Graefe's Arch Clin Exp Ophthalmol
(2002) 240:893–899

CLINICAL INVESTIGATION

DOI 10.1007/s00417-002-0553-0

Norbert Pfeiffer

A comparison of the fixed combination of latanoprost and timolol with its individual components

Received: 25 June 2002
Revised: 5 August 2002
Accepted: 9 August 2002
Published online: 1 November 2002

The author wrote this article with the help and on behalf of his fellow members of the European Latanoprost Fixed Combination Study Group

The author has no financial interests in the products investigated

N. Pfeiffer (✉)
Department of Ophthalmology,
Mainz University, 55101 Mainz, Germany
e-mail: pfeiffer@augen.klinik.uni-mainz.de
Tel.: +49-6131-177286
Fax: +49-6131-176620

Abstract *Purpose:* To evaluate the intraocular pressure (IOP)-reducing effect of the fixed combination of 0.005% latanoprost and 0.5% timolol compared with the individual monotherapies. *Methods:* A 6-month, randomised, double-masked, controlled multicentre study followed by 6 months of open-label treatment was carried out in patients with glaucoma or ocular hypertension with pre-enrolment IOP ≥25 mmHg on glaucoma medication or ≥30 mmHg if untreated. Following a 2- to 4-week run-in period on timolol twice daily, 436 patients were randomised: 140 to fixed combination therapy once daily in the morning, 147 to latanoprost once daily in the morning and 149 to timolol twice daily. During the open-label extension, patients received fixed combination drug once daily in the morning. *Results:* The difference in mean change from baseline in diurnal IOP from week 2 to week 26 was –1.2 mmHg between fixed combination and latanoprost (95% confidence interval. CI: –1.8 to –0.5; $P<0.001$; repeated-measures analysis of covariance). The corresponding difference between fixed combination and timolol was –1.9 mmHg (95% CI –2.5 to –1.2; $P<0.001$). No long-term drift in IOP was detected in patients treated for 12 months with fixed combination. All treatments were well tolerated with no major differences among groups in the incidence of clinically relevant adverse events. *Conclusion:* The fixed combination of 0.005% latanoprost and 0.5% timolol administered once daily in the morning for 6 months was more effective in reducing IOP than the individual components alone and was effective over 12 months.

Introduction

Medical treatment of both high- and normal-tension glaucoma relies predominantly on lowering intraocular pressure (IOP). In patients with primary open-angle glaucoma with IOP reduced to <17 mmHg, visual fields remained stable during 4–11 years of follow-up [12]. The Collaborative Normal-Tension Glaucoma Study Group [6] demonstrated that visual field deterioration was significantly delayed in normal-tension glaucoma patients with IOP reductions of ≥30%. The prostaglandin analogue latanoprost is an effective ocular hypotensive drug that has been shown to lower IOP by 27–32% [1, 4, 13, 16].

In some patients, more than one drug is needed to achieve sufficient IOP levels, and combination treatment is warranted. Several studies have shown that the IOP-reducing effect of the unfixed combination of latanoprost and timolol is additive [2, 3, 15]. The use of more than one IOP-reducing drug requires a more complex instillation schedule, however, and complicated regimens have been associated with reduced compliance in patients with glaucoma [9]. Thus, a fixed combination of two drugs in a single bottle may provide not only greater efficacy but also superior compliance to the therapeutic regimen due to increased convenience.

A 4-week study by Diestelhorst et al. [8] demonstrated that the fixed combination of latanoprost and timolol administered once daily was more effective than the individual monotherapies. The purpose of the present study was to compare the efficacy and side effects of the fixed combination of 0.005% latanoprost and 0.5% timolol applied once daily vs monotherapy with either 0.005% latanoprost once daily or 0.5% timolol twice daily in a large sample of patients followed for 6 months with an open-label extension for an additional 6 months. Such a fixed combination has recently become commercially available.

Materials and methods

Study design

The study was a 6-month, randomised, double-masked, multicentre study with three parallel groups with a further 6 months' follow-up. The long-term safety of the fixed combination was evaluated in a 6-month, open-label extension. The protocol was approved by the appropriate regulatory authorities and ethics committees for each centre and was performed in accordance with the ethical standards maintained in the 1964 Declaration of Helsinki. Written informed consent was obtained from each patient prior to study enrolment.

