

Long-term cost and efficacy analysis of latanoprost versus timolol in glaucoma patients in Germany

Ulrich Thelen¹, Dietmar Schnober², Sonja Schölzel³, Michael S. Kristoffersen⁴, Lindsay A. Nelson⁴, Jeanette A. Stewart⁴, William C. Stewart⁴

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¹ Westfälische Wilhelms-Universität, Augenarztpraxis, Münster, Germany

² Augenarzt, Werdohl, Germany

³ Department of Surgery, Institutes of Molecular Medicine, University of Freiburg, Freiburg, Germany

⁴ PRN Pharmaceutical Research Network, LLC, Cheyenne, WY, USA

Correspondence to: William C. Stewart. 109 East 17th Street, Suite 3407, Cheyenne, WY 82001, USA. info@prnorb.com

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Abstract

• **AIM:** To evaluate 5-year effectiveness and cost between latanoprost or timolol monotherapy in a pilot trial.

• **METHODS:** A retrospective, multi-center trial performed at 6 sites in Germany of patients who had a diagnosis of primary open-angle or pigmentary glaucoma, in at least one eye, initiated on monotherapy with latanoprost or timolol maleate. Qualified consecutive charts were reviewed in which 5-year efficacy, safety and cost data was abstracted.

• **RESULTS:** Seventy-seven latanoprost and 49 timolol patients were included, at the final visit no difference existed between the two groups in disc parameters including: rim area, rim area/disc area ratio, cup volume or vertical cup/disc ratio ($P > 0.05$). There was no difference in intraocular pressure (IOP) between the initial latanoprost (17.4 ± 2.6) and timolol (16.3 ± 2.8 mmHg) groups. There was less change in medicines over the follow-up period (0.1 vs 0.8) and fewer medications at the final visit (1.2 vs 1.8) with latanoprost compared to timolol. No patient treated with latanoprost discontinued therapy during follow-up, while 12% discontinued timolol mostly due to inadequate IOP control. Cost/year was less with initial timolol ($\$458 \pm 236$) as compared to latanoprost ($\$552 \pm 202$).

• **CONCLUSION:** Patients begun on latanoprost or timolol and followed over 5 years may have similar clinical outcomes. However, timolol patients may require more medicines and medicine changes to control IOP for long-term, but at a lower cost.

• **KEYWORDS:** glaucoma; economic; efficacy; safety; latanoprost; timolol; Germany

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INTRODUCTION

Latanoprost (XalatanTM, Pfizer, Inc., NY, USA) was introduced into the market in 1996 and has been shown to reduce the intraocular pressure from baseline by 25%-36% with greater efficacy than timolol, brimonidine, and dorzolamide [1-4]. Nonetheless, timolol remains commonly used as monotherapy in Europe. Although, not as effective as latanoprost it compares favorably against other ocular hypotensive medicines and is well tolerated in most patients [2]. In addition, low cost generic preparations were available for timolol only when patients in this study were examined.

Unfortunately, perhaps due to reduced efficacy of timolol and a worse systemic side effect profile compared to latanoprost, several studies have shown patients not to be as adherent to timolol compared to latanoprost [5,6]. Consequently, additional visits and procedures to treat side effects, and adding additional glaucoma medications, potentially could make timolol more expensive in long-term than latanoprost [5].

Recently Stewart and associates showed, using a Markov model for the United Kingdom and Scandinavia, that initiating latanoprost might reduce costs over five years compared to timolol [7]. In this model timolol more often required additional therapy to control the pressure, was more frequently discontinued, and had a greater incidence of progression and visual loss than latanoprost. Unfortunately, little actual patient data evaluating long-term efficacy, safety, and cost of initiating latanoprost or timolol as monotherapy exists.

The purpose of this study was to evaluate in a pilot trial the cost and effectiveness over five years between initiating latanoprost or timolol monotherapy in patients with primary open-angle glaucoma.

SUBJECTS AND METHODS

Subjects This was a retrospective, multi-center, trial that was performed at six sites in Germany. Ethics Committee approval was not required for this study. This study is adherent to the tenets of the Declaration of Helsinki. Patients who had a diagnosis of primary open-angle or pigmentary glaucoma, in at least one eye, were included and were initiated on monotherapy with latanoprost 0.005% once daily or timolol maleate 0.25% or 0.5% once or twice daily prescribed by the investigator (prior glaucoma therapy was not excluded) who had been initiated on this therapy between 1996 and 2001; had at least five documented follow-up visits (stable patients only, progressed patients had no more data collected from the time point of progression and could have had fewer than five visits included in the study) and had intraocular pressures measured using Goldmann applanation tonometry with a baseline and follow-up Heidelberg retinal tomography (HRT, Heidelberg Engineering, Heidelberg, Germany) reports (at least one every two years) available.

