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Intraocular pressure, safety and quality of life in glaucoma patients switching to latanoprost from adjunctive and monotherapy treatments

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PURPOSE. To evaluate efficacy, safety and quality of life in ocular hypertensive or open-angle glaucoma patients changed to latanoprost from previous therapy.
METHODS. A prospective, multicenter, active-controlled design in which qualified patients had their previous therapy substituted for latanoprost and were followed for at least three months.
RESULTS. In 1068 patients, latanoprost was continued 92% throughout the 36-month observation period. Latanoprost treatment reduced the intraocular pressure (IOP)($p < 0.001$) when compared to previous monotherapies including: beta-blockers (-4.0 ± 3.7 mmHg, 42%), alpha-antagonists (-3.9 ± 3.0 mmHg, 14%), miotics (-3.8 ± 3.5 mmHg, 2%), or carbonic anhydrase inhibitors (CAI) (-3.8 ± 3.6 mmHg, n = 16%), and adjunctive therapy including: beta-blocker and CAI (-3.7 ± 3.1 mmHg, n = 12%), alpha-agonist (-3.7 ± 3.4 mmHg, n = 5%), or pilocarpine (-3.4 ± 3.7 mmHg, n = 6%), or CAI and alpha-agonist (-4.6 ± 6.4 mm Hg, n = 2%)($p < 0.0017$). The most common adverse event with latanoprost was ocular allergy (1.5% incidence). Patients showed a preference for latanoprost for many systemic and ocular quality of life measures on a non-validated questionnaire ($p < 0.05$).
CONCLUSIONS. In a clinical setting, patients who have their mono- and adjunctive therapy treatment substituted for latanoprost may on average experience reduced IOP, decreased side effects and increased quality of life measures. (Eur J Ophthalmol 2004; 14:407-15)

KEY WORDS. Intraocular pressure, Safety, Quality, Glaucoma, Latanoprost

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INTRODUCTION

The prospective multicenter, randomized, parallel, double-masked clinical trial is the standard design in evaluating the comparator efficacy and safety of a new glaucoma agent because it evaluates a medicine in a well-controlled clinical environment. Such a design helps eliminate bias in patient and treatment selection, clinical measures and data analysis.

However, such studies also have several limitations; first, they typically include patients who are sufficiently healthy, with a positive enough attitude, to endure the rigors of a prospective comparative clinical trial using masked medications. Consequently, these patients

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may not reflect the true incidence of adverse events or quality of life problems associated with the study medicines. Second, the sample size is limited due to the expense of a well-controlled trial. Typically, about 1000 patients are treated in regulatory studies prior to drug approval. Consequently, adverse event information may be incomplete as well as the number of comparisons to previously available medications. Last, the manner in which therapy is initiated, either in a crossover or parallel fashion, is not typical of clinical practice when medicines are often switched with each other. Consequently, a prospective randomized trial, although the accepted approach in evaluating the efficacy and safety of a medicine, may not completely reflect a physician's experience when prescribing a new medication in clinical practice.

The purpose of this trial was to prospectively evaluate intraocular pressure changes, adverse events, and quality of life over the first three months after substituting from previous mono- or adjunctive therapies to latanoprost in a large number of patients in order to emulate the clinical experience that might be expected in clinical practice.

METHODS

Patients

A prospective, multicenter, active controlled design that included 196 office-based ophthalmologists as investigators located across Germany. Each investigator enrolled up to 10 patients. Consecutive patients were entered into the study whom the physician had already decided to switch from their previous therapy to latanoprost (Xalatan®, Pfizer Inc, New York, NY) as part of their routine care due to: inadequate intraocular pressure control, an adverse event, poor compliance, or greater ease of dosing. Patients included in this data analysis were those with ocular hypertension or primary open-angle, exfoliation, or chronic angle-closure glaucoma who were treated for at least three months with a monotherapy (beta-blocker, alpha-agonist, miotic or topical carbonic anhydrase inhibitor) or fixed or unfixed combinations of the same agents. Enrolled patients were entered at the clinical site into a computer database. All qualified entries were included in this data analysis.

Patients were excluded from the study who had contraindications to treatment with latanoprost according to the summary of product characteristics, i.e. known hypersensitivity to the components of latanoprost, were pregnant or lactating, or had uveitis in either eye. Patients were excluded from the current data analysis who: were in the early postoperative phase of conventional or laser ocular surgery, had acute angle closure, congenital, low tension or secondary (apart from exfoliation syndrome) glaucoma, had therapy combinations of insufficient numbers to statistically evaluate ($n \leq 20$), or were on no previous glaucoma therapy or three-drug glaucoma therapy.