Patient selection

Included patients were ≥18 years of age with unilateral or bilateral primary open-angle glaucoma, pigmentary glaucoma, pseudoexfoliation glaucoma or ocular hypertension with IOP ≥25 mmHg with prior therapy or ≥30 mmHg without IOP-reducing medication at two separate determinations during the pre-study examination. Patients were excluded if they had a history of angle-closure glaucoma or had had ocular surgery, argon laser trabeculoplasty or ocular inflammation or infection within 3 months prior to the pre-study visit. Patients with known hypersensitivity or contraindication to any component of study drugs (including beta-blockers) also were excluded.

Study visits and procedures

At the pre-study visit 2–4 weeks before the baseline examination, a medical history was taken, visual acuity and refraction were measured, and Goldmann applanation tonometry (two measurements), slit-lamp examination, ophthalmoscopy and gonioscopy were performed. At the conclusion of the pre-study visit, patients received 0.05% timolol to be administered during a run-in period of 2–4 weeks.

During the double-masked study, scheduled visits occurred at baseline (following the timolol run-in period) and weeks 2, 6, 13 and 26; the open-label extension included visits at weeks 28, 39 and 52. IOP was measured in triplicate in each eye at 8 a.m., 10 a.m. and 4 p.m. at the baseline visit and at weeks 2, 13, 26 and 52. At weeks 6, 28 and 39, IOP was measured only at 8 a.m.. At each visit, best-corrected visual acuity was determined and a slit-lamp examination was performed. Refraction was recorded and ophthalmoscopy was performed at weeks 26 and 52. Automated threshold perimetry was performed at baseline and at weeks 13, 26 and 52.

Colour Polaroid photographs of the irides were taken at baseline and at weeks 26 and 52. For each patient, two independent observers compared the first set of photographs with the two later sets to evaluate the presence/absence of darkening of the irides. One observer used the same procedure to assess darkening, thickening or lengthening of eyelashes.

Treatment

After a run-in period of 2–4 weeks on 0.5% timolol, patients were randomised to receive either the fixed combination of 0.005% latanoprost and 0.5% timolol once daily in the morning and placebo in the evening, or 0.005% latanoprost once daily in the morning and placebo in the evening, or 0.5% timolol twice daily in the morning and evening. Patients were instructed to administer study medications at approximately 8:00 a.m. and 8:00 p.m.. All three groups received two different bottles for morning and evening administration in order to preserve masking. Patients received fixed combination therapy during the 6-month open-label extension. In cases of bilateral disease in which only one eye met all eligibility criteria, the contralateral eye could also be treated with study drug provided that there were no exclusion criteria for this eye.

Adverse events were monitored throughout the study and were defined as any undesirable medical event regardless of the relationship to treatment.