The diagnosis of primary open-angle glaucoma was defined generally as patients who had a history of an intraocular pressure of >22 mmHg, demonstrated typical glaucomatous optic disc (neural rim thinning or notching, saucerization, thin nasal rim or total cupping) and visual field changes (typical nerve fiber layer changes, nasal step or paracentral, Seidel's or arcuate scotoma). Further, patients must have had an optic disc evaluated by HRT within \pm six months of the initial visit and at least two subsequent HRT examinations over five years.

For exclusion criteria if the patient has an abnormality preventing reliable applanation tonometry in the study eye(s), or undergone intraocular and laser surgery three months prior to the start of data collection, any media opacity preventing reliable baseline optic nerve or visual field evaluation or enrolled in a prospective clinical trial during the data collection period. Participants diagnosed as primary, acute, chronic angle closure, exfoliation, congenital or secondary glaucoma with any known gonioscopic occludable angles (Grade I or II) were excluded from the study.

Methods Clinical sites were chosen on the basis that the physician was an ophthalmologist and had glaucoma patients with at least five years of follow up data available assessed with the HRT. All data was collected retrospectively from existing medical records of patients who were started on latanoprost or timolol monotherapy. Patient records were reviewed in a consecutive fashion. However, up to a 2:1 admission ratio was allowed between the treatment groups at each site if necessary to assure reasonable comparability in treatment group size.

All sites underwent an initiation visit by a clinical research associate (CRA) to train the staff how to abstract and record the study data. Site personnel afterwards identified

consecutive patient charts and entered the abstracted data into an electronic database. No patient identifying information was captured. The completed data set was monitored later by the CRA to verify its accuracy.

Data collection began from the patient's first visit on which they were initiated on one of the study medicines by the investigator. Data were recorded from each available visit included in the follow-up period. Ophthalmic medications and surgeries were recorded. A systemic medical history was not recorded. Subsequent visits may have occurred at any interval during the five-year follow-up period. Apart from the HRT exam, optic disc and visual field status were recorded, when performed. If both eyes had glaucoma, one eye was randomly chosen to enter into the study using a computer generated randomization list. The patients were evaluated by the same investigator who initially included them in the study.

Patients with stable glaucoma had data extracted over the complete five year follow up period. In contrast, data were collected from the records of progressed patients until the time the glaucoma worsened. Data were not recorded from progressed patients after the visit at which worsening was noted so that the information included in this study would reflect the clinical status that worsened glaucoma.

Glaucomatous progression was determined for each treatment group as a whole by the average change in the optic disc by the ratio of the rim area to the total disc area. Also, apart from the HRT, the investigator determined progression clinically. In each case progression must have been noted in the chart with the associated reason. Generally, criteria for progression were an increase in thinning of the neural rim or a worsening of glaucomatous visual field loss. In patients with total glaucomatous cupping and diffusely depressed visual fields, worsened visual acuity was used also as a sign of progression.

The standard public patient costs in effect in Germany in 2009 were used for both diagnostic and therapeutic procedures as well as for medicine costs, subject to the quarterly billing limitations set by the government. The United States dollar to Euro conversion factor of 0.74 was used (www.oanda.com).

Statistical Analysis The primary efficacy variable, the mean level at the last visit in the rim area/optic disc area ratio, as determined by the HRT, was analyzed by an ANCOVA test between groups using the baseline measurement as a covariate^[8]. The secondary efficacy variable, the level intraocular pressure difference between latanoprost and timolol, were analyzed by a one-way ANCOVA. Additional parameters measured by the HRT also were evaluated by a one-way ANCOVA test^[8]. Study medication related adverse events, and progression rates were analyzed with a Chi-square test or Fisher's Exact test as appropriate^[8]. The

mean length of therapy, the number of visits, changes in medicines, number of medicines and procedures, direct costs (described on a per month basis between therapies) were analyzed by *t*-test [8].

RESULTS

Subjects There were 157 patients, but 31 patients were dropped from the analysis due to missing required data. The patient characteristics for this study are listed in Table 1 (*n*=126). The average length of time in the study was 1716±243 days for the timolol group and 1894 ±352 days for the latanoprost group (*P*=0.002). All but one patient had primary open-angle glaucoma and the other pigmentary glaucoma. A statistically significant number of patients were treated at one of the clinical sites (UT) (*P*=0.003).

Glaucoma Parameters Characteristics of the patient's glaucoma are found in Table 2. There were no statistical differences between treatments in disc parameters at the final visit (*P*>0.05). For the primary efficacy variable, mean level at the last visit in the rim area/optic disc area ratio, the study had an 80% power to detect roughly a 0.2 cup/disc ratio difference between groups. However, at baseline there was a greater rim area in the latanoprost group (*P*<0.04).

