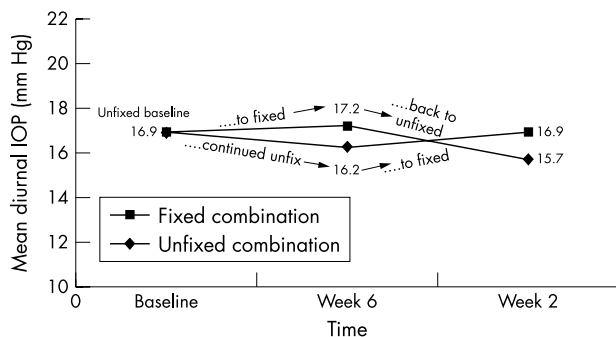


Figure 2 Mean diurnal IOP levels at week 6 and week 12.

smaller boxes. In turn, each smaller box contained one set of three identical dropper bottles labelled MORNING, EVENING (Bottle 1), and EVENING (Bottle 2). Thus, each box provided patients with two spare sets of bottles in case any were lost or should the patient run out of study medication. Patients were instructed to instil one drop per treated eye from the bottle labelled MORNING daily at approximately 08:00, and one drop every evening at approximately 21:00 from both the bottle labelled EVENING (Bottle 1) and from the bottle labelled EVENING (Bottle 2), waiting at least 10 minutes between the two drops. In patients with unilateral disease, only the affected eye was treated. In patients with bilateral disease where only one eye met the eligibility criteria (study eye), the contralateral eye (fellow eye) could be treated if no exclusion criteria were met for that eye. The first eye drops were to be instilled in the evening of the baseline visit day, and the last drops were to be instilled in the morning of the week 12 visit. On scheduled visit days, patients were instructed to instil drops immediately after the 08:00 IOP measurement. Upon arrival in the morning, investigators assessed compliance by asking the patient when the last drop had been instilled. No other ophthalmic or systemic medication known to affect IOP was permitted during the study.

All study related examinations were performed for both eyes. Masked evaluators used Goldmann applanation tonometry to measure IOP on two occasions at least one hour apart at baseline and three times at 10:00 at weeks 2 and 8. At weeks 6 and 12, three IOP measurements were performed at each of three time points: 08:00, 10:00, and 16:00. The mean of the three IOP measures at a given time point was used in statistical analyses. Best corrected visual acuity was determined at the end of each treatment period (weeks 6 and 12), lid and slit lamp examinations were performed at all visits, and ophthalmoscopy was performed at the week 12 visit. Ocular findings and ocular and systemic adverse events were monitored throughout the study beginning after the first dose of study medication and ending two weeks after medication was stopped. Investigators reported all directly observed adverse events and all such events reported spontaneously by patients. At each visit, patients also were asked whether they had experienced any health problems since the previous visit. Serious adverse events considered related to a study medication were followed until they were resolved or deemed chronic or stable.

Variables and analyses

Only study eyes were included in efficacy analyses. If both eyes were study eyes, the mean value of both IOP measurements was used. The primary efficacy variable was the within-patient difference in diurnal IOP after six weeks of treatment between the fixed and unfixed combinations of latanoprost and timolol. Diurnal IOP was defined as the mean of the IOP measurements performed at 08:00, 10:00, and 16:00. The within-patient difference in diurnal IOP level between the fixed and the unfixed combination treatment periods was calculated as the diurnal IOP at week 12 minus the diurnal IOP at week 6 for patients who began treatment with the unfixed combination. For those who began treatment with the fixed combination, the within-patient difference in diurnal IOP was defined as the diurnal IOP at week 6 minus the diurnal IOP at week 12. In both cases, positive values indicated a better effect for the unfixed combination.

An analysis of variance (ANOVA) was used to estimate the mean within-patient difference in IOP level (mmHg) and to calculate corresponding 95% confidence intervals (CI). If a one sided 97.5% CI for the mean difference in IOP level was <1.0 mmHg, the fixed combination was considered not to be inferior to the unfixed combination. A two sample *t* test was

Table 1 Demographic data (observed cases)