Variables and analyses

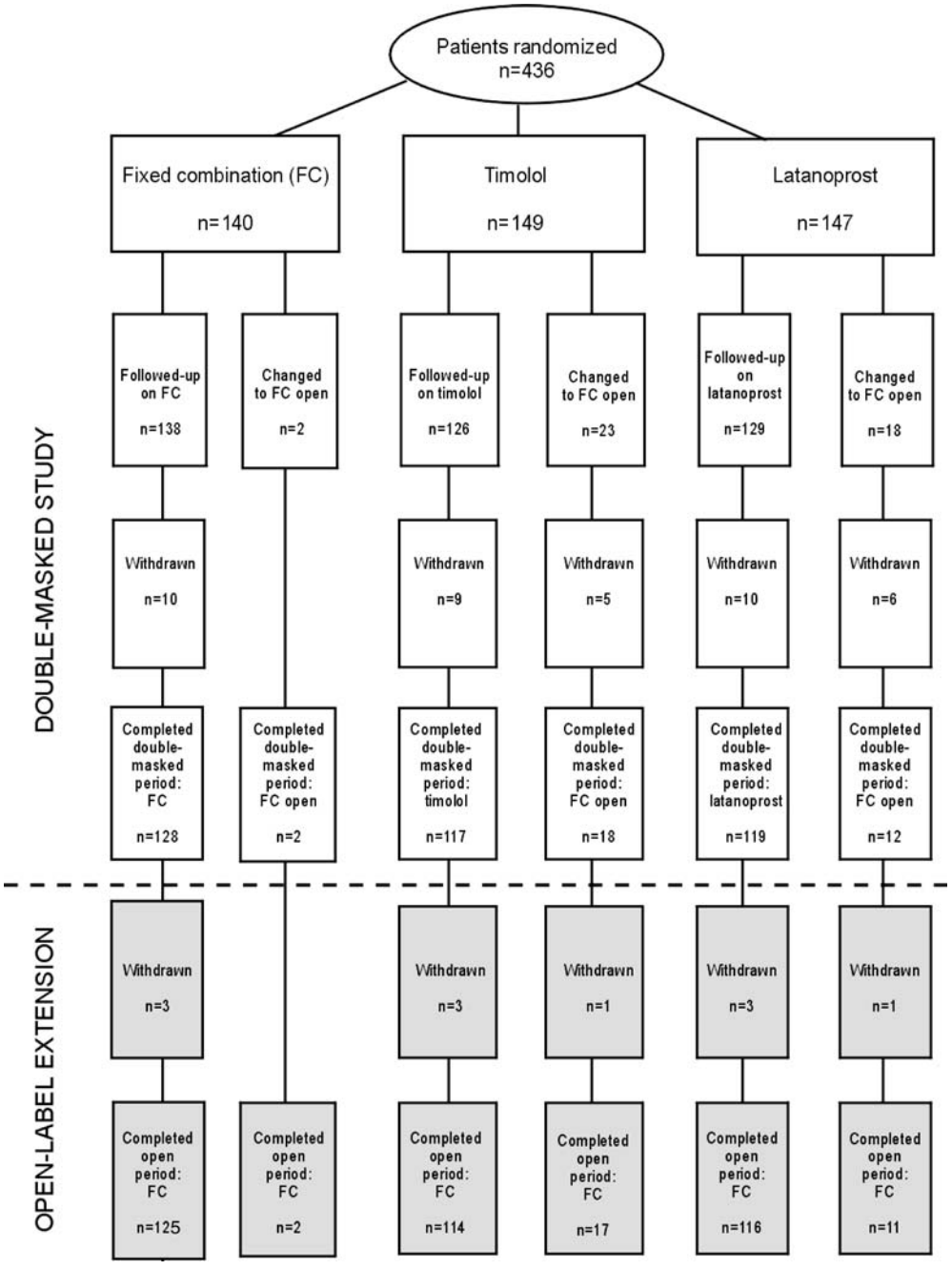
The primary efficacy variable was the difference between the fixed combination and the two monotherapy groups in mean diurnal IOP reduction during 6 months of treatment. Diurnal IOP was calculated as the average of the 8 a.m., 10 a.m. and 4 p.m. measurements in study eyes. Secondary efficacy variables included differences between fixed combination and monotherapy groups with respect to proportions of subjects achieving target diurnal IOP levels at week 26, percentages of patients remaining on therapy from baseline to week 26 and consistency of IOP levels up to week 52 in the fixed combination group.

Treatment failure was defined as an increase in IOP of ≥10% of the mean IOP from baseline and an IOP of ≥23 mmHg on two examinations within two weeks. If treatment failure occurred, the patient was switched to open-label therapy with the fixed combination of latanoprost and timolol. If the IOP remained uncontrolled, the patient was withdrawn from the study.

Intent-to-treat efficacy analyses included all patients receiving at least 1 drop of study medication. Where data were missing, the last available IOP observation was carried forward. A repeated-measures analysis of covariance model evaluated differences between groups with respect to mean diurnal IOP reductions during the 6-month, double-masked study. The main model contained baseline diurnal IOP as a covariate and patient, centre, visit and treatment groups as factors; 95% confidence intervals (CIs) were calculated. Only results for mean diurnal IOP are reported because comparisons among treatment groups gave very similar results for this variable and for IOP at 8 a.m., 10 a.m. or 4 p.m.. Chi-square tests evaluated the significance of differences between groups in proportions of patients reaching target diurnal IOP levels at week 26 and in proportions of patients remaining on fixed combination therapy vs monotherapy in the double-masked study. All tests were two-sided with significance set at $P<0.05$. To determine whether IOP reduction was maintained for up to 52 weeks (open-label extension), one-sided paired *t*-tests (significance set at $P<0.05$) were used to calculate 90% CIs for mean differences between diurnal IOP levels at weeks 26 and 52 in the fixed combination group; equivalence limits were set at ±1.5 mmHg. Safety results were summarised using standard descriptive methods.

