EXTENDED REPORT

Intraocular pressure-lowering efficacy of bimatoprost 0.03% and travoprost 0.004% in patients with glaucoma or ocular hypertension

L B Cantor, J Hoop, L Morgan, D WuDunn, Y Catoira, The Bimatoprost-Travoprost Study Group

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See end of article for authors' affiliations

Correspondence to:
L B Cantor, Department of
Ophthalmology, Indiana
University Medical Center,
702 Rotary Circle,
Indianapolis, IN 46202,
USA;
lcantor@iupui.edu

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Aim: To evaluate the efficacies of bimatoprost and travoprost for lowering of intraocular pressure (IOP) for the treatment of glaucoma and ocular hypertension.

Methods: Prospective, randomised, investigator-blinded, parallel-group clinical trial. After completing a washout of all glaucoma drugs, patients (n=157) were randomised to bimatoprost or travoprost for 6 months. Visits were at baseline, 1 week, and 1, 3 and 6 months. IOP was measured at 09:00 h at each visit and also at 13:00 and 16:00 h at baseline and at 3 and 6 months.

Results: No significant between-group differences were observed in IOP at baseline, at 09:00, 13:00 or 16:00 h ($p \geq 0.741$). After 6 months, both drugs significantly reduced IOP at every time point ($p \leq 0.001$). After 6 months, mean IOP reduction at 09:00 h was 7.1 mm Hg (27.9%) with bimatoprost (n=76) and 5.7 mm Hg (23.3%) with travoprost (n=81; $p=0.014$). At 13:00 h, mean IOP reduction was 5.9 mm Hg with bimatoprost (25.3%) and 5.2 mm Hg (22.4%) with travoprost ($p=0.213$). At 16:00 h, the mean IOP reduction was 5.3 mm Hg (22.5%) with bimatoprost and 4.5 mm Hg (18.9%; $p=0.207$) with travoprost. Both study drugs were well tolerated, with ocular redness the most commonly reported adverse event in both treatment groups.

Conclusions: Bimatoprost provided greater mean IOP reductions than travoprost.

Lowering intraocular pressure (IOP) reduces the risk of visual field loss in patients with glaucoma and ocular hypertension (OHT). Results from the Early Manifest Glaucoma trial have suggested that every millimeter of IOP lowering corresponds to a reduction in the risk of glaucomatous progression of approximately 10%,¹ and the current treatment paradigm for patients with glaucoma or OHT is focused on reducing IOP to a target level sufficiently low to preserve the visual field.

Whenever possible, it is preferable to control IOP with a single drug rather than multiple drugs, because every drug added to the regimen has side effects, and each added drug increases the costs of treatment. Moreover, an effective monotherapy may promote patient compliance.

Bimatoprost 0.03% is a potent and highly efficacious monotherapy that allows many patients to achieve low-target pressures.²⁻³ Furthermore, several clinical trials have shown that bimatoprost monotherapy lowers IOP more effectively than either latanoprost or timolol.²⁻⁵ Bimatoprost is a prostamide and reduces IOP by increasing both pressure-sensitive (presumed trabecular meshwork) and pressure-insensitive (presumed uveoscleral) outflow.⁶

Travoprost 0.004%, a synthetic prostaglandin $F_{2\alpha}$ receptor agonist, lowers IOP by increasing uveoscleral outflow. The IOP-lowering efficacy of travoprost monotherapy has been reported in recent clinical trials to be superior to that of timolol and roughly equivalent to that of latanoprost.⁷⁻⁹

Our study aimed to compare the IOP-lowering efficacies of bimatoprost and travoprost in patients with open-angle glaucoma (OAG) or OHT.

MATERIALS AND METHODS

Study design

This study was a prospective, randomised, multicentre, investigator-blinded, parallel-group clinical trial.

