A 6-Week, Double-Masked, Parallel-Group Study of the Efficacy and Safety of Travoprost 0.004% Compared with Latanoprost 0.005%/Timolol 0.5% in Patients with Primary Open-Angle Glaucoma or Ocular Hypertension

Wendy A. Franks, MD[1]; Jean P. Renard, MD[2]; Ian A. Cunliffe, MD[3]; and Prin Rojanapongpun, MD[4]

[1]Glaucoma Research Unit, Moorfields Eye Hospital, London, United Kingdom; [2]Department of Ophthalmology, Grace Valley Hospital, Paris, France; [3]Department of Ophthalmology, Birmingham Heartlands Hospital, Birmingham, United Kingdom; and [4]Department of Ophthalmology, Chulalongkorn Hospital, Bangkok, Thailand

ABSTRACT

Objective: The objective of this study was to directly compare the intraocular pressure (IOP)-lowering efficacy and safety of travoprost 0.004% eyedrops with the fixed combination of latanoprost 0.005%/timolol 0.5% eyedrops in patients with primary open-angle glaucoma or ocular hypertension.

Methods: This was a randomized, double-masked, multicenter, parallel-group, active-controlled study. Adult subjects with open-angle glaucoma (with or without pseudoexfoliation or pigment dispersion component) or ocular hypertension were eligible to participate if their IOP was inadequately controlled with ≥4 weeks of β-blocker monotherapy, as indicated by IOP of 22 to 36 mm Hg at 9 AM at screening. Patients were randomly assigned in a 1:1 ratio to receive placebo + travoprost or latanoprost/timolol + placebo. Patients in the travoprost group administered travoprost at 9 PM and placebo at 9 AM; patients in the latanoprost/timolol group administered latanoprost/timolol at 9 AM and placebo at 9 PM. IOP measurements were performed using Goldmann applanation tonometry at 9 AM and 5 PM at the week-2 and week-6 visits. Both volunteered and elicited reports of adverse events were collected; all patients who were randomized and received ≥1 dose of study drug were included in the safety analysis.

Results: One hundred ten patients were randomized, of whom 106 patients were evaluable (travoprost, n = 50; latanoprost/timolol, n = 56). There were no statistically significant differences at baseline between the treatment groups, based on age group, sex, race, iris color, or diagnosis. Mean IOP values were not statistically different between groups at baseline or during treatment. In the pooled results for 9 AM assessment at weeks 2 and 6, mean (SEM) IOP reductions for travoprost and latanoprost/timolol were 7.0 (0.5) and 6.4 (0.5) mm Hg, respectively (P = NS). Adverse events related to therapy were mild in nature, and there were no statistically significant differences between the 2 treatment groups. The most frequently experienced adverse events in the travoprost group were ocular hyperemia (9.3%), foreign body sensation (5.6%), abnormal vision (1.9%), allergic reaction (1.9%), conjunctivitis (1.9%), dacryocystitis (1.9%), eye discharge (1.9%), eye pruritus (1.9%), lid edema (1.9%), lid erythema (1.9%), and tearing (1.9%). In the latanoprost/timolol group, the most frequently experienced adverse events were cataract (1.8%), dry eyes (1.8%), eye pruritus (1.8%), foreign body sensation (1.8%), and ocular hyperemia (1.8%).

Conclusions: Mean IOP changes from baseline for travoprost 0.004% and latanoprost 0.005%/timolol 0.5% fixed combination were not significantly different at follow-up in these patients. Both medications were well tolerated. (*Clin Ther.* 2006;28:332–339) Copyright © 2006 Excerpta Medica, Inc.

Key words: glaucoma, intraocular pressure, prostaglandin, latanoprost, timolol, travoprost.

Accepted for publication January 20, 2006.