	Treatment group	
	Fixed combination 1st 6 weeks and unfixed combination 2nd 6 weeks (n = 93)	Unfixed combination 1st 6 weeks and fixed combination 2nd 6 weeks (n = 97)
Sex, n (%)		
Male	40 (43.0)	49 (50.5)
Female	53 (47.0)	48 (49.5)
Age (years)		
Mean	68	67
SD	12	13
Range	22–89	26–83
Race, n (%)		
White	93 (100.0)	97 (100.0)
Eye colour study eye(s), n (%)		
Homogeneously blue, grey, or green	35 (37.6)	42 (43.3)
Homogeneously brown	22 (23.7)	17 (17.5)
Blue-brown/grey-brown	31 (33.3)	31 (32.0)
Green-brown	4 (4.3)	5 (5.2)
Yellow-brown	1 (0.1)	2 (2.1)
Study eye(s), n (%)		
Right	9 (9.7)	17 (17.5)
Left	15 (16.1)	10 (10.3)
Both	69 (74.2)	70 (72.2)
Treated eye(s), n (%)		
Right	5 (5.4)	9 (9.2)
Left	9 (9.7)	4 (4.1)
Both	79 (84.9)	84 (86.6)
Diagnosis study eye(s), n (%)		
Open angle glaucoma	69 (74.2)	66 (68.0)
Capsular glaucoma	13 (14.0)	17 (17.5)
Pigmentary glaucoma	2 (2.2)	2 (2.1)
Ocular hypertension	7 (7.5)	6 (6.2)
Mixed*	2 (2.2)	6 (6.2)

*Different diagnosis in right and left eye.

used to test for a period effect. The ANOVA model was adjusted for the period effect, and treatment period and patient-by-sequence were included as factors. Observed cases analyses included all patients with complete diurnal IOP data at weeks 6 and 12; per protocol analyses included patients who completed the study without a major protocol violation affecting week 6 or week 12 efficacy data.

Safety parameters were assessed for all randomised patients who received at least one drop of study medication. Frequencies of ocular and systemic adverse events and numbers of patients affected were summarised by treatment.

Table 2 Mean (standard deviation) intraocular pressures (mmHg) by visit (observed cases)

	Treatment group	
	Fixed combination 1st 6 weeks and unfixed combination 2nd 6 weeks (n = 93)	Unfixed combination 1st 6 weeks and fixed combination 2nd 6 weeks (n = 97)
Baseline*	16.9 (2.5)	16.9 (2.3)
Week 6	17.2 (2.8)	16.2 (2.7)
08:00	17.6 (3.1)	16.4 (3.0)
10:00	17.4 (3.1)	16.0 (3.0)
16:00	16.7 (3.1)	16.1 (2.7)
Diurnal	17.2 (2.8)	16.2 (2.7)
Week 12		
08:00	15.9 (2.9)	17.1 (3.0)
10:00	15.5 (3.1)	16.9 (2.9)
16:00	15.6 (2.6)	16.6 (3.1)
Diurnal	15.7 (2.7)	16.9 (2.7)

*Mean of two intraocular pressure measurements at least one hour apart.
 †Diurnal intraocular pressure.

Before initiating the study, it was determined that 147 patients were needed to detect a difference of 1.0 mmHg between groups at a significance level of 0.025, a power of 0.80, and a standard deviation of 3.0 mmHg. A total of 180 patients, 90 in each sequence group, were included to allow for withdrawals.

RESULTS

Overall, 195 patients were enrolled in the study, including 116 patients from 11 clinics in Germany and 79 patients in nine clinics in Sweden. Four patients did not have any IOP measurement at Week 12, and one additional patient had no IOP measurement at 16:00; these five patients were not included in the final observed cases analysis ($n = 190$; 93 fixed to unfixed combination; 97 unfixed to fixed combination). Demographic and other baseline characteristics are summarised in table 1. Across treatments, the average age was 68 years, and 135/190 (71.1%) patients were diagnosed with open angle glaucoma. Nearly half of patients (88/190, 46.3%) had received the unfixed combination for >12 months prior to baseline, 85% (166/195) had both eyes treated during the study, and 67% (127/190) had a baseline diurnal IOP ≤ 18 mmHg. Sixteen of the 190 patients were excluded from per protocol analyses ($n = 174$) due to major protocol violations, including five with timeline violations, four whose IOP measurements were not done at the correct time point, three who took study medication incorrectly, three found not to meet study inclusion criteria, and one whose code envelope was opened by mistake.

Efficacy results

Based on observed cases, the mean IOP at baseline was 16.9 mmHg in both treatment sequences (table 2). Mean diurnal IOP levels were lower in the second treatment period than in the first for both regimens. When the fixed combination was administered during the first six weeks, the average diurnal IOP was 17.2 mmHg versus 16.9 mmHg when it was administered during the second six weeks. Similarly, when the unfixed combination was administered first, the mean diurnal IOP at week 6 was 16.2 mmHg as compared with 15.7 mmHg at week 12. This period effect was significant ($p < 0.01$). Overall, the mean diurnal IOP was 17.0 mmHg after fixed combination treatment, compared with 15.9 mmHg after treatment with the unfixed combination ($p < 0.0001$).