Prior to the study, it was estimated that 336 patients needed to be randomised (1:1:1) among the three treatment groups in order to detect a difference of 1.2 mmHg between groups at a signifi-

Fig. 1 Study design



cance level of 0.05, a power of 0.80 and given a standard deviation of 3.2 mmHg for diurnal IOP change from baseline. To allow for withdrawals, 130–140 patients were to be included in each treatment group recruited from 30–40 centres.

Results

In all, 436 patients were included from 37 centres: 140 in the fixed combination group, 147 in the latanoprost group and 149 in the timolol group. Patient characteristics at baseline are summarised in Table 1. Figure 1 depicts the patient flow during the study. During the 26-week double-masked study, 43 patients were switched from monotherapy to fixed combination open-label therapy and an additional 29 patients were withdrawn (10 for non-serious adverse events, 5 for withdrawal of consent, 5 for uncontrolled IOP, 8 for other reasons, 1 lost to follow-up). Withdrawals were evenly distributed among the treatment groups. IOP-reducing drugs had been used prior to study start by 401 patients

Table 1 Demographic characteristics at baseline

Characteristic	Fixed combination (*n*=140)	Latanoprost (*n*=147)	Timolol (*n*=149)
Age (years)			
Mean±SD	64±13	63±12	64±10
Sex			
Male/female	67/73	77/70	52/97
Diagnosis (in study eyes)			
Primary open-angle glaucoma	106	112	118
Pseudoexfoliation glaucoma	2	13	7
Pigmentary glaucoma	3	4	1
Ocular hypertension	27	16	21
Mixed[a]	2	2	2

[a] Different diagnoses in the two eyes

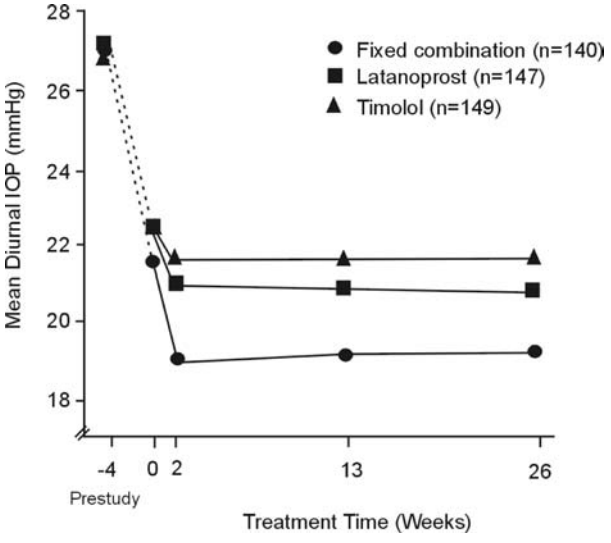


Fig. 2 Changes in mean diurnal IOP levels during the double-masked study (P<0.05 for differences between fixed combination and monotherapies from week 2 to week 16)

(92%); about 60% of these patients had been on monotherapy and 40% on various combination therapies.

Mean diurnal IOP at the beginning of the timolol run-in period was 27.0±2.9 mmHg. At baseline (following the run-in period), mean diurnal IOP was 21.6±3.8 mmHg in the fixed combination group, 22.5±4.0 mmHg in the latanoprost group and 22.5±4.1 mmHg in the timolol group (differences not significant). Figure 2 shows changes in mean diurnal IOP levels throughout the double-masked study, while mean diurnal IOPs±SDs at each visit are provided in Table 2. A significant difference in mean diurnal IOP reduction in favour of the fixed combination compared to the monotherapies was seen from week 2 to week 26. In particular, the difference in mean change in diurnal IOP between fixed combination and latanoprost was –1.2 mmHg (95% CI –1.8 to –0.5 mmHg; P<0.001) and between fixed combination and timolol, –1.9 mmHg (95% CI –2.5 to –1.2 mmHg; P<0.001). Larger proportions of patients receiving fixed combination therapy than those receiving either monotherapy regimen had diurnal IOP levels <15 mmHg, <18 mmHg and <21 mmHg after 26 weeks of follow-up (Table 3). The difference between those receiving fixed combination and those receiving timolol monotherapy was significant at IOP <18 mmHg (P<0.01). In the timolol group mean IOP dropped from 22.5 mmHg at baseline to 21.6 mmHg at week 2 and week 13 and to 21.4 at week 26. We view this drop in IOP as due to increased compliance during the masked period.

