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Intraocular pressure lowering efficacy of travoprost

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PURPOSE. To assess the intraocular pressure lowering effect of travoprost 0.004% in patients previously treated with another topical medication, and in previously untreated patients.
METHODS. This 12-week, open-label trial in 1590 patients was conducted at 219 sites in Switzerland. Primary open-angle glaucoma and ocular hypertension patients discontinued prior medications, and instilled 1 drop of travoprost in each affected eye at 8 pm. Untreated patients were subdivided into 2 groups: baseline IOP of ≥ 21 mmHg, and baseline IOP of ≤ 20 mmHg. Patients returned for follow-up visits at 1 and 3 months. The primary outcome was mean IOP change from baseline to follow-up.
RESULTS. Of 626 patients previously on monotherapy, and 525 previously untreated or newly-diagnosed patients, 479 and 423, respectively, completed 3 months of therapy. The mean changes from baseline at 1 month (mmHg ± SD), by prior treatment group were: beta blocker, -4.9 (±3.6); latanoprost, -2.3 (± 2.8); alpha-agonist, -4.0 (± 3.7); dorzolamide/timolol fixed combination, -3.4 (± 3.9); topical CAI, -4.4 (± 3.1); new IOP ≥ 21 mmHg, -8.6 (± 4.4); new IOP ≤ 20 mmHg, -4.4 (± 3.0). (All changes from baseline were statistically significant ($p < 0.0001$).
CONCLUSIONS. In patients previously treated with a single drug, travoprost decreased IOP to pressures below those achieved on prior therapy. In all groups, travoprost reduced mean IOP below 18 mmHg within 1 month of starting therapy, and control was maintained for at least 3 months. Overall, travoprost was safe and well-tolerated. (Eur J Ophthalmol 2004; 14: 416-22)

KEY WORDS. Glaucoma, IOP, Travoprost, Prostaglandin analogue

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INTRODUCTION

Glaucoma affects as many as 67 million people worldwide, and is a leading cause of vision loss and blindness (1). The risk of developing primary open-angle glaucoma, the most common form of the disease in the Western Hemisphere, is correlated with chronically increased intraocular pressure (IOP). Optic nerve injury and visual field loss may already be severe by the time of diagnosis. To prevent the progression of glaucoma and to preserve vision, mean IOP should be reduced to a target pressure that is patient-dependent, and diurnal IOP fluctuation should be minimized.

Most patients can be treated with a single drug, but some require multiple-drug therapy. Unfortunately, tachyphylaxis is common with many of the currently available drugs. Though the number of available drugs has increased significantly during the last 10 years, an

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ideal agent has not yet been found. Because of their effectiveness and prolonged action, prostaglandin analogues, such as travoprost, have recently provoked great interest. Travoprost is approved in the United States, Europe, and other countries for the treatment of open-angle glaucoma and ocular hypertension. In the European Union, travoprost has been approved as first-line therapy. Travoprost begins to reduce IOP within about 2 hours after dosing, maximum reduction occurs within 12 hours, and the reduction is maintained for at least 24 hours (2). Travoprost may be used alone, or as adjunctive therapy.

Travoprost has been shown to be effective in newly-diagnosed and untreated patients (3-6). However, whether travoprost is effective in patients who require a change in therapy is unknown. We designed this trial to assess the intraocular pressure lowering effect of travoprost 0.004% in patients previously treated with another single drug, and in previously untreated patients.

METHODS

This 12-week, open-label trial was conducted at 219 sites in Switzerland. Patients 18 years or older were enrolled if, in the investigator's opinion, they required a change from their current therapy to travoprost therapy; or, if they had newly diagnosed or untreated ocular hypertension or POAG, and required prostaglandin therapy. Patients were excluded from enrollment for known hypersensitivity to travoprost, or to any of the ingredients in the solution. Women were excluded if they were pregnant, or intended to become pregnant. Before starting the trial, the investigator verbally explained the details of the trial to each eligible patient.