Express Track online publication March 3, 2006.
doi:10.1016/j.clinthera.2006.03.001
0149-2918/06/$19.00

INTRODUCTION

Prostaglandin analogues (PGAs) are currently the most efficacious single agents available for lowering intraocular pressure (IOP).[1] These agents provide reductions in IOP of up to 35%.[1] PGAs are agonists of the FP receptor. Travoprost* has previously been reported to be a full agonist at this receptor[2] and to activate FP receptors in both human trabecular meshwork cells and ciliary muscle cells.[3–5] PGAs, as a class, act to reduce IOP by increasing the outflow of aqueous humor, primarily via the uveoscleral route.[6–9] In addition, travoprost is associated with activation of FP receptors in the trabecular meshwork and has been reported to enhance aqueous humor outflow through the conventional pathway.[5,10] PGAs are also thought to both promote matrix metalloproteinase release from the ciliary muscle and relax the ciliary muscle order to enhance uveoscleral outflow.[11–14]

Timolol, betaxolol, and other β-blockers inhibit adrenergic receptors in the nonpigmented ciliary epithelial cell.[15,16] This inhibition is associated with a reduction in aqueous humor production and a decrease in IOP. A meta-analysis found that these therapeutic agents provided IOP reductions that were slightly lower than those provided by the PGAs travoprost, latanoprost, and bimatoprost.[1]

Latanoprost is a PGA that has been reported to be effective for lowering IOP in primary open-angle glaucoma and ocular hypertension.[17] Latanoprost 0.005%/timolol 0.5%† is a combination eyedrop that is approved in Europe and other countries outside of the United States for lowering IOP in patients with open-angle glaucoma and ocular hypertension. Both latanoprost 0.005% and timolol 0.5% have been reported to be effective for reducing IOP in clinical trials with patients with ocular hypertension, chronic open-angle glaucoma, exfoliation syndrome, and pigment dispersion syndrome.[17,18] Travoprost 0.004% monotherapy has been found to lower IOP >24 hours after the last dose.[19]

Prostaglandin agonists are the most potent class of eyedrops for lowering IOP, have few side effects, and have the benefit of once-daily administration.[1] Travoprost is the only selective full FP receptor agonist; this activity is thought to be associated with its duration of action.[2–6,19,20] In an open-label study of 21 patients with open-angle glaucoma, travoprost lowered IOP for up to 84 hours after administration of the last dose.[19]

Previous studies have reported significantly greater reductions in IOP with travoprost 0.004% than latanoprost 0.005%.[19–21] In a large, multicenter, open-label trial, Przydryga and Egloff[21] found a 2.3–mm Hg reduction in IOP among patients who were immediately switched, without a washout period, from latanoprost 0.005% monotherapy to travoprost 0.004% monotherapy ($P < 0.001$).

The objective of the present study was to directly compare the IOP-lowering efficacy and safety of travoprost 0.004% eyedrops with the fixed combination of latanoprost 0.005%/timolol 0.5% eyedrops in patients with primary open-angle glaucoma or ocular hypertension.

METHODS

The protocol for this randomized, double-masked, multicenter, parallel-group, active-controlled study was reviewed and approved for each participating site by an independent ethics committee/institutional review board before initiation of the study. The study was conducted in accordance with the ethical principles set forth in the Declaration of Helsinki.[22] All patients signed an informed consent form indicating that they understood the requirements of the study and agreed to participate. This study was conducted by 15 investigators from 6 countries (Germany, France, United Kingdom, Sweden, Finland, and Thailand).

Inclusion Criteria

Inclusion criteria for the study were as follows: age ≥18 years, diagnosis of open-angle glaucoma (with or without pseudoexfoliation or pigment dispersion component), or ocular hypertension. For each qualifying eye, the mean IOP after ≥4 weeks of treatment with a nonselective β-blocker or after ≥4 weeks of treatment with a combination of treatments including a nonselective β-blocker (excluding any previous treatment with a PGA) was required to be between 22 and 36 mm Hg (inclusive) at the 9 AM eligibility visit. Subjects for whom all selection procedures and the first IOP measurement were performed before 9 AM ± 1 hour at the screening visit were allowed to have the eligibility visit procedures performed on the same day. If the subject was seen after 10 AM, the eligibility visit was performed during the following days. The eligibil-

*Trademark: Travatan® (Alcon Laboratories Inc., Fort Worth, Texas).