Of patients assigned to treatment with fixed combination therapy, 97.1% were IOP-controlled during the double-masked study compared with 87.1% of patients assigned to latanoprost and 83.2% of those assigned to

Table 2 Diurnal intraocular pressure (mean±SD) during double-masked study[a]

Measurement time	Fixed combination (*n*=140)	Latanoprost (*n*=147)	Timolol (*n*=149)
Baseline[b]	21.6±3.8	22.5±4.0	22.5±4.1
Week 2	18.9±3.3	20.9±4.4	21.6±4.9
Week 13	19.0±3.6	20.7±4.7	21.6±5.1
Week 26	19.0±3.5	20.4±4.9	21.4±5.4

[a] Intent-to-treat analysis with last observation carried forward for missing data
[b] Following the timolol run-in period

Table 3 Patients reaching target IOP levels during double-masked study: *n* (%)[a]

Therapy	Target IOP		
	<15 mmHg	<18 mmHg	<21 mmHg
Fixed Combination (*n*=140)	14 (10.0)	54 (38.6)	110 (78.6)
Latanoprost (*n*=147)	8 (5.4)	48 (32.7)	101 (68.7)
Timolol (*n*=149)	7 (4.7)	37 (24.8)	83 (55.7)

[a] At week 26 or up to treatment failure or withdrawal due to uncontrolled IOP

Table 4 Ocular adverse events seen in ≥1% of any treatment group in the double-masked study: number of patients in whom the event occurred at least once

Adverse event	Fixed combination (*n*=140)	Latanoprost (*n*=147)	Timolol (*n*=149)
Eye irritation	10	11	3
Visual field change (suspected)	6	10	5
Hypertrichosis	4	1	0
Hyperaemia	4	2	1
Vision decreased	3	1	3
Increased iris pigmentation	2	4	1
Corneal disorder	2	0	1
Cataract	2	6	0
Optic atrophy	1	2	0
Conjunctivitis	0	0	4
Iritis	0	0	2
Change in refraction	0	2	0
Blepharitis	0	2	1

Table 5 Non-ocular adverse events seen in ≥1% of any treatment group in the double-masked study: number of patients in whom the event occurred at least once

Adverse event	Fixed combination (*n*=140)	Latanoprost (*n*=147)	Timolol (*n*=149)
Cardiovascular disorder	5	1	2
Influenza-like symptoms	5	3	1
Metabolic disorders	4	1	0
Respiratory disorders	3	6	7
Cerebrovascular disorders	2	1	0
Vertigo	2	1	3
Sleep disorders	1	0	3
Headache	0	3	1
Liver/biliary disorders	0	2	2

timolol ($P<0.01$ for difference between fixed combination and monotherapy). Among those switched from monotherapy to fixed combination treatment during the double-masked study, 17/23 originally treated with timolol and 11/18 of those originally treated with latanoprost continued fixed combination therapy through week 52. The IOP-reducing effect of fixed combination therapy was maintained in patients randomised to receive the fixed combination: in patients who finished the 52 week open-labelled period mean diurnal IOP levels were 18.5±2.8 mmHg at week 26 vs 18.2±2.7 mmHg at week 52 (difference –0.3 mmHg, 95% CI –0.6 to 0.0 mmHg; P<0.001).

Ocular and non-ocular adverse events seen in ≥1% of cases in any treatment group during the double-masked study are summarised in Tables 4 and 5. The most common ocular adverse events were eye irritation (5.5%), suspected visual field changes (4.8%), cataract (1.8%), decreased vision (1.6%), increased iris pigmentation (1.6%), conjunctival hyperaemia (1.6%) and hypertrichosis (1.1%). The most common non-ocular adverse events included upper respiratory tract infection (2.3%), influenza-like symptoms (2.1%), arterial hypertension (1.8%) and vertigo (1.4%). Most adverse events were mild or moderate in severity. Ten patients discontinued the study due to adverse events (three receiving fixed combination; four receiving latanoprost; three receiving timolol). Overall, 26 serious adverse events were reported during the double-masked study and 16 during the open-label extension. Most were classified as serious because they involved patient hospitalisations; no hospitalisation was related to the glaucoma treatment, however.