Patients

Enrolled patients were men or women of at least 18 years of age with a clinical diagnosis of primary OAG or OHT. Patients using ocular hypotensive drugs completed a washout of all drugs of appropriate duration before study entry (6 weeks for prostaglandin analogues; 4 weeks for topical β -blockers; 2 weeks for adrenergic agents or carbonic anhydrase inhibitors; and 1 week for miotics). The untreated IOP in each eye was at least 21 mm Hg and no more than 34 mm Hg. All participants affirmed their ability to follow study instructions and complete all required visits.

Criteria for exclusion included: uncontrolled systemic disease; active ocular disease other than OAG or OHT that would interfere with study parameters; sensitivity or allergy to any component of either study drug; pregnancy, planning a pregnancy, breast feeding, or lack of usage of an adequate birth control method in women of childbearing potential; functionally marked visual field loss; ocular surgery within the last 3 months; concomitant usage of ocular drugs (except intermittent use of artificial tears); and planned change of ongoing systemic treatment that might affect IOP.

This study was conducted in accordance with the Declaration of Helsinki and with applicable institutional review board regulations (United States 21 Code of Federal Regulations (US 21 CFR) part 56.103). Study participants gave informed consent before initiation of any study-related procedures, and the study was conducted in compliance with informed consent regulations (US 21 CFR part 50). This study was approved by the institutional review board at Indiana University Purdue University at Indianapolis.

Abbreviations: IOP, intraocular pressure; OAG, open-angle glaucoma; OHT, ocular hypertension

Intervention and outcome measures

After meeting all inclusion criteria and completing a washout of any ocular hypotensive agents (if needed), patients were randomised to receive either bimatoprost 0.03% once daily or travoprost 0.004% once daily. Patients were instructed to instil their study drugs between 19:00 and 21:00 h. Study drugs were dispensed in brown cardboard boxes, with subject number and site number labelled on the outside of the box. The investigators were blinded to the randomisation, and the randomisation code was maintained at the central coordination centre. Patients were not completely blinded to their assigned drugs as the bottles were not changed, just overlabelled, and it is possible that patients could determine which drug they were instilling as the bottles were of different shapes and sizes.

Patients were evaluated at baseline, 1 week, and 1, 3 and 6 months. Diurnal IOP was measured at 09:00 (± 1 h), 13:00 (± 1 h) and 16:00 (± 1 h), at baseline, 3-month and 6-month study visits. These times were selected to allow for an accurate assessment of diurnal IOP, yet still allow the flexibility in IOP measurement usually noted in daily practice. IOP was measured only at 09:00 (± 1 h) at 1 week and 1 month. IOP measurement was conducted in a blinded manner (the technician or assistant carried out the IOP measurement, and a blinded technician, assistant or investigator read the pressure from the tonometer). Central corneal thickness was not measured.

Baseline evaluations included medical and ophthalmic history and a complete ophthalmic examination (visual acuity, external exam, slit-lamp biomicroscopy and measurement of IOP). Biomicroscopic findings were rated on a 5-point scale of severity (0, none; 0.5, trace; 1, mild; 2, moderate; and 3, severe). Study drug was initiated after the examination and randomisation.

Follow-up study visits included an interim history and complete ocular examination (visual acuity, external exam, slit-lamp biomicroscopy and measurement of IOP). Patients were asked about adverse events and compliance, and their responses recorded at each follow-up study visit.

At the final study visit, the blinded investigator was asked to complete a clinical success evaluation. A patient was considered to be clinically successful if the investigator, after considering IOP-lowering efficacy, tolerability and any adverse events, continued the patient on his or her study drug. An exit pregnancy test was carried out on women of childbearing potential.

The primary outcome measures were the mean change in IOP from baseline and the percentages of patients who reached target IOP reductions at 6 months. Secondary outcome measures included mean IOP, the incidence of adverse events, and the doctor's evaluation of clinical success.