The intraocular pressure was similar between groups both at baseline (*P*=0.08) and the final visit (*P*=0.29). Latanoprost was 19.2±3.7 [95% confidence interval (CI) 18.4, 20.0] at baseline and 17.4±2.6mmHg (95% CI 16.8, 18.0) at the final visit while timolol was 18.1±3.3 (95% CI 17.2, 19.0) at baseline and 16.3±2.8mmHg (95% CI 15.5, 17.1) at the final visit. One patient in each group was noted by the investigator to have developed progressive glaucomatous changes during the study, both by worsening in of the HRT parameters(*P*=0.75). Follow-up treatment data are observed in Table 3. There were fewer changes in medicines over the follow up period (*P*<0.001) and less number of medications at the final visit (*P*<0.001)in the latanoprost group. The number of diagnostic procedures and visits during follow-up did not differ between groups (*P*>0.05). No glaucoma laser or conventional surgical procedures were reported in the study.

Discontinuation and Adverse Events No patient treated with latanoprost discontinued therapy during the five year follow-up while six (12%) patients discontinued with timolol (*P*<0.001). Of these, four patients discontinued because of inadequate intraocular pressure control (all did not exceed 20mmHg), one for poor compliance and one due to an adverse event. Only two adverse events were noted from the patient records during the five year follow-up. Both patients were treated with timolol: one patient had bradycardia leading to discontinuation of the medicine and the other experienced dyspnea, both recovered without sequelae. There was no significant difference in the incidence of adverse events noted between treatments (*P*=0.07).

Table 1 Patient characteristics

Characteristic	Patients	Percentage
Study medication		
Latanoprost	77	61
Timolol	49	39
Gender		
Female	69	55
Male	57	45
Race		
Caucasian	66	52
Unavailable	60	48
Study investigator initials (six sites)		
UT	60	48
DS	51	40
SS	15	12

Table 2 Glaucoma parameters

Parameter	Latanoprost (<i>n</i> =77)		Timolol (<i>n</i> =49)		¹ <i>P</i>
	Mean	SD	Mean	SD	
Rim area (mm ²)					
Baseline	1.6	0.7	1.4	0.4	0.04
Final visit	1.5	0.1	1.3	0.4	0.29
Disc area (mm ²)					
Baseline	2.4	1.0	2.3	0.5	0.24
Final visit	2.4	0.8	2.3	0.5	0.67
Rim area/disc area					
Baseline	0.6	0.2	0.6	0.2	0.16
Final visit	0.7	0.6	0.6	0.2	0.39
Cup volume (mm ³)					
Baseline	0.2	0.2	0.3	0.2	0.37
Final visit	0.3	0.2	0.3	0.2	0.49
Vertical cup-to-disc ratio					
Baseline	0.4	0.3	0.4	0.3	0.29
Final visit	0.4	0.3	0.4	0.3	0.63
Intraocular pressure (mmHg)					
Baseline	19.2	3.7	18.1	3.3	0.08
Final visit	17.4	2.6	16.3	2.8	0.29

¹One-way ANCOVA; SD: standard deviation.

Costs The cost analysis is presented in Table 4. Mean cost per year in United States dollars was less with the group of patients begun initially on timolol monotherapy (*P*=0.02) which appeared related to the lower costs of medicines in this group (*P*=0.01). This cost difference remained even in the final year of therapy (*P*<0.001). In contrast, diagnostic procedure costs were lower in the latanoprost group(*P*=0.01).

DISCUSSION

Latanoprost is an F₂α prostaglandin analog that reduces the intraocular pressure by increasing ocular uveoscleral outflow [9]. Data from several worldwide (United Kingdom, Japan, Scandinavia, United States), multi-center, regulatory trials have suggested that latanoprost given once daily is more effective than timolol given twice daily in reducing the intraocular pressure at 08:00-09:00, although these data have not been completely consistent [9-11].

Table 3 Patient follow-up data

Parameter	Latanoprost (n=77)		Timolol (n=49)		¹ P
	Mean	SD	Mean	SD	
Length of therapy (days)	1894	352	1716	284	0.002
Number of visits	7.0	1.7	6.9	2.0	0.77
Changes in medication	0.1	0.4	0.8	0.8	<0.001
Number of medications	1.2	0.5	1.8	0.7	<0.001
Number of procedures	19.7	6.4	17.8	6.1	0.10

¹t-test; SD: standard deviation.