At the end of the double-masked study, observer 1 and observer 2 noted increased iris pigmentation in 15% and 15%, respectively, of patients in the fixed combination group, in 26% and 24%, respectively, of patients treated with latanoprost monotherapy, and in 5% and 6%, respectively, of those treated with timolol. After 52 weeks, increased iris pigmentation was noted in 26% and 23%, respectively, of patients randomised to receive the fixed combination. In patients treated first with latanoprost then with fixed combination in the open-label extension, increased iris pigmentation was observed in 37% and 32% of cases, respectively. For those originally assigned to receive timolol, the corresponding figures were 23% and 18%, respectively. The incidence of iris pigmentation was higher in patients with mixed-colour irides. It is notable that investigators at study sites reported increased iris pigmentation in only seven patients: two treated with fixed combination, four with latanoprost and one with timolol (Table 4).

After 26 weeks of therapy, darkening, thickening or lengthening of eyelashes was seen in 37% of patients on fixed combination therapy, 42% of those receiving

latanoprost and 1% of those treated with timolol. After 1 year, eyelash changes were seen in approximately 40% of patients, including nearly 20% of those who received timolol during the double-masked study. Eyelash changes were evenly distributed among eye colours.

Discussion

This research demonstrated that the fixed combination of 0.005% latanoprost and 0.5% timolol applied once daily lowered IOP more effectively than monotherapy with either 0.005% latanoprost once daily or 0.5% timolol twice daily. The difference in IOP reduction was larger between fixed combination and timolol (1.9 mmHg) than between fixed combination and latanoprost (1.2 mmHg). The magnitude of the effect is similar to that reported by Rulo et al. [15], who noted an additional 2.6 mmHg (13%) IOP reduction when latanoprost and timolol were co-administered twice daily, but is smaller than that reported by Alm et al. [2], in whose study mean diurnal IOP was reduced by an additional 37% when latanoprost instilled once daily was added to timolol administered twice daily.

In the present study, baseline mean diurnal IOP was 22.5 mmHg in both the latanoprost and the timolol group but 21.6 mmHg in the fixed combination group. The somewhat (but not statistically significantly) lower baseline IOP in the latter group may have suppressed the IOP-lowering effect of the combination drug. Nevertheless, while the clinical significance of an IOP reduction of 1–2 mmHg is not known, such a decrease may be helpful, as even small differences in IOP may contribute to glaucoma damage. Thus, Cartwright et al. [5] reported that in 12 of 14 patients with bilateral normal-tension glaucoma, cupping and field loss was greater in the eye with higher pressure – even where differences in pressure were small. Crichton et al. [7] confirmed that, in the presence of unequal IOP levels in patients with bilateral normal-tension glaucoma, visual field damage is almost always greater in the eye with the higher mean IOP level.

It is important that drugs used to treat chronic conditions not lose their effectiveness over time. The current research demonstrates that there was no loss of effect during 12 months of treatment with the fixed combination of 0.005% latanoprost and 0.5% timolol. That IOP levels were similar after 6 and after 12 months of treatment in patients who continued in the open-label extension supports the stable IOP-reducing effect of latanoprost reported by Racz et al. [14] and by Lindén et al. [11]. Patients treated with fixed combination drug also were less likely to experience treatment failure during the double-masked study. Thus, by the criteria used in this study, IOP levels were controlled in 97.1% of patients assigned to fixed combination therapy vs 87.1% of those assigned to latanoprost and 83.2% assigned to timolol. In addition, 17/23 patients treated initially with timolol and 11/18 treated first with latanoprost who switched to fixed combination during the double-masked study continued that therapy for the full open-label extension.

All three treatments were well tolerated with no major differences among groups in the incidence of adverse events. Most adverse events were judged to be mild or moderate, and no serious adverse event was held to be treatment related. Thus, there was no indication that use of the fixed combination resulted in more clinically relevant adverse events than did use of the individual therapies alone. The primary differences in ocular side effects among groups reflected the known class effect of prostaglandins, i.e. increased iris pigmentation and hypertrichosis [1, 10]. A small difference was observed with regard to patients' subjective assessments of discomfort, such as burning, stinging and itching, which were more frequent in those treated with fixed combination (n=10) and latanoprost (n=11) than in those treated with timolol (n=3). The numbers of patients who discontinued the study due to adverse events were similar across groups.

