Latanoprost Therapy In Primary Open-Angle Glaucoma Patients: A Three-Month Study In Al-Anbar Province

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Abstract

Background: Primary open angle glaucoma (POAG) is the most common form of glaucoma throughout world, accounting for about two-thirds of cases. Latanoprost is a prostaglandin (PG) F2α derivative and has a strong effect on lowering the intraocular pressure (IOP) in patients with POAG and in normal eyes.
Objectives: The aim of this study is to evaluate the IOP lowering effect and safety of latanoprost in POAG naïve patients and in patients on timolol exhibited insufficient response, in Al-Ramadi Teaching Hospital.
Patients and Methods: Forty-seven Iraqi patients (47 eyes) with POAG were enrolled in a single center (Al-Ramadi Teaching Hospital) in prospective uncontrolled observational cohort study. The mean age (± S.D) was 57.09±2.04. The baseline IOP of 38 naïve patients stratified into ≥ 21 ≤30 vs. >30mmHg. Nine patients who had been treated with timolol but exhibited insufficient response, they were shifted to latanoprost and enrolled in this study. All participants were treated with 0.005% latanoprost once daily (evening) for 3 months. IOP levels were measured at baseline and after 1, 2 and 3 months. The efficacy outcome was mean change and mean percent change in IOP from baseline to month 1, 2 and 3.
Results: At all follow-up visits there was a significant reduction in IOP compared with the baseline value in naïve patients treated by latanoprost as 1st line (P<0.0001) and in patients shifted from timolol to latanoprost (P<0.001). The baseline IOP was 26.69±3.22 (mean±SD) mmHg, 36.43 ±3.67 mmHg and 22.00 ±4.15 mmHg in ≥ 21 ≤30 mmHg group, >30mmHg group and in patients shifted from timolol to latanoprost respectively. After 3 months, the IOP was reduced by 12.31±3.22 mmHg (45.63±8.26%), 21.43±4.16 mmHg (58.40±6.33%) and 8.00±3.74 mmHg (34.88±10.02%) respectively. No evidence of an upward drift in the IOP was observed during the treatment period. The most frequently reported adverse ocular effects were mild conjunctival hyperemia. No adverse systemic effects were observed. Timolol has been added to latanoprost in five naïve patients (14.2%) to achieve the desired therapeutic objective. Three naïve patients were lost to follow up. None of the patients needed shifting from medical to surgical treatment.
Conclusion: It is highly justified to use latanoprost as 1st line monotherapy in POAG naive patients and in patients whose IOP is insufficiently controlled on β-blocker monotherapy (timolol) by shifting them to latanoprost.
Key Words: Primary open angle glaucoma, Latanoprost, efficacy, safety.

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Introduction

The majority (70%) of glaucoma cases are classified as "Primary open-angle glaucoma" (POAG)[1]. The goal of current glaucoma treatment is to lower IOP, the only modifiable risk factor, to a level that prevents or minimizes the progressive loss of vision[2]. Despite continued advances in laser and incisional surgery, medical therapy continues to be the primary means by which IOP is controlled[3]. Prostaglandins (PGs) rapidly replaced topical β-blockers as first-line IOP-lowering agents, mostly because of their potency, safe systemic side-effect profile, and once-daily dosing[4]. They represent the most important advance in the medical treatment of glaucoma[5, 6].

The U.S. Food and Drug Administration (FDA) has approved the once-daily prescription eye drop latanoprost as an initial treatment for elevated IOP associated with POAG[7]. PGs reduce IOP by increasing outflow of aqueous humor mostly by enhancing the uveoscleral pathway. Latanoprost doubles the outflow of aqueous humour through the non-conventional uveoscleral route[8]. Some studies showed an increase in trabecular outflow facility[9, 10]. Nakanishi *et al*[11] reported that latanoprost exerts neuroprotective activity *in vitro* and *in vivo*. Ethnic differences in the theraputic outcome to latanoprost have been suggested; Hedman and Larsson[12] reported that the Asian and Mexican patients showed a larger difference in mean diurnal IOP reduction with the use of latanoprost than the European and U.S. patients. Up to our knowledge, no clinical study using latanoprost therapy has been conducted on Iraqi patients. The aim of this study is to evaluate the IOP lowering effect and safety of latanoprost in POAG naïve patients and in patients on timolol exhibited insufficient response, in Al-Ramadi Teaching Hospital.

