European Journal of Ophthalmology / Vol. 13 / Suppl. 4, 2003 / pp. S21-S29

Persistency and clinical outcomes associated with latanoprost and beta-blocker monotherapy: Evidence from a European retrospective cohort study

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PURPOSE. *To evaluate persistency (time on initial therapy) and the clinical impact of latanoprost versus beta-blocker monotherapy in treating glaucoma.*
METHODS. *This observational, multicenter, retrospective medical chart review study conducted in four European countries included patients with primary open-angle glaucoma or ocular hypertension who began their first glaucoma treatment with latanoprost or a beta-blocker between November 1996 and November 1998. Persistency and glaucoma-related clinical outcomes data were abstracted for the 2 years following treatment initiation.*
RESULTS. *In all, 260 patient charts were analyzed (94 latanoprost, 166 beta-blocker). Patients in the latanoprost group stayed on therapy twice as long as those who received a beta-blocker ($p<0.0001$). After adjusting for baseline characteristics, patients receiving a beta-blocker as initial therapy were 3.8 times more likely to change therapy than those initially treated with latanoprost ($p<0.0001$). Patients in the latanoprost group also experienced greater mean decreases in intraocular pressure (IOP) than those receiving a beta-blocker (7.4 mmHg versus 4.6 mmHg, respectively; $p<0.0001$), and fewer had worsened optic nerve head excavation (1.7% versus 14.2%, respectively; $p<0.05$) by the time of their first therapy change or last study visit, whichever came first.*
CONCLUSIONS. *Over a 2-year period, latanoprost was associated with significantly greater persistency and better clinical IOP outcomes compared with beta-blocker therapy.* Eur J Ophthalmol 2003; 13 (Suppl. 4): S21-S29

KEY WORDS. *Beta-blocker, Intraocular pressure, Latanoprost, Ocular hypertension, Primary open-angle glaucoma*

Accepted: May 21, 2003

INTRODUCTION

Glaucoma is a group of diseases of the eye characterized by progressive visual field loss and potentially irreversible blindness through optic nerve damage (1). An estimated five to seven million cases of bilateral blindness worldwide are directly associated with glaucomatous damage to the optic nerve (2, 3). Open-angle glaucoma, the most common form of the disease in Western countries (4), is due to obstruction of aqueous humor outflow through the trabecular meshwork (5). The prevalence of the condition

 1120-6721/S21-09$04.50/0

increases with age, affecting 1.2% to 5.7% of persons over age 65 in western European countries (6-8). In the United States, the prevalence of open-angle glaucoma is approximately 0.5% in people between the ages of 60 and 70 years and 4.4% in those 90 years of age or older (9). Medical resource use associated with glaucoma and its complications is substantial and will increase as the population ages (10, 11).

Sustained elevated intraocular pressure (IOP) is a primary risk factor for damage to the optic nerve (5). Given that reduction of IOP has been shown to effectively delay disease progression (12-14), the primary aim of glaucoma therapy is to reduce elevated IOP levels (5, 15). First-line medical therapies for glaucoma historically have been topical beta-blockers but more recently have included topical prostaglandin analogues, such as latanoprost, which is the only prostaglandin approved for first-line use. Patients often proceed to a range of second-line medications, which include pilocarpine, adrenergic agonists, selective alpha agonists, carbonic anhydrase inhibitors, and prostaglandins or combinations of these. When medical therapy is not effective in reducing IOP levels, glaucoma patients may require argon laser trabeculoplasty or other surgical procedures, such as trabeculectomy or cyclodiode therapy.

At a minimum, patients must fill their prescriptions over time (persistency) to provide them with an opportunity to comply with the therapeutic regimen and to allow the medication to be effective. Persistency, which is affected by the physician's evaluation of a medication's effectiveness as well as the patient's assessment of its tolerability (16), is low among glaucoma patients, particularly among patients receiving topical beta-blockers (17-20). Use of topical beta-blockers has been associated with serious cardiopulmonary side effects and central nervous system adverse effects, including depression, fatigue, confusion, and memory loss (21-24). In contrast, latanoprost has been shown to more effectively lower IOP levels while producing fewer systemic side effects than beta-blockers (25-27). Moreover, latanoprost is instilled once a day versus the twice-daily administration required with beta-blockers.