Two issues raised by the present study deserve further investigation. First, in line with what many patients prefer, fixed combination therapy was instilled in the morning, although some evidence suggests that the IOP-reducing effect of the drug might be stronger when it is administered in the evening [1]. Second, the relative simplicity of fixed combination therapy may increase patient compliance – a possibility not evaluated here. Previous research has documented, however, that simple therapeutic regimens involving fewer instillations of medication are associated with increased medication compliance in glaucoma patients [9].

In conclusion, the fixed combination of 0.005% latanoprost and 0.5% timolol applied once daily in the morning produced a greater reduction in IOP levels than did monotherapy with 0.005% latanoprost applied once daily or 0.5% timolol applied twice daily. The effect of the fixed combination on IOP was maintained for 12 months. All three drugs were well tolerated, and no serious side effect considered to be related to treatment was observed. The fixed combination of latanoprost and timolol administered once daily may provide superior efficacy and convenience for patients with glaucoma or ocular hypertension.

Acknowledgement This study was supported by Pharmacia Inc., producer of latanoprost (Xalatan) and a fixed combination of latanoprost and timolol (Xalacom).

Stefanie Schmickler, Privat-Praxis, Augenheilkunde (P45), Ahaus
Paul Schmitz-Valckenberg, Privat-Praxis, Augenheilkunde (P43), Koblenz
Achmed Schmucker, Privat-Praxis, Augenheilkunde (P158), Hirschaid
Waiming Schneider-Lam, Privat-Praxis, Augenheilkunde (P142), Mainz
Johann Schock, Privat-Praxis, Augenheilkunde (P145), Erlangen

Hans B. Schwind, Privat-Praxis, Augenheilkunde (P28), Aschaffenburg
Richard Stodtmeister, Privat-Praxis, Augenheilkunde (P146), Pirmasens
Reinhard Terlinde, Privat-Praxis, Augenheilkunde (P25), Coesfeld
Martin Utsch, Privat-Praxis, Augenheilkunde (P26), Siegburg
Winfried Weiler, Privat-Praxis, Augenheilkunde (P149), Offenbach
Thomas Wesendahl, Albert-Ludwigs-Universität, Augenklinik, Freiburg
F. Wilhelm, Ernst-Moritz-Arndt-Universität, Klinik und Poliklinik für Augenheilkunde, Greifswald
R. Winter, Medizinische Hochschule Hannover, Augenklinik, Hannover
Ismet Özer, Privat-Praxis, Augenheilkunde (P147), Alzey
Ernst-Norbert Schmack, Privat-Praxis, Augenheilkunde (P44), Iserlohn
Oliver Arend, Med. Einrichtungen Der R W T H, Aachen
Gert Aurig, Privat-Praxis, Augenheilkunde (P150), Parsberg
Liliane Banyái, Privat-Praxis, Augenheilkunde (P156), Leonberg
Hartmut Benning, Privat-Praxis, Augenheilkunde (P142), Mainz
Bernhard Dembinsky, Privat-Praxis, Augenheilkunde (P157), Waldfischbach
R. Eder-Schmid, Privat-Praxis, Augenheilkunde (P148), Nürnberg
Bernd Ellerhorst, Privat-Praxis, Augenheilkunde (P24), Trier
Erich Hahner, Privat-Praxis, Augenheilkunde (P31), Osnabrück
U. Heine, Privat-Praxis, Augenheilkunde (P36), Berlin
Michael Janke, Privat-Praxis, Augenheilkunde (P91), Hannover
Karin Kernt, Privat-Praxis, Augenheilkunde (P151), München
Frank Kommerell, Privat-Praxis, Augenheilkunde (P41), Freising
Barbara Konopizky, Privat-Praxis, Augenheilkunde (P29), München
Stefan Kremmer, Heinrich-Heine-Universität, Zentrum für Augenheilkunde, Essen
Steffen Kresse, Privat-Praxis, Augenheilkunde (P33), Berlin
Besin Lam, Privat-Praxis, Augenheilkunde (P159), Leverkusen
Ulrich Mesler, Knappschafts-Krankenhaus, Augenklinik, Sulzbach
Ulrich Neisskenwirth, Privat-Praxis, Augenheilkunde (P27), Eitorf
Stefanie Pahlitzsch, Privat-Praxis, Augenheilkunde (P153), Berlin
Konstantin Papakostas, Privat-Praxis, Augenheilkunde (P23), Gummersbach
Eckhard Paust, Privat-Praxis, Augenheilkunde (P35), Münster
René Petri, Privat-Praxis, Augenheilkunde (P152), Fulda
Hans Christian Pfeiffer, Augenarztpraxis (P39), Landau/Pfalz
Norbert Pfeiffer, Johannes-Gutenberg-Universität, Augenklinik und Poliklinik, Mainz
H. Pähr, Privat-Praxis, Augenheilkunde (P155), Bad Abbach
Adolf Pöllmann, Privat-Praxis, Augenheilkunde (P154), Weiden
Winfried Angele, Privat-Praxis, Ophthalmologie (P85), Aalen
Detlef Pötzsch, Privat-Praxis, Augenheilkunde (P32), Dillingen
Klaus Rosbach, Privat-Praxis, Augenheilkunde (P142), Mainz
H. Rösing Gen. Storck, Privat-Praxis, Augenheilkunde (P34), Mülheim