At the first visit, the investigator obtained demographic information and baseline intraocular pressures in each eye. Previously treated patients were instructed to discontinue their prior medications. All patients were started on a regimen of 1 drop of travoprost in each affected eye once daily at 8 pm. Patients returned for follow-up IOP measurements in 1 month and 3 months. Investigators were instructed to take IOP measurements for each patient at same time of day to avoid diurnal variations.

For analysis, patients were divided into 3 groups: newly diagnosed patients started on initial therapy; patients previously treated with a single drug; and, patients previously treated with multiple drugs. For this report, only the first 2 groups were analyzed. The data was imported into a SAS v8.2 database repository for analysis using DATA steps and PROC IMPORT. A within-subjects design with repeated measures on IOP was used for each monotherapy replacement. Only patients with non-missing IOP values for all three examinations were eligible for evaluation. Descriptive analysis was accomplished using MEANS, UNIVARIATE, and FREQ procedures. Using PROC GLM, a Repeated Measures Analysis of Variance with planned comparisons among the three IOP measurements was executed independently on the replaced monotherapy treatment. The p-values reported are those of the contrasts (equivalent to paired t-test). Efficacy was assessed by calculating the mean IOP change from the baseline visit to each follow-up visit (per-protocol patients). Side effects were recorded as adverse events reported by the patients.

RESULTS

Of the 1590 enrolled patients, 449 were on multiple-drug therapy and were not included in the analysis. Of the remaining 1151 patients (intent-to-treat population), 626 were on monotherapy, and 525 were either not on treatment or were newly-diagnosed (hereafter called "untreated"). Of the untreated patients, 85 had a baseline IOP ≤ 20 mmHg, and 440 had a baseline IOP ≥ 21 mmHg. Table I shows, by treatment, the number of patients who completed 3 months of follow-up, and who were eligible for per-protocol analysis. The exact reasons the 249 other patients withdrew from the study were not recorded.

Of the 902 patients in the per-protocol population, 370 (41%) were men, 522 (58%) were women, and for 10 (1%), the patient's sex was not recorded. For patients whose age was recorded (n = 851), the mean age was 68.0 ± 12.4 years (range 22 to 94 years). Table II shows the number of per-protocol patients by diagnosis.

Table III shows baseline, 1-month, and 3-month mean IOPs for per-protocol patients previously treated with beta-blockers, latanoprost, alpha-agonists, dorzolamide/timolol fixed combination, or carbonic anhydrase inhibitors (CAIs); for untreated patients with a baseline IOP ≥ 21 mmHg; and, for untreated patients

TABLE I - NUMBER OF PATIENTS COMPLETING THREE MONTHS OF FOLLOW-UP

Group	Intent-to-Treat	Per-Protocol (completed 3 months of follow-up)
Beta-blocker	216	169
Latanoprost	223	164
Alpha-agonist	49	38
Dorzolamide/timolol FC	57	45
Topical CAI	63	52
Latanoprost/timolol FC[a]	14	8
Unoprostonea	4	3
Newly-diagnosed or untreated; IOP ≥ 21 mmHg	440	351
Newly-diagnosed or untreated; IOP ≤ 20 mmHg	85	72
Total	1151	902

[a] Because of the small number of patients, the data from these groups were not analyzed
FC = Fixed combination

TABLE II - NUMBER OF PATIENTS BY DIAGNOSIS (n = 902)

Diagnosis	Number (%)
Primary open-angle glaucoma	665 (74)
Pseudoexfoliation syndrome	116 (13)
Ocular hypertension	80 (9)
Narrow-angle glaucoma	21 (2)
Other, or not reported	20 (2)

TABLE III - MEAN (SD) INTRAOCULAR PRESSURES (Per-Protocol Data Set)