Because controlled clinical trials are designed to demonstrate a medical therapy's safety and efficacy, they incorporate protocol-driven selection criteria and medical care guidelines that may not reflect routine practice. In contrast, observational studies evaluate a medication's effectiveness in a real-world setting. The present study compared persistency of use and clinical outcomes associated with latanoprost versus beta-blockers in patients with primary open-angle glaucoma (POAG) or ocular hypertension (OH) treated in uncontrolled practice settings.

METHODS

This observational, multicenter, retrospective medical chart review study followed treatment-naive patients who received latanoprost or beta-blocker monotherapy between November 1996 and November 1998 for 2 years. The study was conducted at 13 centers in Germany, Italy, Spain, and the United Kingdom (UK) that reflected standard practice in each country. Physician ophthalmology practices participated in Germany (n=3) while hospitals with outpatient ophthalmology clinics participated in Italy (n=4), Spain (n=4), and the UK (n=2).

Study inclusion criteria were age 18 years or older, diagnosis of POAG (including pigment dispersion or exfoliation syndrome) or OH, and initial treatment for POAG or OH with either latanoprost or beta-blocker monotherapy between November 1996 and November 1998. Patients were excluded if they had a concomitant diagnosis of closed-angle glaucoma, had participated during the 2-year study period in an ophthalmology clinical trial in which protocol-scheduled visits diverged from regular clinical practice, or had changed their treatment center during the study period. At each center, a consecutive sample of eligible patient charts up to a maximum number was identified based on date of treatment initiation. By protocol, included patients were followed for 2 years, with a 2-month "window" that allowed data for visits occurring within 26 months of baseline to be evaluated. Trained staff abstracted data on glaucoma-related clinical outcomes using standardized data collection forms. These data included baseline characteristics, IOP level, optic nerve head excavation, visual field defect, and therapy changes.

Analyses

The analysis compared persistency with therapy and clinical outcomes between patients whose initial ocular hypotensive was latanoprost monotherapy and

those whose initial ocular hypotensive was beta-blocker monotherapy. Persistency was defined as time on initial therapy. A patient was determined to have changed therapy if the medical chart documented that the physician prescribed either an additional antiglaucoma medication or an alternate ocular hypotensive. Changes (switching or adding) were recorded and tabulated throughout the 2-year study period. Patients were assumed to have filled their prescriptions. A Cox regression model was used to examine the likelihood of changing therapies, and the time horizon for the model was the entire study. The dependent variable, time to therapy change, was defined as the period from treatment initiation (baseline) to first change in therapy; it was assumed that a patient did not discontinue therapy throughout the study if no clinical assessment showed a change in therapy. Independent variables included study group, age, sex, time since diagnosis, baseline visual field defect, and frequency of ophthalmology visits.

Analyses of clinical outcomes focused on the patient's worst eye at baseline. The worst eye was defined as the eye with the highest IOP at the baseline visit. If both eyes had the same IOP at baseline, the baseline value for the cup-to-disc ratio and, if necessary, the visual field defect were used to identify the worst eye. If all three measures were equal between the eyes, the worst eye was selected randomly. The glaucoma-related clinical outcomes data, including changes in IOP level, visual field defect, and nerve head excavation, were analyzed for the period from baseline to the date of the last recorded measurement prior to change in therapy or prior to study completion, whichever occurred first. Information was pooled across countries. The Wilcoxon test was used to compare continuous variables, and the Fisher's exact test was used to compare categorical variables. Two-tailed statistical tests were performed, and significance was determined at the $p<0.05$ level.