†Trademark: Xalcom® (Pfizer Inc., New York, New York).

ity visit was the baseline measurement. There was no washout period in this study.

Patients had to be willing and able to make all required study visits. An informed consent statement that had been read, signed, and dated by the patient or legally authorized representative was obtained before the screening exam. Nonprescription and prescription topical ophthalmic products and systemic medications other than those mentioned in the exclusion criteria were allowed during the study.

Contact lens wearers were allowed to participate in the study. Contact lenses were to be removed before instilling the study medication and reinserted ≥15 minutes after drug instillation. Contact lenses could not be worn on study visit days.

Exclusion Criteria

Patients were excluded from the study for the following reasons. Females of childbearing potential were excluded if they were currently pregnant or had a positive result on the urine pregnancy test at the screening visit, or if they intended to become pregnant during the study period. Best corrected visual acuity was measured in units of log of the minimum angle of resolution (log MAR); a lower limit of 0.6 log MAR in either eye had to be met for the patient to remain eligible for the study.

Other exclusion criteria included history of chronic or recurrent severe inflammatory eye disease (ie, scleritis, uveitis, herpes keratitis); ocular trauma within the past 6 months; ocular infection or ocular inflammation within the past 3 months; clinically significant or progressive retinal disease, such as retinal degeneration, diabetic retinopathy, or retinal detachment; and severe ocular pathology (including severe dry eye) in either eye that would preclude the administration of a topical PGA or β-blocker. Patients who had been treated with a PGA previously were excluded. Any abnormality preventing reliable applanation tonometry of either eye caused the patient to be ineligible for participation in the study. Patients with a recent history of intraocular/ocular surgery were not eligible for this study.

Patients with a history of severe or serious hypersensitivity to prostaglandins, PGAs, β-blockers, or any components of the study medications were not enrolled. A history of bronchial asthma or cardiovascular/pulmonary disease also precluded participation in the study.

Study Design

Patients were randomly assigned in a 1:1 ratio to receive placebo + travoprost or latanoprost/timolol + placebo. β-Blocker therapy was discontinued before switching the patients to either travoprost or latanoprost/timolol. Twice-daily administration (9 AM and 9 PM) was performed, with placebo used to mask the 2 groups. To maintain masking, patients in the travoprost group administered travoprost at 9 PM and placebo (ie, vehicle) at 9 AM, whereas patients in the latanoprost/timolol group administered latanoprost/timolol at 9 AM and placebo (ie, vehicle) at 9 PM. Study medication was dispensed after the completion of all baseline evaluations at the eligibility visit, with the instructions to administer drops from the bottle marked *evening medication* at 9 PM and drops from the bottle marked *morning medication* at 9 AM.

Travoprost and latanoprost/timolol were administered once a day for 6 weeks. Dosages for both travoprost and latanoprost/timolol were determined according to their respective package inserts (1 drop in the evening for travoprost and 1 drop in the morning for latanoprost/timolol).[23,24] Patients administered the eyedrops themselves, and drops were applied to both eyes unless the investigator determined that there was a safety issue with doing so. To minimize potential bias regarding the safety, efficacy, or comfort of the products being studied and toward the outcome of this study by patients, investigators, and study personnel, the study was double masked.

All patients, investigators, and staff who had contact with patients were masked with regard to treatment assignments while the study was in progress. In addition, statisticians who were directly involved in the analysis of study results remained masked to treatment assignments while the study was in progress.

Measurements

All IOP measurements were performed using a Goldmann applanation tonometer calibrated for accuracy ≤2 months before screening the first patient. Mean IOP was calculated for each eye using the mean of 2 consecutive measurements.

Both volunteered and elicited reports of adverse events were collected. At each visit, patients were questioned about whether adverse events had occurred since the last visit. Adverse events were also identified through visual acuity, biomicroscopy, and dilated fundus exams.