Procedures

Patients changed to latanoprost underwent an anterior segment examination including: slit lamp biomicroscopy, Goldmann applanation tonometry and Snellen visual acuity. Patients then were placed on latanoprost once each evening in the study eye(s) and re-examined at month 3 (Visit 2). Within two weeks the patients were asked to complete a quality of life survey to document the difference between previous and latanoprost therapy. The survey was designed specifically to address potential ocular and systemic symptoms that might occur with commonly used medicines and had not been previously validated. Physicians also had the choice to schedule patients for two optional safety visits between Visits 1 and 2 to ensure adequate tolerance and efficacy of latanoprost. This was an open-labeled trial and visit times were scheduled according to patient and doctor convenience.

Statistics

Data in this study were evaluated using a two-sided analysis and a 0.05 alpha level to declare significance. The primary efficacy variable, intraocular pressure, was evaluated by a Student's paired t-test between latanoprost and the individual preparations that were substituted, as well as the study population as a whole (1). An average eye analysis was used (average of the pressure response in both eyes). If an eye was not treated with latanoprost then only the opposite treated eye was used in the analysis. The quality of life questionnaire was evaluated between latanoprost and the previous therapy by a McNemar test (2).

RESULTS

Study sample and clinical characteristics (demographic data)

In this study data from 1830 patients were collected. Out of this total sample 1068 patients were evaluable according to the diagnostic and treatment group exclusion criteria for this study analysis. A small portion of the patients had missing data points and were not evaluable for some parameters. Table I includes the characteristics of patients included in this analysis. Table II shows the reason why patients were switched from previous therapy to latanoprost.

Intraocular pressure

The intraocular pressure across all treatment groups decreased from 21.3 ± 3.8 to 17.4 ± 2.8 mmHg after switching to latanoprost from either a mono- or adjunctive therapy ($p < 0.001$), which reflects an additional intraocular pressure reduction of 18%. Table III shows the pressure change after switching to latanoprost from previous medication classes. Latanoprost allowed for a further statistically significant reduction in intraocular pressure when compared to each individual previous monotherapy class ($p < 0.001$). In addition, latanoprost caused a similar statistically significant reduction when switched from each evaluated adjunctive treatment ($p \leq 0.0017$). Four patients were excluded from the β-blocker efficacy analysis because of a missing data pressure point.

TABLE I - PATIENT CHARACTERISTICS*

	Mean or number of patients	%
Age (years)	63.1 ± 12.9	
Gender		
Male	464	43.5
Female	601	56.3
Duration of disorder (years)	5.3 ± 5.5	
Duration of observation period (days)	115.0 ± 44.8	
Number of visits		
1	2	0.2
2	108	10.1
3	330	30.9
4	628	58.8
Diagnosis		
Primary open-angle glaucoma	953	89.2
Ocular hypertension	65	6.1
Exfoliation glaucoma	34	3.2
Chronic angle-closure glaucoma	16	1.5

* Data collection was not complete in three patients

TABLE II - REASONS FOR SWITCHING TO LATANOPROST* (more than one choice possible)

Reason	Number of patients	%
Improved pressure control	684	64.0
Better compliance	463	43.3
Fewer side effects	438	41.0
Overall disease picture	27	2.5
Greater convenience	8	0.7
Patient desire	2	0.2

* Five patients had “missing” answers to this question

TABLE III - INTRAOCULAR PRESSURE CHANGES AFTER SWITCHING TO LATANOPROST BY NUMBER OF MEDICINES AND CLASS (mmHg ± standard deviation)

	Sample	Baseline	Treated	Difference	p-value
Monotherapy					
β-blocker	451	21.3 ± 4.0	17.3 ± 2.7	-4.0 ± 3.7	< 0.001
α-agonist	154	21.2 ± 3.5	17.3 ± 2.4	-3.9 ± 3.0	< 0.001
CAI	170	20.7 ± 3.8	17.0 ± 3.0	-3.8 ± 3.6	< 0.001
Pilocarpine	21	21.4 ± 3.2	17.5 ± 2.7	-3.8 ± 3.5	< 0.001
Two drug therapy					
β-blocker + α-agonist	50	22.0 ± 3.7	18.3 ± 2.7	-3.7 ± 3.4	< 0.001
β-blocker + CAI	133	21.7 ± 3.3	18.0 ± 2.7	-3.7 ± 3.1	< 0.001
β-blocker + pilocarpine	62	21.3 ± 3.4	17.9 ± 3.1	-3.4 ± 3.7	< 0.001
CAI + α-agonist	25	22.1 ± 5.9	17.6 ± 3.1	-4.6 ± 6.4	0.0017

CAI = Carbonic anhydrase inhibitor

Adverse events

The incidences of ocular and systemic adverse events on latanoprost were generally low. The side effects believed "possibly", "probably" or "definitely" related to latanoprost by the physician are shown in Tables IV and V. Symptoms of ocular allergy, visual disturbance or ocular pain were most common and reported in ≤ 1.5% of cases. Iris pigmentation and uveitis events occurred in 0.1% (n = 1) and 0.6% (n = 6) respectively. There was no reported eyelash growth noted during the trial. Overall, there were 54 ocular events during the observation period.