References

1. Alm A, Stjernschantz J, the Scandinavian Latanoprost Study Group (1995) Effects on intraocular pressure and side effects of 0.005% latanoprost applied once daily, evening or morning. A comparison with timolol. Ophthalmology 102:1743–1752
2. Alm A, Widengård I, Kjellgren D, et al (1995) Latanoprost administered once daily caused a maintained reduction of intraocular pressure in glaucoma patients treated concomitantly with timolol. Br J Ophthalmol 79:12–16
3. Bucci MG and the Italian Latanoprost Study Group (1999) 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 8:24–30
4. Camras CB, the United States Latanoprost Study Group (1996) Comparison of latanoprost and timolol in patients with ocular hypertension and glaucoma. A six-month, masked, multicenter trial in the United States. Ophthalmology 103:138–147
5. Cartwright MJ, Anderson DR (1988) Correlation of asymmetric damage with asymmetric intraocular pressure in normal-tension glaucoma (low-tension glaucoma). Arch Ophthalmol 106:898–900
6. Collaborative Normal-Tension Glaucoma Study Group (1998) Comparison of glaucomatous progression between untreated patients with normal-tension glaucoma and patients with therapeutically reduced intraocular pressures. Am J Ophthalmol 126:487–497
7. Crichton A, Drance SM, Douglas GR, Schulzer M (1989) Unequal intraocular pressure and its relation to asymmetric visual field defects in low-tension glaucoma. Ophthalmology 96:1312–1314
8. Diestelhorst M, Almegård B (1998) Comparison of two fixed combinations of latanoprost and timolol in open-angle glaucoma. Graefes Arch Clin Exp Ophthalmol 236:577–581
9. Gurwitz JH, Glynn RJ, Monane M, Mack RJ, Lass JH (1993) Treatment of glaucoma: adherence by the elderly. Am J Public Health 83:711–716
10. Johnstone MA (1997) Hypertrichosis and increased pigmentation of eyelashes and adjacent hair in the region of the ipsilateral eyelids of patients treated with unilateral topical latanoprost. Am J Ophthalmol 124:544–547
11. Lindén C, Nuija E, Alm A (1997) Effects of IOP restoration and blood-aqueous barrier after long term treatment with latanoprost in open angle glaucoma and ocular hypertension. Br J Ophthalmol 81:370–372
12. Mao LK, Williams CS, Shields MB (1991) Correlation between intraocular pressure control and progressive glaucomatous damage in primary open-angle glaucoma. Am J Ophthalmol 111:51–55
13. Mishima HK, Masuda K, Kitazawa Y, Azuma L, Araie M (1996) A comparison of latanoprost and timolol in primary open-angle glaucoma and ocular hypertension. A 12-week study. Arch Ophthalmol 114:929–939
14. Rácz P, Ruzsonyi MR, Nagy ZT, Bito LZ (1993) Maintained intraocular pressure reduction with once-a-day application of a new prostaglandin F2 alpha analogue (PhXA41). An in-hospital, placebo-controlled study. Arch Ophthalmol 111:657–661
15. Rulo AH, Greve EL, Hoyng PF (1994) Additive effect of latanoprost, a prostaglandin $F_{2\alpha}$ analogue, and timolol in patients with elevated intraocular pressure. Br J Ophthalmol 78:899–902
16. Watson P, Stjernschantz J, the Latanoprost Study Group (1996) A six-month, randomized, double-masked study comparing latanoprost with timolol in open-angle glaucoma and ocular hypertension. Ophthalmology 103:126–137