RESULTS

Patient population

In all, 260 evaluable patient charts met the eligibility criteria (Germany: 82; Italy: 76; Spain: 73; and the UK: 29); 94 patients (36.2%) received latanoprost initially, and 166 patients (63.8%) received a beta-blocker initially. Table I summarizes baseline patient demographics. Study groups were comparable with regard to patient age and sex. At baseline, a higher percentage of patients receiving latanoprost initially had respiratory/pulmonary disease ($p<0.0001$), and higher percentages were treated for asthma and diabetes ($p<0.05$).

Baseline ocular demographics generally also were comparable across groups (Tab. II). A larger proportion of patients in the latanoprost group was diagnosed with POAG compared to those receiving beta-blockers (91.5% versus 81.3%, respectively; $p<0.05$), and more patients who received latanoprost had moderate or severe visual field defects at baseline compared to those treated with beta-blockers (77.7% versus 63.4%, respectively; $p<0.05$). These findings suggest that patients receiving latanoprost may have had more severe disease at baseline than those who first received a beta-blocker, although mean IOP levels and cup-to-disc ratios recorded in medical charts were nearly identical in the two treatment groups.

Persistency with therapy

Patients who initially received latanoprost stayed on therapy more than twice as long as did those treated first with a beta-blocker (median time on therapy: 21.8 months versus 10.8 months, respectively; $p<0.0001$) (Tab. III). Patients in the beta-blocker group experienced an average of 1.3 therapy changes during the 2-year period compared to 0.5 changes for those in the latanoprost group ($p<0.0001$). Overall, 70.5% of patients treated first with beta-blockers had at least one change in therapy compared with 26.7% of patients treated with latanoprost; 39.2% of beta-blocker-treated patients versus 8.6% of patients treated with latanoprost had two or more changes in therapy ($p<0.0001$ for each comparison) (Tab. III). Among those who changed therapy, the average IOP at the time of the first change was 22.5 mmHg in patients who initially received beta-blockers compared to 21.0 mmHg in those treated initially with latanoprost.

After adjusting for baseline characteristics, the Cox regression analysis showed that patients initially treated with beta-blockers were 3.8 times more likely to change therapy than were those treated initially with latanoprost ($p<0.0001$; 95% confidence inter-

TABLE I - BASELINE PATIENT DEMOGRAPHICS

	Latanoprost (n=94)	Beta-blocker (n=166)
Age (years), mean (95% CI)	67.7 (65.4-70.0)	65.2 (63.4-67.0)
Sex, n (%)*		
Male	39 (41.5)	68 (42.2)
Female	55 (58.5)	93 (57.8)
Clinical history, n (%)		
Cardiovascular disease	16 (17.0)	15 (9.0)
Diabetes	22 (23.4)	23 (13.9)
Extreme myopia	1 (1.1)	2 (1.2)
Eye trauma	1 (1.1)	1 (0.6)
Family history of glaucoma	9 (9.6)	31 (18.7)
Hypothyroidism	1 (1.1)	1 (0.6)
Respiratory/pulmonary disease†	12 (12.8)	1 (0.6)
Vascular disease	8 (8.5)	16 (9.6)
Other	7 (7.4)	14 (8.4)
Concomitant medications, n (%)		
Cardiovascular	16 (17.0)	16 (9.6)
Asthma‡	8 (8.5)	3 (1.8)
Diabetes‡	16 (17.0)	13 (7.8)

* Missing data for five patients in the beta-blocker group; †p<0.0001; ‡p<0.05; CI=Confidence interval

val, 2.4 to 6.0). Figure 1 provides Kaplan-Meyer curves comparing time to therapy change for patients in the two groups.