There were 27 systemic adverse events during the observation period with headache being the most common (0.5%, n = 5). One patient died during the treatment period due to an unspecified systemic condition that was not believed related to the study medicine.

Discontinued patients

After beginning latanoprost 92% of patients persisted with therapy until the end of the observation period. Eighty-three patients (8%) had their latanoprost monotherapy altered prior to three months. Most often this change in therapy was the addition of a new medication in 31 (37%) of patients, or a change to another medication in 23 (38%) patients.

When a reason was provided for changing therapy, physicians indicated most often it was because of an adverse event in 37 (48%) patients. These events were not necessarily believed by the physician to be related to treatment. The adverse events leading to discontinuation are listed in Table VI. Ocular itching (n = 6), burning (n = 5) and headache (n = 5) were the most common reasons cited to discontinue latanoprost. In addition, 33 (43%) patients were discontinued because the physician believed that they failed to reach their desired efficacy goal of therapy.

Quality of life survey

The results from the quality of life survey for previous therapy and latanoprost are shown in Tables VII and VIII. Latanoprost generally showed statistically improved symptoms after three months of therapy compared to each previous therapy for burning, itching, foreign body sensation, hyperemia, blurred vision, taste disturbance, headache, dry mouth, respiratory problems, nausea/fatigue, cardiovascular symptoms (i.e.,

TABLE IV - OCULAR ADVERSE EVENTS WITH LATANOPROST (number of patients thought to have an event possibly related to latanoprost, two or more events)

	(n = 1068)	
Symptom	**Number of patients**	**%**
Allergy	16	1.5
Pain	12	1.1
Visual disturbance	9	0.8
Uveitis	6	0.6
Foreign body sensation	3	0.3
Periocular edema	2	0.2
Chemosis	2	0.2
Conjunctival hyperemia	2	0.2

TABLE V - SYSTEMIC ADVERSE EVENTS (two or more events, number of patients thought to have an event possibly related to latanoprost)

	(n = 1068)	
Side effect	**Number of patients**	**%**
Headache	5	0.5
Dry mouth	2	0.2
Shortness of breath	2	0.2
Change in heart condition	2	0.2

TABLE VI - ADVERSE EVENTS LEADING TO DISCONTINUATION OF LATANOPROST* (number of patients, three or more events, more than one event per patient was possible)

	(n = 1068)	
Reason	**Number of patients**	**%**
Ocular itching	6	0.6
Burning	5	0.5
Headache	5	0.5
Visual symptom	4	0.4
Ocular pain	4	0.4
Ocular inflammation	3	0.3
Nonspecific systemic disorder	3	0.3
Ocular hyperemia	3	0.3

* The physician may not have thought a relationship between the drug and adverse event existed

TABLE VII - QUALITY OF LIFE SURVEY ON LATANOPROST (After) COMPARED TO OTHER SINGLE THERAPY AGENTS (Before)* (number of patients providing positive response)

	Beta-blocker			CAI			Alpha-agonist			Pilocarpine		
Symptom	n		%	n		%	n		%	n		%
Burning, itching												
Before	297	*	(67)	138	*	(86)	106	*	(71)	17	*	(81)
After	216		(48)	75		(44)	72		(47)	10		(47)
Itching, redness												
Before	227	*	(52)	116	*	(71)	92	*	(63)	9		(43)
After	153		(35)	61		(36)	63		(41)	6		(29)
Impaired vision												
Before	102	*	(23)	49	*	(30)	41	*	(28)	9	*	(47)
After	51		(11)	23		(14)	19		(13)	1		(5)
Unpleasant taste												
Before	80	*	(18)	85	*	(52)	39	*	(26)	3		(14)
After	47		(11)	30		(18)	18		(12)	3		(14)
Headache												
Before	88	*	(20)	39	*	(24)	35	*	(24)	9	*	(45)
After	57		(13)	16		(96)	20		(13)	2		(95)
Dry mouth												
Before	130	*	(29)	68	*	(43)	54	*	(37)	5		(25)
After	69		(15)	40		(24)	33		(22)	7		(35)
Difficulty breathing												
Before	51	*	(16)	10	*	(6)	8		(6)	3		(14)
After	7		(2)	0		(0)	3		(2)	0		(0)
Cardiovasc. symptoms												
Before	121	*	(28)	41	*	(25)	44	*	(30)	4		(19)
After	45		(10)	28		(17)	17		(11)	3		(14)
Nausea/fatigue												
Before	67	*	(15)	32	*	(20)	25	*	(17)	5		(24)
After	35		(8)	20		(12)	15		(10)	5		(24)
Impaired quality of life												
Before	241	*	(55)	117	*	(72)	93	*	(63)	16		(76)
After	159		(35)	60		(36)	66		(43)	9		(43)