Statistical analysis

Continuous variables were analysed using paired-sample *t* tests for within-group differences (eg, difference in mean IOP between baseline and follow-up study visits) and two-sample *t* tests for between-group differences (difference in mean IOP and mean change in IOP from baseline at each study visit). Nominal variables were evaluated using χ^2 or Fisher's exact tests, as appropriate. The analyses were of the intent-to-treat population with the last observation carried forward. All analyses were carried out using StatView software (SAS Institute). The a-priori level of significance was 0.05 and all tests were of a two-tailed null hypothesis. A sample size of 69 patients per group was needed to achieve 80% power with a difference of 1.2 mm Hg and a standard deviation (SD) of 2.5 mm Hg.

RESULTS

Patient demographics and disposition

In all, 157 patients were enrolled at eight sites throughout the USA. No significant between-group differences were observed in any demographic variable at baseline (table 1). More patients in the bimatoprost group completed the 6 months of evaluation than patients in the travoprost group. Of the 76 patients randomised to bimatoprost, 70 (92.1%) completed the study as planned. Of the 81 patients randomised to travoprost, 70 (86.4%) completed the study as planned. Reasons for discontinuation in the bimatoprost group were loss to follow-up (*n* = 2) and adverse events (*n* = 4). The single most common reason for discontinuation in the travoprost group was lack of efficacy (*n* = 4; *p* = 0.045 *v* bimatoprost). Five patients discontinued due to adverse events and two were lost to follow-up.

Outcome measures

No significant differences were observed in mean baseline IOP at any diurnal time point. The mean (SD) IOP at 09:00 h at baseline was 24.6 (3.3) mm Hg in the bimatoprost group and 24.4 (3.2) mm Hg in the travoprost group (*p* = 0.741). Both study drugs provided significant IOP reductions from baseline at 09:00 h at all study visits (*p* < 0.001), but the mean reductions in the bimatoprost group were significantly greater than those in the travoprost group at every study visit (*p* ≤ 0.014). Bimatoprost provided mean IOP reductions that ranged from 7.1 to 8.2 mm Hg (28% to 33%), and travoprost provided mean IOP reductions that ranged from 5.7 to 6.5 mm Hg (23% to 26%; fig 1A).

The mean (SD) IOP at 13:00 h baseline visit was 22.5 (3.5) mm Hg in the bimatoprost group and 22.6 (3.7) mm Hg in the travoprost group (*p* = 0.820). Both study drugs provided significant IOP reductions from baseline at 13:00 h at each study visit during which diurnal IOP was measured (3 and 6 months; *p* < 0.001). Bimatoprost provided mean IOP reductions that ranged from 5.9 to 6.2 mm Hg (25% to 26%) and travoprost provided mean IOP reductions that ranged from 5.2 to 5.3 mm Hg (22% to 23%; fig 1B). Although the mean IOP reductions in the bimatoprost group were greater than the reductions in the travoprost group at 13:00 h at every study visit, these differences were not significant at 3 months (*p* = 0.114) or 6 months (*p* = 0.213).

No significant between-group differences were found at 16:00 h at the baseline evaluation (*p* = 0.860). The mean

Table 1 Patient demographics

	Bimatoprost, n (%)	Travoprost, n (%)	p Value
Age			0.34
Mean (SD), years	64.1 (11.8)	65.8 (9.5)	
Diagnosis			0.894
OAG	53 (69.7)	55 (67.9)	
OHT	23 (30.2)	25 (30.9)	
OAG/OHT	0 (0)	1 (1.24)	
Sex			0.516
Male	32 (42.1)	30 (37.0)	
Female	44 (57.9)	51 (63.0)	
Race			0.487
Black	14 (18.4)	15 (18.5)	
Caucasian	59 (77.6)	59 (72.8)	
Hispanic	2 (2.6)	2 (2.5)	
Others	1 (1.3)	5 (6.2)	
Eye colour			0.389
Blue	22 (28.6)	31 (38.3)	
Brown	39 (51.3)	36 (44.4)	
Green	5 (6.6)	6 (7.4)	
Hazel	9 (11.8)	7 (8.6)	
Others	1 (1.3)	1 (1.2)	

OAG, open-angle glaucoma; OHT, ocular hypertension.