Prior Therapy	n	Baseline (mmHg)	Month 1 (mmHg)	Month 3 (mmHg)
Beta-blocker	169	21.2 (3.9)	16.3 (3.7)	16.3 (3.6)
Latanoprost	164	19.6 (3.7)	17.3 (3.0)	17.5 (3.5)
Alpha-agonist	38	21.6 (5.8)	17.6 (5.3)	17.4 (6.3)
Dorzolamide/timolol FC	45	20.6 (3.9)	17.2 (3.2)	17.5 (3.2)
Topical CAI	52	20.6 (3.3)	16.2 (3.0)	16.1 (2.6)
Newly-diagnosed or untreated; IOP ≥ 21 mm Hg	351	26.2 (4.3)	17.6 (3.2)	17.7 (3.0)
Newly-diagnosed or untreated; IOP ≤ 20 mm Hg	72	18.5 (1.8)	14.1 (2.7)	14.2 (2.4)

FC = Fixed combination

with a baseline IOP ≤ 20 mmHg. Figure 1 shows the mean IOPs for patients switched to travoprost from alpha-agonists, beta-blockers, CAIs, dorzolamide/timolol fixed combination, or latanoprost. Figure 2 shows the mean IOPs for untreated patients.

Table IV shows the mean IOP change from baseline by prior treatment group. Table V shows the number and percent of patients in each group whose IOPs were improved, unchanged, or worse after 3 months of travoprost therapy.

All 1151 patients in the intent-to-treat group were included in the safety analysis. One hundred sixty-

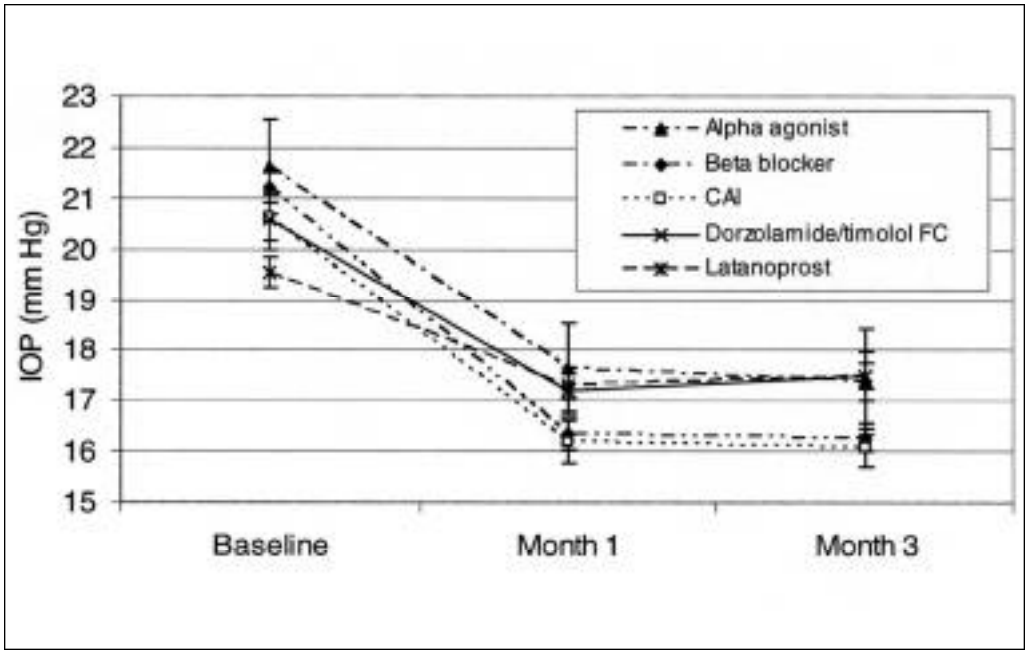

Fig. 1 - Mean IOPs (±SEM) for patients switched to travoprost from alpha-agonists, beta-blockers, CAIs, dorzolamide/timolol fixed combination, or latanoprost.