* Significant to a level of $p < 0.05$; Several patients failed to answer every question

slow pulse, less energy and resilience) and overall quality of life. In contrast, there was no noted difference between groups for temporary impotence, intestinal disturbance or perceived visual capacity ($p > 0.05$). In addition, 85.0% of patients indicated that once a day dosing was important to them.

DISCUSSION

Latanoprost was first released into the commercial market over six years ago. Since then it has become the leading individually prescribed medicine worldwide to treat elevated intraocular pressure. Seven of eight prospective, multicenter, regulatory trials have shown that latanoprost is more effective than timolol maleate in reducing the intraocular pressure (3-5). Further, in additional monotherapy comparisons, Stewart and coworkers have shown that latanoprost demonstrates greater effectiveness than brimonidine throughout the daytime diurnal curve and unoprostone at morning trough (6, 7). Fechtner and associates and Konstas and coworkers have noted latanoprost monotherapy to show similar intraocular pressure ef-

TABLE VIII - QUALITY OF LIFE SURVEY ON LATANOPROST (After) COMPARED TO PREVIOUS TWO AGENTS THERAPY (Before)* (number of patients providing positive response)

	ß-blocker + CAI			ß-blocker + Alpha-agonist			ß-blocker + Pilocarpine			CAI + Alpha-agonist		
Symptom	n		%	n		%	n		%	n		%
Burning, itching												
Before	108	*	(84)	32	*	(65)	40	*	(69)	22	*	(92)
After	54		(41)	16		(33)	24		(40)	12		(48)
Itching, redness												
Before	86	*	(68)	29	*	(60)	38	*	(63)	17	*	(71)
After	51		(39)	19		(39)	16		(26)	9		(38)
Impaired vision												
Before	46	*	(37)	11	*	(23)	31	*	(53)	7		(29)
After	19		(15)	3		(6)	8		(14)	5		(20)
Unpleasant taste												
Before	60	*	(47)	9	*	(18)	16	*	(28)	8	*	(32)
After	20		(15)	3		(24)	7		(12)	1		(4)
Headache												
Before	41	*	(32)	9	*	(18)	23	*	(41)	6		(24)
After	23		(17)	4		(8)	10		(17)	4		(16)
Dry mouth												
Before	50	*	(39)	147	*	(29)	18	*	(33)	7		(28)
After	26		(20)	6		(12)	14		(23)	2		(8)
Difficulty breathing												
Before	14	*	(11)	4	*	(8)	5		(9)	2		(9)
After	3		(2)	0		(0)	2		(3)	2		(8)
Cardiovasc. symptoms												
Before	36	*	(28)	11	*	(23)	16	*	(29)	6		(24)
After	15		(12)	2		(4)	9		(16)	3		(12)
Nausea/fatigue												
Before	31	*	(24)	5		(10)	12	*	(22)	6		(24)
After	13		(10)	2		(4)	11		(18)	3		(12)
Impaired quality of life												
Before	84	*	(67)	28	*	(58)	41	*	(73)	16	*	(64)
After	47		(36)	13		(27)	14		(24)	9		(36)

* Significant to p <0.05; Several patients failed to answer every question

ficacy as the dorzolamide/timolol fixed combination in daytime hours (8, 9). Latanoprost shows a similar efficacy to bimatoprost and travoprost (10, 11).

Besides efficacy, latanoprost has the advantage of once a day dosing that potentially could increase compliance. In addition, latanoprost demonstrates a favorable side effect profile. Very few systemic adverse events have been reported with latanoprost. Latanoprost does cause iris color change and eyelash growth. However, no serious adverse events have been reported associated with these changes (12). Cautions are suggested regarding uveitis, cystoid macular edema, and the reactivation of ocular herpes (12). Mild conjunctival hyperemia may be the most common side effect, but appears to be benign (13).