Statistics

All patients who received study medication and completed ≥1 on-therapy study visit were considered evaluable for the intent-to-treat analysis. Similarly, all patients who received study medication were considered evaluable for the safety analysis. A repeated-measures analysis of variance (ANOVA) was performed to assess the mean IOP across on-therapy visits and time points, and the primary inference was based on the intent-to-treat data set. Mean IOP change from baseline was also estimated using a repeated-measures ANOVA. Two-sided 95% CI was also determined for the difference in mean IOP between the 2 treatment groups at each visit/time point. Descriptive statistics were calculated for IOP, IOP change from baseline, and IOP percentage change from baseline.

The target enrollment to support the statistical power of the study was 50 evaluable patients per group, with an estimated difference in mean IOP between treatment groups to within 1.4 mm Hg, based on the expected width of a 2-sided 95% CI. This estimate was based on an SD of 3.5 mm Hg for IOP in each group, resulting in a pooled SD of 3.5 mm Hg for IOP and a 5% chance of a type-I error.

RESULTS

One hundred ten patients were randomized to either the travoprost or latanoprost/timolol group. Of the 110 randomized patients, all received study medication and were included in the safety analysis, and 4 discontinued the study before collection of any on-therapy study visit data; therefore, 106 patients were evaluable (travoprost, n = 50; latanoprost/timolol, n = 56) and included in the intent-to-treat analysis. There were no statistically significant differences at baseline between the treatment groups, based on age group, sex, race, iris color, or diagnosis (**Table I**).

Table I. Baseline demographic and clinical characteristics of patients with primary open-angle glaucoma or ocular hypertension who were randomized to receive travoprost 0.004% (n = 50) or latanoprost 0.005%/timolol 0.5% (n = 56) once daily for 6 weeks.

Characteristic	Travoprost, No. (%)	Latanoprost/Timolol, No. (%)	*P**
All patients	50 (47.2)	56 (52.8)	
Age group			<0.317
<65 y	15 (30.0)	22 (39.3)	
≥65 y	35 (70.0)	34 (60.7)	
Sex			<0.610
Female	27 (54.0)	33 (58.9)	
Male	23 (46.0)	23 (41.1)	
Race			<0.773
White	42 (84.0)	45 (80.4)	
Asian	7 (14.0)	8 (14.3)	
Black	1 (2.0)	3 (5.4)	
Iris color			<0.285
Blue	20 (40.0)	23 (41.1)	
Brown	18 (36.0)	25 (44.6)	
Gray	6 (12.0)	6 (10.7)	
Green	4 (8.0)	0 (0.0)	
Hazel	2 (4.0)	2 (3.6)	
Diagnosis			<0.259
Open-angle glaucoma	29 (58.0)	33 (58.9)	
Pseudoexfoliation glaucoma	2 (4.0)	7 (12.5)	
Pigmentary glaucoma	1 (2.0)	0 (0.0)	
Ocular hypertension	18 (36.0)	16 (28.6)	

*Based on χ^2 or Fisher exact test.

Mean IOP values were not significantly different between groups at baseline or during treatment (**Figure**). Because there were no differences between groups at the individual time points, the results for the 9 AM and 5 PM time points at each follow-up visit were pooled. Again, no significant differences were found (**Table II**). Mean (SEM) IOP reductions for travoprost and latanoprost/timolol were −7.0 (0.5) and −6.4 (0.5) mm Hg, respectively, for the pooled results at 9 AM, and −6.8 (0.5) and −6.1 (0.5) mm Hg, respectively, for the pooled results at 5 PM.

The adverse events were rated as mild and were not significantly different between travoprost and latanoprost/timolol (**Table III**). Patients receiving travoprost experienced the following adverse events: ocular hyperemia (5 patients [9.3%]), foreign body sensation (3 patients [5.6%]), abnormal vision (1 patient [1.9%]), allergic reaction (1 patient [1.9%]), conjunctivitis (1 patient [1.9%]), dacryocystitis (1 patient [1.9%]), eye discharge (1 patient [1.9%]), eye pruritus (1 patient [1.9%]), lid edema (1 patient [1.9%]), lid erythema (1 patient [1.9%]), and tearing (1 patient [1.9%]). Latanoprost/timolol patients experienced these adverse events: cataract (1 patient [1.8%]), dry eyes (1 patient [1.8%]), eye pruritus (1 patient [1.8%]), foreign body sensation (1 patient [1.8%]), and ocular hyperemia (1 patient [1.8%]).