Figure 1 (A) Mean intraocular pressure (IOP) reduction from baseline at 09:00 h in each treatment group at each study visit. Both study drugs provided significant IOP reductions from baseline at 09:00 h at all study visits ($p < 0.001$), but the mean reductions in the bimatoprost group were significantly greater than those in the travoprost group at every study visit ($*p \leq 0.014$). (B) Mean IOP reduction from baseline at 13:00 h in each treatment group at 3 and 6 months. Both study drugs provided significant IOP reductions from baseline at 13:00 h at each study visit during which diurnal IOP was measured (3 and 6 months; $p < 0.001$). (C) Mean IOP reduction from baseline at 16:00 h in each treatment group at 3 and 6 months. Both study drugs provided significant IOP reductions from baseline at 16:00 h at each study visit during which diurnal IOP was measured (3 and 6 months; $p < 0.001$).

(SD) IOP at 16:00 h at baseline was 22.1 (3.7) mm Hg in the bimatoprost group and 22.0 (4.2) mm Hg in the travoprost group. Both study drugs provided significant IOP reductions from baseline at 13:00 h at each study visit during which diurnal IOP was measured (3 and 6 months; $p < 0.001$). Bimatoprost provided mean IOP reductions that ranged from 5.3 to 5.6 mm Hg (23% to 24%) and travoprost provided mean IOP reductions that ranged from 4.5 to 5.4 mm Hg (19% to 23%; fig 1C). The mean reductions in the bimatoprost group were greater than the reductions in the travoprost group at every study visit, but these differences were not significant ($p \geq 0.207$).

Throughout the day bimatoprost provided mean IOP that was lower than that provided by travoprost and these differences were significantly different at 09:00 h ($p = 0.022$). In addition, there was a trend towards lower mean IOP with bimatoprost compared with travoprost at 13:00 h ($p = 0.143$). At the 6-month study visit, mean IOP of the bimatoprost-treated group ranged from 16.6 to 17.5 mm Hg and mean IOP of the travoprost-treated group ranged from 17.3 to 18.7 mm Hg (fig 2).

Patients were more likely to achieve clinically relevant IOP reductions of $\geq 20\%$, 25% or 30% with bimatoprost than with

Figure 2 Diurnal mean intraocular pressure (IOP) at the 6-month study visit. Bimatoprost provided mean IOP that was lower than that provided by travoprost and these differences were significantly different at 09:00 h ($*p = 0.022$). In addition, there was a trend towards lower mean IOP with bimatoprost compared with travoprost at 13:00 h ($p = 0.143$).

travoprost at 09:00 h after 6 months of treatment. More patients treated with bimatoprost (77.6%, 59/76) had an IOP reduction of $\geq 20\%$ compared with those treated with travoprost (64.2%, 52/81), and this difference trended towards significance ($p = 0.065$). Furthermore, 64.5% of the patients treated with bimatoprost (49/76) had an IOP reduction of $\geq 25\%$ compared with 39.5% (32/81) of those treated with travoprost ($p = 0.002$).

In addition, 38.2% (29/76) of patients treated with bimatoprost had an IOP reduction $\geq 30\%$ compared with 28.4% (23/81) of patients treated with travoprost ($p = 0.194$; fig 3). In addition, the rate of clinical success was higher in the patients treated with bimatoprost: 78.1% of patients treated with bimatoprost and 68% of those treated with travoprost were considered to be clinically successful ($p = 0.167$).