With regard to the primary efficacy variable, the difference in mean within-patient diurnal IOP between the fixed combination and the unfixed combination was 1.1 mmHg (95% CI 0.8 to 1.4 mmHg). Differences in mean within-patient IOP levels at each time point favoured the unfixed combination: 1.1 mmHg at 08:00 (95% CI 0.8 to 1.5 mmHg), 1.4 mmHg (95% CI 1.1 to 1.8 mmHg) at 10:00, and 0.8 mmHg (95% CI 0.4 to 1.2 mmHg) at 16:00. Results of the per protocol analyses confirmed these findings.

Safety results

Safety profiles were similar for both treatments. No adverse event was reported for 170/195 (87.2%) patients during fixed combination treatment and 177/195 (90.8%) patients during unfixed combination therapy. Overall, patients reported 27 and 20 adverse events during the fixed and unfixed combination treatment phases, respectively. Six ocular adverse events believed related to study medication occurred during fixed combination treatment, and five occurred during treatment with the unfixed combination. No such event was considered to be serious. Only one ocular adverse event, hypertrichosis, observed in a patient during treatment with the fixed combination as the first sequence, resulted in withdrawal from the study. Vision disorders were the most

commonly reported ocular adverse events. The most frequently reported adverse event during fixed combination treatment was abnormal vision (five patients), and during treatment with the unfixed combination five patients reported eye irritation. Altogether, there were four serious adverse events reported, none of which was considered related to study medication. No systemic adverse event was considered related to study medication.

DISCUSSION

The results of this study demonstrate that both the fixed combination of latanoprost 0.005% and timolol 0.5% and the concomitant use of the individual components effectively and safely control IOP in patients with open angle glaucoma or ocular hypertension. Although a favourable treatment response was shown in patients receiving both therapeutic sequences, the difference in mean within-patient diurnal IOP levels between the fixed combination treatment and the unfixed combination treatment after 12 weeks was 1.1 mmHg (95% CI 0.8 to 1.4 mmHg) favouring the unfixed combination. Thus, by study design, we were unable to show that the IOP reducing effect of the fixed combination was not inferior to the concomitant use of the individual components because the one sided 97.5% CI for the difference between treatments was not < 1.0 mmHg.

The reason for the 1.1 mmHg difference in within-patient diurnal IOP between the unfixed and fixed treatment combinations cannot be fully explained. It is likely, however, that the difference in instillation times contributed to the discrepancy. In the present study, patients in the unfixed combination group instilled latanoprost drops in the evening whereas patients in the fixed combination group dosed latanoprost in the morning. Evidence suggests that latanoprost is more effective when administered in the evening,¹¹ and previous research has found that morning dosing of either latanoprost²² or of concomitant latanoprost and timolol²³ is associated with lower IOP levels in the evening and that evening dosing of either regimen provides better morning IOP control. Moreover, the maximal effect of the fixed combination of latanoprost and timolol has been noted to be six to seven hours after dosing.²¹ Thus, in the present study, the maximum effect of latanoprost administered at 08:00 as part of the fixed combination would be expected to occur after 14:00 and would be reflected only in the 16:00 IOP measurement, whereas the maximum effect of latanoprost dosed in the evening as part of the unfixed combination would have occurred before the two morning IOP measurements. These factors suggest that, although many patients prefer morning dosing, additional studies are needed to determine whether evening dosing of the fixed combination is more effective in controlling IOP.

It also is possible that the additional evening dose of timolol in the unfixed combination treatment arm contributed to the result as patients received twice as much timolol during unfixed compared with fixed combination treatment. Other investigators have also reported small, but not clinically significant, differences in mean IOP reduction in patients with chronic open angle glaucoma when timolol was administered twice daily as compared with once daily.^{24 25} Interestingly, we found a somewhat better response for both treatment sequences when IOP levels were measured at the end of the second 6 weeks of study, and, even if this difference in IOP reduction was rather small, it was statistically significant. This period effect, which indicates that both drug combinations continued to be effective throughout the treatment period with no loss of efficacy, deserves further evaluation.

The safety of the fixed combination of latanoprost and timolol has been previously demonstrated.^{18–20} In the present

study, both treatment sequences were safe and well tolerated with similar safety profiles. One patient withdrew from the study due to hypertrichosis of the eyelashes of one eye during the fixed combination as the first treatment sequence. Although there were no systemic adverse events related to study medication, once daily dosing of timolol may be associated with decreased long term adverse systemic events. In addition, the fixed combination of latanoprost and timolol requires instillation of only one drop daily, an advantage that may enhance patient compliance.

In conclusion, both the fixed combination of latanoprost and the concomitant use of the individual components controlled IOP levels in patients with primary open angle glaucoma or ocular hypertension. Once daily administration of the fixed combination of latanoprost and timolol is safe and effective and provides a convenient alternative to twice daily dosing with the individual components.