Clinical outcomes

Compared to patients in the beta-blocker group, those treated initially with latanoprost experienced a greater mean decrease in IOP (7.4 mmHg versus 4.6 mmHg, respectively; p<0.0001). Information related to optic nerve head excavation, as measured by the cup-to-disc ratio, was available for 164 (63.1%) patients; optic nerve head excavation had worsened in significantly fewer patients who received latanoprost initially than in those who first received beta-blockers (1.7% versus 14.2%, respectively; p<0.05). Data concerning visual field defect were available for 153 (58.8%) patients; although not statistically significant, such defects had worsened in a somewhat higher proportion of patients treated initially with beta-blockers compared with those first treated with latanoprost (15.3% versus 10.9%, respectively; p=0.62).

DISCUSSION

This observational, retrospective, medical chart review study conducted in routine clinical practices

TABLE II - BASELINE OCULAR DEMOGRAPHICS*

	Latanoprost (n=94)	Beta-blocker (n=166)
Diagnosis, n (%)†		
Primary open-angle glaucoma	86 (91.5)	135 (81.3)
Ocular hypertension	8 (8.5)	31 (18.7)
Time since diagnosis (months), mean (95% CI)	0.9 (-0.2-2.1)	1.2 (0.5-2.0)
IOP (mmHg), mean (95% CI)	25.0 (24.2-25.9)	25.5 (24.9-26.2)
Optic nerve excavation (cup-to-disc ratio), mean (95% CI)‡	0.6 (0.6-0.6)	0.6 (0.5-0.6)
Visual field defect, n (%)§		
None/minor	19 (22.4)	52 (36.6)
Moderate	61 (71.8)	78 (54.9)
Severe	5 (5.9)	12 (8.5)

*Data reflect the worst eye at baseline; †p<0.05; 8 patients in the latanoprost group and 12 patients in the beta-blocker group had an additional mention of exfoliation syndrome in their medical charts while 5 patients in the latanoprost group and 4 patients in the beta-blocker group had an additional mention of pigment dispersion; ‡Eighteen patients in the beta-blocker group and 6 patients in the latanoprost group were missing optic nerve excavation data; §p<0.05 for difference between groups in proportions with moderate and severe defects combined versus none/minor defects; 24 patients in the beta-blocker group and 9 patients in the latanoprost group were missing visual field defect data; CI=Confidence interval; IOP=Intraocular pressure

located in four European countries found that persistency and clinical outcomes associated with initial latanoprost monotherapy were superior to those associated with initial beta-blocker monotherapy in patients with POAG or OH. In particular, patients treated initially with latanoprost stayed on therapy more than twice as long as those treated initially with beta-blockers, and only about 30% of patients treated first with beta-blockers remained on therapy at the end of 2 years. This result is similar to findings of three retrospective cohort studies conducted in managed care health plans in the United States (17, 19, 20). These studies each included more than 1000 patients who were followed for persistency for 18 to 30 months. Patients treated initially with latanoprost monotherapy were consistently found to be significantly more likely to continue therapy compared with those treated with beta-blockers, carbonic anhydrase inhibitors, or brimonidine. Extending these findings, the present research revealed that a large proportion (39.2%) of the subset of patients initially treated with beta-blockers who changed therapies experienced multiple therapeutic changes.

Previous research suggests that the low level of persistency found in patients treated initially with a beta-blocker may have substantial financial consequences over time. Studies conducted in Germany, Sweden, and the United States in the mid-1990s found that fewer than one half of patients initially treated with timolol, a beta-blocker, remained on therapy after 2 years (18, 28). In addition, changes in therapy have been associated with periods of intense resource utilization and increased costs (18, 29). In Sweden, for example, the average 2-year cost per patient with no treatment change was 7,136 kroners (SEK) compared with 12,095 SEK for those with two changes and 45,720 SEK for patients having more than three changes (30). Similar to results of controlled clinical trials, patients treated with latanoprost in the present study experienced a greater decrease in IOP levels compared to those treated with beta-blockers. An analysis of pooled data from three 6-month, ran-