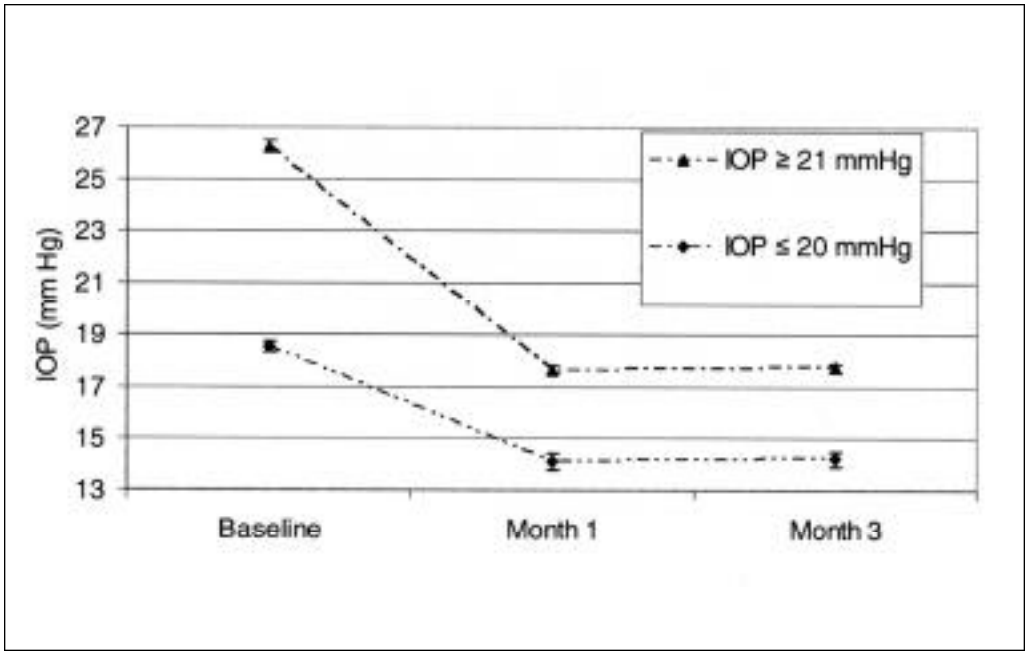

Fig. 2 - Mean IOPs (±SEM) for untreated patients.

four patients (14.3%) had an adverse event. One patient died from causes unrelated to the study. Only 3 patients (0.3%) had a serious adverse event: 2 had hyperpigmentation of the iris, and 1 had what was recorded only as "strong side effects." Table VI shows the distribution of adverse events.

DISCUSSION

The results of this study show that travoprost decreases IOP in patients previously treated with either beta-blockers, latanoprost, alpha-agonists, dorzolamide/timolol fixed combination, or topical CAIs. Ex-

TABLE IV - MEAN IOP CHANGE FROM BASELINE (Per-Protocol Data Set)

Prior Therapy	Month 1 IOP Change[a] from baseline (SD)	Month 3 IOP Change[a] from baseline (SD)
Beta-blocker	- 4.9 (3.6)	- 4.9 (2.5)
Latanoprost	- 2.3 (2.8)	- 2.1 (2.9)
Alpha-agonist	- 4.0 (3.7)	- 4.2 (2.1)
Dorzolamide/timolol FC	- 3.4 (3.9)	- 3.1 (2.5)
Topical CAI	- 4.4 (3.1)	- 4.5 (2.3)
Newly-diagnosed or untreated; IOP ≥ 21 mmHg	- 8.6 (4.4)	- 8.5 (2.8)
Newly-diagnosed or untreated; IOP ≤ 20 mmHg	- 4.4 (3.0)	- 4.3 (2.3)

[a] All changes from baseline were statistically significant ($p < 0.0001$)
FC = Fixed combination

TABLE V - RESPONSE (%) TO THREE MONTHS OF TRAVOPROST THERAPY

Prior Therapy	n	Improved	Unchanged	Worse
Beta-blocker	169	90	5	5
Latanoprost[a]	164	73	9	18
Alpha-agonist	38	87	8	5
Dorzolamide/timolol FC[a]	45	73	9	18
Topical CAI	52	88	10	2
Newly-diagnosed or untreated; IOP ≥ 21 mmHg	351	98	1	1
Newly-diagnosed or untreated; IOP ≤ 20 mmHg	72	96	3	1