DISCUSSION

This study found that in a group of patients with IOP that was inadequately controlled with a topical β-antagonist, switching to travoprost monotherapy or

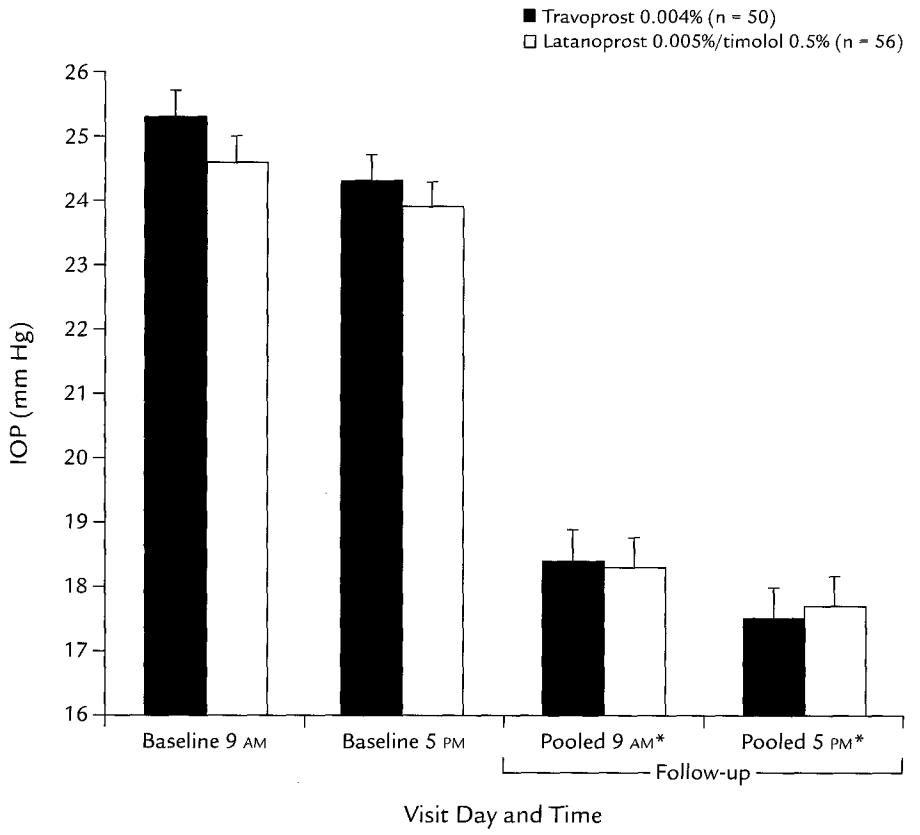

Figure. Mean intraocular pressure (IOP) values among patients with primary open-angle glaucoma or ocular hypertension who were randomized to receive travoprost 0.004% (n = 50) or latanoprost 0.005%/timolol 0.5% (n = 56) once daily for 6 weeks. Travoprost was administered at 9 PM; latanoprost/timolol was administered at 9 AM. No significant differences between groups were found. *Pooled results were derived from the combined 2- and 6-week data for each time point.

Table II. Mean intraocular pressure at baseline and change from baseline in pooled 2- and 6-week data for each time point, in units of mm Hg, among patients with primary open-angle glaucoma or ocular hypertension who were randomized to receive travoprost 0.004% (n = 50) or latanoprost 0.005%/timolol 0.5% (n = 56) once daily for 6 weeks.