TABLE III - CLINICAL OUTCOMES*

	Latanoprost (n=94)	Beta-blocker (n=166)
Time on initial therapy (months),†‡		
median (range)	21.8 (0.2-25.5)	10.8 (0.1-25.8)
Number of changes,†§		
mean (95% CI)	0.5 (0.2-0.7)	1.3 (1.1-1.5)
Patients who changed initial therapy, n (%)§⋆		
None	69 (73.4)	49 (29.5)
Changed once	17 (18.1)	52 (31.3)
Changed twice	4 (4.3)	41 (24.7)
Changed >2 times	4 (4.3)	24 (14.5)
Overall decrease in IOP (mmHg), mean (95% CI) †‡ ¶	7.4 (6.5-8.3)	4.6 (3.7-5.5)
Optic nerve excavation (cup-to-disc ratio), n (%)‡#		
Number reported	58	106
Worsened	1 (1.7)	15 (14.2)
Stayed the same	57 (98.3)	91 (85.8)
Visual field defect, n (%)‡		
Number reported	55	98
Worsened	6 (10.9)	15 (15.3)
Stayed the same	49 (89.1)	83 (84.7)

*Data reflect the worst eye at baseline; †p<0.0001; ‡Reflects period from baseline to date of last recorded measurement prior to change in therapy or completion of study, whichever occurred first; §Change defined as any change in drug therapy regimen; ⋆p<0.0001 for difference in proportions of patients in each group with ≥1 change in therapy and also for the difference in proportions with ≥2 changes in therapy; ¶Three patients in the beta-blocker group and 2 patients in the latanoprost group were missing IOP data at change or last measurement; #p<0.05; CI=Confidence interval; IOP=Intraocular pressure

domized, double-masked clinical trials in patients with POAG or OH found diurnal IOP levels were reduced an average of 31% in latanoprost-treated and 26% in timolol-treated patients (p<0.001) (31). Persistency with latanoprost also may be enhanced by the fact that its IOP-lowering effect is not associated with upward drift over a 12-month period (32) and is durable over 2 years (33). In contrast, timolol, the most commonly used beta-blocker, has been associated with an upward IOP drift of 2 mmHg to 5 mmHg over a 1- to 2-year period (34-37).

Although target IOP levels typically are defined on an individual patient basis, levels <17 mmHg have been shown to be generally clinically favorable whereas patients with IOPs ≥17 mmHg are more likely to experience progressive glaucomatous damage (14). In the current study, the mean IOP at therapy change or last study visit was 21.0 mmHg in the be-