FC = Fixed combination

TABLE VI - ADVERSE EVENTS

Adverse events	n	Percent
Conjunctival hyperemia	57	4.9
Burning	15	1.3
Other	50	4.3
Conjunctival hyperemia plus burning	17	1.5
Conjunctival hyperemia plus other	18	1.6
Burning plus other	4	0.4
Conjunctival hyperemia plus burning plus other	3	0.3
Total	164	14.3

cellent IOP control was also achieved in patients with either untreated or newly diagnosed glaucoma or ocular hyperemia, irrespective of baseline IOP. In all groups, travoprost reduced the mean IOP below 18 mmHg within 1 month of starting therapy, and IOP was controlled for at least 3 months.

Intraocular pressures after 3 months of travoprost therapy were below those produced by the patient's prior medication. Interestingly, IOP decreased most in patients previously treated with beta-blockers. As expected, the smallest decrease occurred in patients previously treated with latanoprost, another prosta-

glandin analogue. Travoprost was also very effective in newly diagnosed or untreated patients. The largest decreases occurred in previously untreated patients whose baseline IOP was greater than or equal to 21 mmHg.

The response to travoprost in patients previously treated with concomitant therapies was not part of the analysis. Analyzing their responses to a change of only one of their medications to travoprost would not lead to any meaningful interpretation due to the small number of patients.

Chronic elevation and diurnal fluctuations in IOP are correlated with visual field loss (7). On the other hand, sustained IOP reductions below 18 mmHg are correlated with stability of the visual fields (8). In all groups, travoprost reduced both the 1-month and 3-month mean IOPs below the 18 mmHg upper limit recommended for adequate control (9). These results agree with those of previous trials showing that travoprost controls IOP (3-6) Prior studies have also shown that travoprost effectively lowers IOP throughout the day (10).

In this study, travoprost was generally safe and well-tolerated. When used for long periods, topical prostaglandins have been associated with eyelash growth and iris pigmentation. Although two patients had iris pigmentation, this study's 3-month duration was not long enough to accurately estimate the incidence of eyelash growth or iris pigmentation. The overall adverse event rate of 14% was comparable to the 10% rate reported with latanoprost (11). Except for three patients, the adverse events were not clinically important. The majority of adverse events were conjunctival hyperemia and burning, either alone or in combination.

Travoprost is a synthetic prostaglandin $F_{2\alpha}$-analogue that is highly selective for the FP prostaglandin receptor (12-16). This high selectivity makes travoprost less likely to produce side effects such as pain, itching, and hyperemia that are mediated by other prostanoid and non-prostanoid receptors. Travoprost's effectiveness probably results from its full-agonist activity at the FP receptor, and its more potent, prolonged action. Patients may also comply better with travoprost's once-a-day dosing regimen, and may tolerate treatment better because travoprost has fewer side effects.

This study had some limitations. An open-label study is susceptible to either positive or negative observer bias. In addition, there was no placebo or active control group for comparison. There was no washout period between prior medications. Despite these limitations, it should be noted that the study design approximates actual clinical practice. This study may thus give practicing physicians an idea of the results they can expect when changing patients from another medication to travoprost.

In conclusion, travoprost decreases IOP in patients previously treated with either beta-blockers, latanoprost, alpha-agonists, dorzolamide/timolol fixed combination, or topical CAIs. Excellent IOP control was also achieved in patients with either untreated or newly diagnosed glaucoma or ocular hypertension, regardless of whether their baseline IOPs were above or below 20 mmHg. In all groups, travoprost reduced the mean IOP below 18 mmHg within 1 month of starting therapy, and IOP was controlled for at least 3 months. Travoprost was generally safe and well-tolerated.

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