The incidence and types of adverse events were similar in both groups. The most commonly reported adverse event in both groups was ocular redness, which occurred in 21.1% (16/76) of patients of the bimatoprost group and in 14.8% (12/81) of the patients in the travoprost group ($p = 0.326$). Ocular itching was reported more often in the travoprost group than in the bimatoprost group (7.4% of patients treated with travoprost compared with 2.3% of those treated with bimatoprost; $p = 0.278$). No significant between-group differences were found in biomicroscopic findings. Conjunctival hyperaemia scores peaked at 1 week in both groups (mean of 1.4 in patients treated with either drug; $p = 0.792$) and

Figure 3 Percentage of patients achieving target intraocular pressure (IOP) reductions at 09:00 h at the 6-month study visit. Patients were more likely to achieve clinically relevant IOP reductions of $\geq 20\%$, 25% or 30% with bimatoprost than with travoprost at 09:00 h after 6 months of treatment.

decreased throughout the 6-month study. No significant differences were observed in mean hyperaemia findings at any study visit ($p \geq 0.138$). No significant changes were found in visual acuity in either group. One patient in the bimatoprost group and no patient in the travoprost group experienced an increase in iris pigmentation.

Few patients in either group discontinued because of adverse events. In the bimatoprost group, one patient discontinued because of blurry vision and photophobia, one because of ocular redness and one because of lid erythema and ocular redness. One additional patient treated with bimatoprost discontinued because of congestive heart failure unrelated to study drug. In the travoprost group, two patients discontinued because of ocular redness and lid erythema, one due to ocular dryness and itching and one because of allergic conjunctivitis. One patient died from causes unrelated to the study drug.

DISCUSSION

In this cohort, bimatoprost provided greater IOP lowering than travoprost. Although both bimatoprost and travoprost considerably lowered IOP in patients with glaucoma or OHT, bimatoprost provided greater mean IOP reductions from baseline than travoprost at every time point at every study visit, reaching statistical significance at all 09:00 h time points.

The American Academy of Ophthalmology preferred practice patterns suggest that reductions of at least 20% from untreated IOP levels should be targeted as a goal of treatment to prevent glaucomatous progression.¹⁰ In the present study, more patients in the bimatoprost group than in the travoprost group achieved reductions of this magnitude, and almost 40% had a reduction of at least 30% from baseline. Patients treated with bimatoprost were also more likely than those treated with travoprost to be clinically successful. In addition, patients in the travoprost group were more likely than patients in the bimatoprost group to discontinue because of lack of efficacy.

Our findings support other trials that reported superior efficacy of bimatoprost relative to travoprost. In a study by Parrish *et al.*,⁹ the IOP-lowering efficacy of latanoprost, bimatoprost and travoprost was evaluated. In this large-scale 12-week clinical study, there were no significant among-group differences in mean IOP, but bimatoprost consistently provided lower mean IOP than travoprost. Interestingly, the IOP lowering in our study was actually slightly less than the IOP lowering observed in the Parrish study (mean IOP lowering throughout the study was 8.7 mm Hg with bimatoprost and 7.9 mm Hg with travoprost). This is probably due to differences in the baseline IOP levels: mean baseline IOP in the present study was approximately 1.1 mm Hg lower than in the Parrish study.

Bimatoprost has been shown to provide effective IOP lowering in patients of all races.²⁻³ Conversely, travoprost has been shown to be more effective in black patients than in Caucasians.⁷ An investigator-blinded, parallel-design trial compared bimatoprost with travoprost in African-Americans with glaucoma or OHT.¹¹ Both drugs comparably lowered IOP, but bimatoprost was more likely than travoprost to allow achievement of every target pressure from 12 to 19 mm Hg at 3 months. At 3 months, the mean IOP reduction from baseline was 8.4 mm Hg (34%) in the bimatoprost group and 7.9 mm Hg (30%) in the travoprost group.

In this study, both bimatoprost and travoprost were safe and well tolerated. The incidence of hyperaemia was higher in the bimatoprost group than in the travoprost group, but this difference was not statistically significant. Moreover, a

recent large-scale patient survey suggests that patients with glaucoma are willing to tolerate cosmetic side effects of IOP-lowering drugs (such as red eyes) if the drug is the most effective and provides them with the lowest pressures.¹² These findings and the negligible between-group difference in the incidence of hyperaemia suggest that hyperaemia was not an issue in this study.