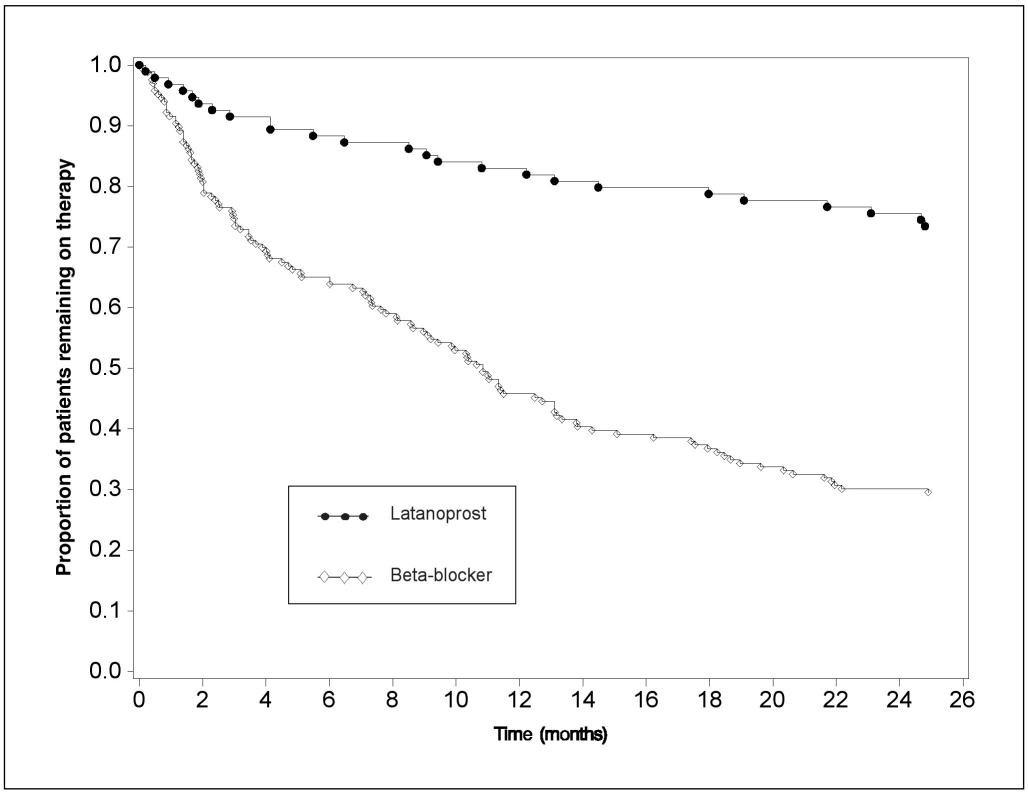

Fig. 1 - *Time to therapy change (Kaplan-Meyer curves).*

ta-blocker group compared to 17.7 mmHg in the group receiving latanoprost first. In addition, optic nerve head excavation and visual field defects were more stable in patients treated with latanoprost. These findings suggest that early treatment with latanoprost maintains IOPs at clinically favorable levels and may delay disease progression.

This observational study has the advantage of reflecting care in routine clinical practice settings. In addition, data for 2 years of follow-up were included, a much longer time frame than that reported for most clinical trials. Nevertheless, several limitations should be considered. First, as in all retrospective studies, clinical data were not recorded uniformly. Because the frequency of missing or incomplete data was comparable across groups, we believe that the results are not biased. Only patients naive to antiglaucoma therapy met study inclusion criteria; however, some patients with more severe disease who were treated previously but whose charts were incomplete in this regard may have been included. In addition, despite its 2-year time frame, the study could not evaluate differences between therapies with regard to long-term changes in visual fields and cup-to-disc ratios. Studies spanning 5 years or more are needed to characterize the impact of ocular hypotensives on these parameters. It also is important to point out that although participating centers were selected to reflect standard practice in each country, the extent to which they actually represent the practice in each country or the European union more generally is unknown. Intercountry differences may have been masked in the pooled analyses, but numbers of patients were insufficient to support subanalyses.

A future, larger study might examine whether patients treated in physician ophthalmology practices (Germany) have less severe disease than those seen in hospital outpatient ophthalmology clinics and whether such differences affect outcomes. Finally, the chart review method allowed persistency but not compliance with medication regimens to be evaluated; data collected via patient or physician interviews or questionnaires could be used to assess actual adherence.

CONCLUSIONS

In conclusion, results of this observational study conducted in four European countries demonstrate that persistency with therapy and clinical outcomes associated with initial latanoprost monotherapy are superior to those obtained with initial beta-blocker monotherapy.

ACKNOWLEDGMENTS

The authors would like to acknowledge the following team of physicians that contributed to data collection: M. Teus (Madrid), A. Conte (Barcelona), M. Sanchez Salorio and A. Martínez-García (Santiago de Compostela), J. Hernandez-Barahona (Sevilla), H-P. Car (Munich), H. Maier (Gerolzhofen), A. Hagel (Witten), P. Fogagnolo (Milan), M. Mosca (Milan), R. Mencucci (Florence), L. Quaranta (Brescia), S. Roxburgh (Dundee), and S. Pourjavan (Torquay). The authors would like to thank Jennifer Nordin, M.S. and Yu-Chen Yeh, M.S. for their help in project coordination and data management and Jane G. Murphy, Ph.D. for her editorial assistance.

This study was sponsored by Pharmacia Corporation, Peapack, NJ, USA.

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