In this current trial we evaluated patients treated with latanoprost substituted from previous mono- or adjunctive therapy. We wished to evaluate the efficacy, safety and quality of life over the first three months of treatment in which latanoprost would typically be prescribed clinically. This study showed that latanoprost caused a further lowering of intraocular pres-

sure between 3.4 to 4.6 mmHg at three months in 1068 patients when switched from other common treatments including: monotherapy with a beta-blocker, alpha-agonist, miotic or topical carbonic anhydrase inhibitor; or combination therapy with dorzolamide, pilocarpine, or an alpha-agonist added to beta-blocker, or a carbonic anhydrase inhibitor prescribed with an alpha-agonist.

The reason for the greater efficacy with latanoprost is not known completely, but several reasons may exist; first, latanoprost may have provided greater efficacy than each previous mono- or adjunctive therapy evaluated. These findings are consistent with previous monotherapy trials versus timolol, brimonidine, pilocarpine and dorzolamide and versus the combination of timolol/pilocarpine (3-5,14). However, previous data has indicated only equal daytime pressures versus the dorzolamide/timolol combination (8, 9). Little previous data exist that evaluate latanoprost versus the timolol/ brimonidine or dorzolamide/brimonidine combinations.

Second, latanoprost may have demonstrated more efficacy in this trial because patients potentially were more compliant due to ease of administration or better tolerance. Although no data yet exist in the literature that signify if once a day dosing over twice a day dosing further helps compliance. However, 85% of patients in this trial indicated that once a day dosing was important to them. Third, patients were more compliant due to receiving greater attention and positive reinforcement from the clinical staff or the knowledge that they were enrolled in a clinical trial. Last, the intraocular pressure that caused the physician to switch the patient to latanoprost may have been higher than the patient's average. By the next visit the pressure may have returned to its mean regardless of the treatment. However, the marked reduction in pressure with latanoprost (3.6 to 4.6 mmHg), and that 36% were switched for non-pressure related reasons, indicates this regression phenomenon probably could not be the sole cause of the added ocular hypotensive response.

After treatment with latanoprost the incidence of side effects was low, with ocular itching, visual disturbance and ocular pain being the most common, showing a maximum incidence of 1.5%. Iris pigmentation changes occurred in one patient, which is a lower incidence than noted in the latanoprost regulatory trials (3-5). The difference may be due to the duration of this current study; usually iris pigmentation occurs following three months of therapy (3-5). In addition, iris color changes in the regulatory trials were determined by photographs. The incidence in the current trial may more closely resemble how often patients and doctors actually note this side effect clinically. The incidence of uveitis was 0.6% over three months. Uveitis has been rarely noted in previous studies (15). However, the exact relationship between uveitis and latanoprost therapy remains unclear.

Latanoprost therapy was continued in 92% of patients within the three-month observation period. Most of the 83 patients were discontinued during the observation period due to an adverse event or for failing to reach the clinician's desired clinical efficacy goal. In general discontinuance rates in routine clinical practice are not publicly known. In one previous retrospective switch study, derived from data in clinical practices, Stewart and co-workers showed an altered therapy rate of 80% for brimonidine and 40% for latanoprost six months after changing from timolol (16).

In the quality of life survey latanoprost showed generally fewer solicited symptoms with burning, itching, impaired vision, taste disturbance, headache, dry mouth, respiratory problems, cardiovascular symptoms including low pulse, nausea and overall impairment of quality of life. No difference between groups was noted for impotency, intestinal disturbance and visual capacity. Previous quality of life studies generally have attempted to differentiate beta-blocker therapies from each other and from non-beta-blocker therapies. Stewart and associates found no difference between timolol and carteolol whereas Javitt and coworkers found no differences between timolol and brimonidine, or betaxolol and brimonidine (17-19). In addition, recently the CIGTS trial noted no differences in quality of life between glaucoma patients treated with medicine or surgery (20). Our survey differed because it generally focused on side effects common to glaucoma medications and had not been previously validated.

This study suggests that, in a clinical setting, patients who have their mono- and adjunctive therapy treatment substituted for latanoprost may on average experience reduced intraocular pressure, decreased side effects and increased quality of life measures. This study did not evaluate latanoprost compared to

the other medications in a double-masked, randomized fashion. In such a clinical trial, patient populations might provide different intraocular pressure readings and different continuation rates. In addition, continuation rates for latanoprost were not compared directly to other medications within the same population. Further investigation is needed to completely understand the efficacy, safety and persistency issues related to latanoprost and other glaucoma medicines.

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