Patients and Methods

A single-center prospective open-labeled uncontrolled observational cohort study was performed in Al-Ramadi Teaching Hospital from 2/11/2010 to 1/10 /2011. Forty-seven Iraqi patients with POAG were enrolled in the study. Thirty-eight were naïve patients and nine patients, who have been exhibited insufficient response on timolol, were shifted to latanoprost and enrolled in this study. All participants were treated with 0.005% latanoprost once daily for 3 months.

Inclusion and exclusion criteria

Eligible subjects had to be 18 years of age or older, had a baseline (initial visit) IOP of ≥21 mmHg with optic disk changes and visual field defect related to a diagnosis of unilateral or bilateral POAG. Only subjects who, in the opinion of the expert ophalmologist, required initiation of ocular hypotensive treatment were eligible. Subjects were excluded if they had baseline IOP < 21 mmHg, had angle closure, traumatic, inflammatory, pseudoexfoliation, pigmentary or neovascular glaucoma; had any ophthalmic or systemic disorder, including uncontrolled asthma, had previous filtering surgery or argon laser trabeculoplasty and had history of ocular inflammation or infection. In addition, women of childbearing potential who were not using adequate contraceptive methods or who were pregnant or nursing were not included.

Study design and plan

During the 1st visit (baseline) demographic information, ocular and medical histories, and concomitant medications were documented; visual acuity was measured; thorough slit-lamp

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biomicroscopy including eyelid examination, gonioscopy, and fundoscopy were performed by ophthalmologist using (+90) Volk lens.

A manual visual field examination was conducted at baseline (using Goldmann perimeter) and IOP was measured prior to pupil dilation using an air-pulsed tonometer and a calibrated Goldmann applanation tonometer.

Patients were treated with latanoprost 0.005% once daily at night (9 p.m.). Follow-up visits were scheduled after 1 week (2nd visit), 2 weeks (3rd visit), 4 weeks (4th visit), 8 weeks (5th visit) and 12 weeks (6th visit) after starting the treatment. At each visit, thorough slit-lamp biomicroscopy including eyelid examination, gonioscopy, and fundoscopy were performed. IOP was measured at the same time (±1 hour) as at the baseline visit and prior to pupil dilation using the methods employed at baseline. Visual field examination was performed at month 1 and 3. All adverse events were recorded at each follow-up visit.

Analysis

All participants enrolled in this study were diagnosed as POAG. Efficacy analysis used only IOP measurements of one study eye per subject. If both eyes of a subject were eligible, the eye with the highest IOP at baseline was considered the study eye; if the baseline IOP was the same in both eyes, the right eye was considered the study eye. The efficacy analysis endpoint was mean change and mean percent change in IOP from baseline to month 1, 2 and 3; percentage of subjects achieving different percentage of IOP reduction and different target IOP levels from baseline to month 3.

The statistical significance of within-stratum changes in mean IOP levels from baseline to months 1, 2, and 3 was evaluated using paired t tests. The significance of between-strata differences in frequencies of subjects achieving percentage of IOP reductions and target IOP levels was assessed using t tests for two-sample assuming unequal variances. The two-sided significance level was set at the 0.05 level. The significance of IOP reduction among 1st, 2nd and 3rd month was assessed using Anova test.

Patients who qualified for the study and they were being treated with timolol, but exhibited insufficient response to treatment, they instructed to stop timolol and to instill latanoprost 0.005% in each affected eye once daily in the evening starting the following day. The IOP at which the patient got no adequate response, it is considered baseline on timolol. Follow-up visits were scheduled as for naïve patients treated by latanoprost described above.

Results

Three naïve patients were excluded before the study termination because of the loss to follow up and five patients treated by adding timolol to latanoprost to achieve therapeutic objective. Demographic characteristic are presented in Table 1.

Table 1: Baseline demographic characteristics of all patients.