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REFERENCES

- 1 **Alward WLM**. Medical management of glaucoma. *N Engl J Med* 1998;**339**:1298-307.
- 2 **Lundberg LU**, Thygesen J, Damgaard-Jensen L, *et al*. Glaucoma patients treated by practicing ophthalmologists in Denmark. Estimated number of patients and the extent of visual field defects. *Ugeskr Laeger* 2000;**162**:3028-33.
- 3 **Realini T**, Fechtner RD. 56,000 ways to treat glaucoma. *Ophthalmology* 2002;**109**:1955-6.
- 4 **Arici MK**, Sayici M, Toker M, *et al*. A short-term study of the additive effect of timolol and brimonidine on intraocular pressure. *Eye* 2002;**16**:39-43.
- 5 **Bucci MG for the Italian Latanoprost Study Group**. Intraocular pressure-lowering effects of latanoprost monotherapy versus latanoprost or pilocarpine in combination with timolol: a randomized, observer-masked multicenter study in patients with open-angle glaucoma. *J Glaucoma* 1999;**8**:24-30.

- 6 **Diestelhorst M**, Nordmann J-P, Toris CB. Combined therapy of pilocarpine or latanoprost with timolol versus latanoprost monotherapy. *Surv Ophthalmol* 2002;**47**(Suppl 1):S155-61.
- 7 **Rulo AH**, Greve EL, Hoyng PF. Additive effect of latanoprost, a prostaglandin F_{2a} analogue, and timolol in patients with elevated intraocular pressure. *Br J Ophthalmol* 1994;**78**:899-902.
- 8 **Zimmerman TJ**, Kaufman HE. Timolol: a β-adrenergic blocking agent for the treatment of glaucoma. *Arch Ophthalmol* 1977;**95**:601-4.
- 9 **Zimmerman TJ**, Harbin R, Pett M, *et al*. Timolol and facility of outflow. *Invest Ophthalmol Vis Sci* 1977;**16**:623-4.
- 10 **Coakes RL**, Brubaker RF. The mechanism of timolol in lowering intraocular pressure. In the normal eye. *Arch Ophthalmol* 1978;**96**:2045-8.
- 11 **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**:1743-52.
- 12 **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**:138-47.
- 13 **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**:126-37.
- 14 **Toris CB**, Camras CB, Yablonski ME. Effects of PhXA42, a new prostaglandin F_{2a} analog, on aqueous humor dynamics in human eyes. *Ophthalmology* 1993;**100**:1297-304.
- 15 **Lee P-Y**, Shao H, Camras CB, *et al*. Additivity of prostaglandin F_{2a}-1-isopropyl ester to timolol in glaucoma patients. *Ophthalmology* 1991;**98**:1079-82.
- 16 **Patel SC**, Spaeth GL. Compliance in patients prescribed eyedrops for glaucoma. *Ophthalmic Surg* 1995;**26**:233-6.
- 17 **Weinreb RN**. Compliance with medical treatment of glaucoma. *J Glaucoma* 1992;**1**:134-6.
- 18 **Diestelhorst M**, Almegård B. Comparison of two fixed combinations of latanoprost and timolol in open-angle glaucoma. *Graefe's Arch Clin Exp Ophthalmol* 1998;**236**:577-81.
- 19 **Pfeiffer N**, and The European Latanoprost Fixed Combination Study Group. A comparison of the fixed combination of latanoprost and timolol with its individual components. *Graefe's Arch Clin Exp Ophthalmol* 2002;**240**:893-9.
- 20 **Higginbotham EJ**, Feldman R, Stiles M, *et al*. Latanoprost and timolol combination therapy versus monotherapy: one-year randomized trial. *Arch Ophthalmol* 2002;**120**:915-22.
- 21 **Larsson L-I**. The effect on diurnal intraocular pressure of the fixed combination of latanoprost 0.005% and timolol 0.5% in patients with ocular hypertension. *Acta Ophthalmol Scand* 2001;**79**:125-8.
- 22 **Konstas AGP**, Maltezos AC, Gandi S, *et al*. Comparison of 24-hour intraocular pressure reduction with two dosing regimens of latanoprost and timolol maleate in patients with primary open-angle glaucoma. *Am J Ophthalmol* 1999;**128**:15-20.
- 23 **Konstas AGP**, Nakos E, Tersis I, *et al*. A comparison of once-daily morning vs evening dosing of concomitant latanoprost/timolol. *Am J Ophthalmol* 2002;**133**:753-7.
- 24 **Akafo SK**, Thompson JR, Rosenthal AR. A cross-over trial comparing once daily levobunolol with once and twice daily timolol. *Eur J Ophthalmol* 1995;**5**:172-6.
- 25 **Soll DB**. Evaluation of timolol in chronic open-angle glaucoma: once a day vs twice a day. *Arch Ophthalmol* 1980;**98**:2178-81.



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