In conclusion, bimatoprost provided greater control of IOP throughout the day and significantly greater mean IOP reductions from baseline at 09:00 h at every visit, and allowed more patients to achieve the magnitude of IOP lowering recommended by the American Academy of Ophthalmology. These findings suggest that bimatoprost is an effective ocular hypotensive agent for patients with glaucoma or OHT.

Authors' affiliations

L B Cantor, J Hoop, L Morgan, D WuDunn, Y Catoira, Department of Ophthalmology, Indiana University School of Medicine, Indianapolis, Indiana, USA

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The Bimatoprost-Travoprost Study Group included: Thomas Bournias, Northwestern University, Chicago, Illinois; Louis Cantor, Indiana University School of Medicine, Indianapolis, Indiana; Monte Dirks, Black Hills Regional Eye Institute, Rapid City, South Dakota; Efraim Duzman, Lakeside Vision Center, Irvine, California; Arash Mansouri, Access Eye Centers, Fredericksburg, Virginia; Thomas Mundorf, Mundorf Eye Center, Charlotte, North Carolina; Steven Simmons, Glaucoma Consultants of the Capital Region, Slingerlands, New York; Robert Williams, Taustine Eye Center, Louisville, Kentucky.

REFERENCES

- Heijl A, Leske C, Bengtsson B, *et al.* Reduction of intraocular pressure and glaucoma progression: results from the early manifest glaucoma trial. *Arch Ophthalmol* 2002;**120**:1268-79.
- Higginbotham E, Schuman J, Goldberg I, *et al.* One-year, randomized study comparing bimatoprost and timolol in glaucoma and ocular hypertension. *Arch Ophthalmol* 2002;**120**:1286-93.
- Noecker RJ, Dirks MS, Choplin NT, *et al.* A six-month randomized clinical trial comparing the intraocular pressure-lowering efficacy of bimatoprost and latanoprost in patients with ocular hypertension or glaucoma. *Am J Ophthalmol* 2003;**135**:55-63.
- Gandolfi S, Simmons ST, Sturm R, *et al.* Three-month comparison of bimatoprost and latanoprost in patients with glaucoma and ocular hypertension. *Adv Ther* 2001;**18**:110-21.
- Simmons ST, Dirks MS, Noecker RJ. Bimatoprost versus latanoprost in lowering intraocular pressure in glaucoma and ocular hypertension: results from parallel-group comparison trials. *Adv Ther* 2004;**21**:247-62.
- Brubaker RF. Mechanism of action of bimatoprost (LumiganTM). *Surv Ophthalmol* 2001;**45**(Suppl 4):S347-51.
- Netland PA, Landry T, Sullivan EK, *et al.* Travoprost compared with latanoprost and timolol in patients with open-angle glaucoma or ocular hypertension. *Am J Ophthalmol* 2001;**132**:472-84.
- Orengo-Nania S, Landry T, Von Tress M, *et al.* Evaluation of travoprost as adjunctive therapy in patients with uncontrolled intraocular pressure while using timolol 0.5%. *Am J Ophthalmol* 2001;**132**:860-8.
- Parrish RK, Palmberg P, Sheu WP, *et al.* A comparison of latanoprost, bimatoprost, and travoprost in patients with elevated intraocular pressure: a 12-week, randomized, masked-evaluator multicenter study. *Am J Ophthalmol* 2003;**135**:688-703.
- American Academy of Ophthalmology. *American Academy of Ophthalmology preferred practice pattern: primary open-angle glaucoma*. San Francisco: American Academy of Ophthalmology, 2000.
- Noecker RJ, Earl ML, Mundorf T, *et al.* Bimatoprost 0.03% versus travoprost 0.004% in black Americans with glaucoma or ocular hypertension. *Adv Ther* 2003;**20**:121-8.
- Rollins J. *Doctor-patient communication in US glaucoma patients: The Glaucoma Research Foundation Patient Survey*. Rockville, MD: ARVO, 2004.