	Baseline		Pooled	
Variable	9 AM	5 PM	9 AM	5 PM
Travoprost				
Mean (SEM) value, mm Hg	25.3 (0.4)	24.3 (0.4)	18.4 (0.5)	17.5 (0.5)
Mean (SEM) change, mm Hg*			-7.0 (0.5)	-6.8 (0.5)
Latanoprost/timolol				
Mean (SEM) value, mm Hg	24.6 (0.4)	23.9 (0.4)	18.3 (0.5)	17.7 (0.5)
Mean (SEM) change, mm Hg*			-6.4 (0.5)	-6.1 (0.5)
Difference between groups				
Mean, mm Hg*	0.7	0.4	-0.6	-0.6
P	<0.256	<0.483	<0.401	<0.367

*These values were derived from the mean of the individual patient data for reductions from baseline, which may be slightly different from a simple arithmetic subtraction of the mean reductions for all patients.

Table III. Most common adverse events (≥1% of subjects) among patients with primary open-angle glaucoma or ocular hypertension who were randomized to receive travoprost 0.004% (n = 50) or latanoprost 0.005%/timolol 0.5% (n = 56) once daily for 6 weeks.

Adverse Event	Travoprost, No. (%)	Latanoprost/ Timolol, No. (%)
Ocular hyperemia	5 (9.3)	1 (1.8)
Foreign body sensation	3 (5.6)	1 (1.8)
Abnormal vision	1 (1.9)	0 (0.0)
Allergic reaction	1 (1.9)	0 (0.0)
Conjunctivitis	1 (1.9)	0 (0.0)
Dacryocystitis	1 (1.9)	0 (0.0)
Eye discharge	1 (1.9)	0 (0.0)
Eye pruritus	1 (1.9)	1 (1.8)
Lid edema	1 (1.9)	0 (0.0)
Lid erythema	1 (1.9)	0 (0.0)
Tearing	1 (1.9)	0 (0.0)
Cataract	0 (0.0)	1 (1.8)
Dry eyes	0 (0.0)	1 (1.8)

the latanoprost/timolol fixed-combination preparation was associated with similar reductions in IOP.

Topical β-antagonists act by reducing aqueous production,[15,16] whereas prostaglandin agonists improve aqueous outflow.[6–9] In the current study, latanoprost/timolol was used in the morning and travoprost in the evening, in accordance with their approved use in the European Union at the time the study was conducted.[23,24] Greater reductions in mean (SD) IOP were reported with the unfixed combination of latanoprost and timolol in a prospective, single-center, double-masked, crossover comparison of 36 patients with ocular hypertensive or primary open-angle glaucoma who were randomized to either evening or morning administration of concomitant latanoprost 0.005% and timolol maleate 0.5% therapy for 7 weeks (evening, 16.4 [2.3] mm Hg; morning, 17.9 [2.8] mm Hg [$P = 0.01$]).[25]

Studies comparing diurnal IOP curves in patients treated with the latanoprost/timolol combination, either in the morning or the evening, reported greater effectiveness with evening administration.[26–29] Prostaglandin agonists have greater effect when administered in the evening and are well tolerated.[30] Topical β-antagonists may have potentially serious adverse effects on heart rate and respiratory func-

tion.[31,32] With nighttime administration of a topical β-antagonist, there may be some risk of reducing blood pressure and adversely affecting ocular blood flow, thereby potentially worsening glaucoma.[33]

CONCLUSIONS

Mean IOP changes from baseline for travoprost 0.004% and latanoprost 0.005%/timolol 0.5% fixed combination were not significantly different at follow-up in these patients with primary open-angle glaucoma or ocular hypertension that had previously been inadequately controlled with β-blocker monotherapy. Both medications were well tolerated.

ACKNOWLEDGMENTS

This study was supported by Alcon Research, Ltd., Fort Worth, Texas. The authors wish to acknowledge Julie Crider, PhD, for her medical writing contributions to this manuscript.

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Address correspondence to: Wendy A. Franks, MD, Glaucoma Research Unit, Moorfields Eye Hospital, 162 City Road, London EC1V 2 PD, United Kingdom. E-mail: wendy.franks@moorfields.nhs.uk