Table 4 Cost analysis

Parameter	Latanoprost (n=77)		Timolol (n=49)		¹ P
	Mean	SD	Mean	SD	
Mean cost of procedures per year	\$105	\$24	\$115	\$21	0.01
Mean cost of medications per year	\$447	\$200	\$342	\$234	0.01
Mean overall costs per year	\$552	\$202	\$458	\$236	0.02
Mean cost of medications for final year of study only	\$388	\$113	\$252	\$152	<0.001

¹t-test; SD: standard deviation.

In contrast, timolol generally has been shown to reduce the pressure between 18%-34% [12]. It decreases the pressure by reducing aqueous production [13]. Long-term data has shown that the intraocular pressure reduction in latanoprost maintains for at least for two years and for timolol for up to 10 years [14]. However, few prior studies have evaluated the long-term outcomes of patients begun on latanoprost or timolol data.

The purpose of this study was to evaluate the cost and effectiveness over five years between initiating latanoprost or timolol monotherapy in patients with open-angle glaucoma.

This study showed over five years in patients originally prescribed either latanoprost or timolol as monotherapy that there were no differences in: the final intraocular pressure, incidence of glaucomatous progression, neural rim area by disc area ratio, optic disc cup volume or vertical cup/disc ratio as measured by HRT.

However, the latanoprost group had fewer changes in medication and in the number of glaucoma medications prescribed at the final visit. Further, patient discontinuations during the five year follow up occurred only in the timolol group (n=6) most commonly due to inadequate intraocular pressure control. These discontinuations may have caused the lower treatment term in the timolol cohort. However, the exact cause of this disparity was not clear by our results.

The similar optic nerve head findings and intraocular pressure control over five years, despite the greater known efficacy of latanoprost, are probably explained by the greater number of changes to adjust therapy, and ultimately the higher number of medicines prescribed at the final visit in the timolol treatment group.

Nonetheless, timolol demonstrated lower overall costs over five years than patients begun on latanoprost. The exact

reason for this finding was not known precisely by our results but probably resulted from the availability of generic timolol preparations, when these patients were seen, which cost less than the branded latanoprost product. Latanoprost generics are now available. In contrast, procedure costs were lower in the latanoprost group. The standard deviation levels for costs probably reflect the differing clinical course among individual patients.

Hollo and associates recently evaluated a European retrospective patient cohort of patients treated with timolol and latanoprost over five years and found higher intraocular pressures and more progression in the timolol group [15]. The reasons for the differences in our findings and Hollo's trial are not apparent. The current trial involved HRT and was performed in Germany whereas Hollo's trial was pan-European.

Van Gestel and coworkers have shown that patients treated to a lower intraocular pressure may be a more cost effective rationale in keeping cost low in the long-term [16]. This would speak perhaps to the use of a stronger hypotensive ocular agent as first line treatment.

There were several unusual findings from our data. First, our groups were dissimilar at baseline in that more patients were treated with latanoprost as allowed by the protocol in up to 2:1 ratio. This finding probably reflects the general popularity of latanoprost as monotherapy [17].

Second, there was less rim area (1.6 vs 1.4mm²) at baseline in the timolol group. This implies that patients who were begun on timolol originally had slightly more damage than in the latanoprost group. This finding was a surprise to the authors since latanoprost is generally considered a more effective medicine than timolol. However, we believe this difference did not influence the results of our study as the

initial level was damage was generally mild in both groups.

Third, several findings typically found in clinical studies similar to ours were underrepresented in this trial, such as the lack of reported adverse events and that no laser or conventional surgical procedures were performed. The reasons for these findings are unclear by our data. Patients included in the study begun on only monotherapy are assumed to have had only mild damage and consequently over five year's follow-up probably did not require a laser or surgical procedure. The lack of adverse events probably reflects that these medicines are generally well-tolerated when patients contradicted for beta-blocker therapy (reactive airway disease, cardiac block) are excluded^[18,19]. The lack of adverse events also may have resulted from the retrospective design of the study because precise adverse event reporting may not have been in mind when the patient was examined. However, the authors do not believe that the slight differences in the patient groups at baseline influenced the results of the study.

This study suggests that patients begun on either latanoprost or timolol and followed over five years will have similar clinical outcomes, but timolol patients will require more medicines and medicine changes to control the intraocular pressure long-term, while at a lower cost.

This trial was not intended to provide treatment recommendations based solely on costs. Physicians need to weigh all factors of patient treatment, including costs, when making treatment recommendations. Further, this study did not evaluate clinical outcomes in patients initiated on latanoprost or timolol monotherapy long-term in a prospective randomized trial. Indeed 5 years may be too short a time period to adequately evaluate clinical outcomes and costs, for which longer follow up (*i.e.* 10-15 years) might provide a more complete answer. Further study is required to more fully evaluate clinical outcomes in terms of vision and costs between latanoprost and timolol to gain more precise understanding of the effects of beginning patients on either of these medications as monotherapy.

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