Characteristic	Baseline IOP ≥21 to ≤30mmHg	Baseline IOP >30mmHg	Patients shifted from timolol to latanoprost
Number of patients	16	14	9
Gender Male Female	 12(75)* 4(25)	 8(57.1) 6(42.9)	 4(44.4) 5(55.5)
Age, years Mean ± SD	61.44 ±13.93	57.07 ±11.96	48.89±19.07
Baseline IOP, mmHg Mean ± SD	26.69±3.22	36.43±3.67	22.00 ±4.15

*n (%)

At baseline the mean IOP of the total naïve patients (N=30) was 31.23± 5.99 mmHg (mean± SD) and was reduced to 14.67±1.79 mmHg ($p < 0.0001$) at the end of 3rd month. The baseline IOP was 26.69 ±3.22 mmHg (mean± SD) in ≥ 21 ≤30 mmHg group, 36.43 ±3.67 in >30mmHg group of naïve patients and 22.00 ±4.15 mmHg in patients shifted from timolol to latanoprost. At the end of 3rd month the mean IOP levels had decreased from baseline by 12.31±3.22 mmHg ($p < 0.0001$), 21.43±4.16 mmHg ($p < 0.0001$) and 8.00±3.74 mmHg ($p < 0.001$) respectively (Table 2).

Table 2: Intraocular pressure (IOP) at baseline, 1st, 2nd and 3rd month (mmHg).

	Baseline IOP ≥21 to ≤30mmHg	Baseline IOP >30mmHg	Patients shifted from timolol to latanoprost
Baseline IOP, mmHg Mean ± SD	**26.69±3.22**	**36.43 ±3.67**	**22.00 ±4.15**
1st Month IOP, mmHg Mean ± SD	**15.56±2.50**	**15.21±2.39**	**14.56±1.94**
IOP change from baseline to month 1, mmHg Mean± SD	-11.13±3.34	-21.21±4.89	-7.44±3.05
p-value*	<0.0001	<0.0001	<0.001
% change in IOP from baseline to month 1 Mean± SD	-39.73±11.94	-57.69±8.42	-32.84±8.74
2ndMonth IOP, mmHg Mean ± SD	**15.25±2.72**	**15.21±1.63**	**14.11±0.93**
IOP change from baseline to month 2, mmHg Mean± SD	-11.44±3.98	-21.21±4.21	-7.89±3.79
p-value*	<0.0001	<0.0001	<0.001
% change in IOP from baseline to month 2 Mean± SD	-42.16±11.99	-57.79±6.47	-34.28±10.46
3rd Month IOP, mmHg Mean ± SD	**14.38±1.93**	**15.00±1.62**	**14.00±1.12**
IOP change from baseline to month 3, mmHg Mean± SD	-12.31±3.22	-21.43±4.16	-8.00±3.74
p-value*	<0.0001	<0.0001	<0.001
% change in IOP from baseline to month 3 Mean± SD	-45.63±8.26	-58.40±6.33	-34.88±10.02

*p-value based on *t* test for paired data. SD = standard deviation

In 1st two groups (≥ 21 ≤30 mmHg and >30mmHg) the percentages of subjects achieved IOP reduction from baseline to month 3 were higher in the >30 mmHg group than ≥ 21 ≤30 mmHg group. In contrast, smaller percentages of those in the higher IOP group achieved IOP levels ≤15 or ≤13 mmHg at month 3, while all subjects in each group (100%) achieved IOP level ≤18 mmHg (Table 3).

Table 3: Naïve patients achieving reduction in IOP from baseline to month 3.

	Baseline IOP	
	≥21 to ≤30mmHg	**>30mmHg**
Number of patients	16	14
≥30% IOP reduction from baseline to month 3 (**p < 0.0001)	15(93.75)*	14(100)
≥40% IOP reduction from baseline to month 3 (**p < 0.0001)	12(75)	14(100)
≥50% IOP reduction from baseline to month 3 (**p < 0.0001)	6(37.5)	13(92.8)
≥60% IOP reduction from baseline to month 3	1(6.25)	7(50)
≤18 mmHg target IOP at month 3	16(100)	14(100)
≤15 mmHg target IOP at month 3 **p =0.21	10(62.5)	7(50)
≤13 mmHg target IOP at month 3 **p =0.14	6(37.5)	3(21.4)

*n (%) **p- value for between-group difference; t-test: two-sample assuming unequal variances SD = standard deviation.

The baseline IOP of the patients treated by adding timolol to latanoprost was 33.6±6.88 mmHg (mean± SD). After two weeks on latanoprost, it decreased to 24.4±1.34 mmHg (24.2±8.92%) (P=0.029) and after one month from adding timolol the IOP decreased to 15.8±3.11 mmHg (34.9±6.37%) (P=0.003) (Table 4).

Table 4: Naïve patients treated by adding timolol to latanoprost.

	Patients treated by adding timolol to latanoprost
Number of patients	**5**
Baseline IOP, mmHg (Mean ± SD)	33.6±6.88
2nd week IOP, mmHg (on latanoprost) Mean ± SD	24.4±1.34
*P-value	P=0.029
% change in IOP from baseline to week 2 (Mean± SD)	-24.2±8.92
1st month IOP, mmHg (on timolol & latanoprost) (Mean± SD)	15.8±3.11
*P-value	P=0.003
% change in IOP from 2nd week to month 1 (Mean± SD)	-34.9±6.37
3rd month IOP, mmHg (on timolol & latanoprost) (Mean± SD)	15.4±1.63
*P-value	P=0.003
% change in IOP from 2nd week to month 3 (Mean± SD)	-36.8±6.81

*p-value based on *t* test for paired data. SD = standard deviation

In patients shifted from timolol to latanoprost group, the percentages of subjects achieved different percentage of IOP reduction and different target IOP level at month 3 are shown in Table 5.

Table 5: Patients shifted from timolol to latanoprost achieving reduction in IOP from baseline to month 3.

	Patients shifted from timolol to latanoprost
Number of patients	9
Baseline IOP, mmHg Mean ± SD	22.00 ±4.15
3rd Month IOP, mmHg Mean ± SD	14.00±1.12
% change in IOP from baseline to month 3 Mean± SD	-34.88±10.02
≥20% IOP reduction from baseline to month 3	9(100)*
≥30% IOP reduction from baseline to month 3	5(55.5)
≥40% IOP reduction from baseline to month 3	4(44.4)
≤18 mmHg target IOP at month 3	9(100)
≤15 mmHg target IOP at month 3	8(88.8)
≤13 mmHg target IOP at month 3	2(22.2)

*n (%)

After 3 months adverse effect profiles were nearly similar in subjects in the two baseline IOP strata, where the most frequently reported effects are conjunctival hyperemia occurring in 3 patients (18.75%) in ≥ 21 ≤30 mmHg group and 4 patients (28.57%) in >30 mmHg group. Other side effects are shown in Table 6.

Table 6: Number (%) of treatment-related ocular adverse events at the end of month 3 in naïve patients.

Subjects with:	Baseline IOP ≥20 to ≤30mmHg	Baseline IOP >30mmHg
Number of patients	16	14
blurred vision	0	3(21.42)
burning and stinging	2(12.5)	3(21.42)
conjunctival hyperemia	3(18.75)	4(28.57)
foreign body sensation	1(6.25)	3(21.42)
Itching	2(12.5)	3(21.42)
increased iris pigmentation	0	0
dry eye	1(6.25)	1(7.14)
excessive tearing	0	1(7.14)
eye pain	1(6.25)	1(7.14)
Photophobia	0	
punctuated epithelial keratopathy	0	0
Lid crusting	3(18.75)	0
Lid pain	1(6.25)	1(7.14)
Lashes Hypertricosis	1(6.25)	2(14.28)
Increase lashes pigmentation	0	0
Iritis	0	0
cystoid macular oedema	0	0

Discussion

The Early Manifest Glaucoma Trial demonstrated a 10% decrease in the risk of progression with each mm Hg reduction in IOP from baseline[13]. At the end of month 3, this study showed that the treatment of naïve patients with latanoprost reduced IOP by 12.31±3.22 mmHg (45.63±8.26%) and 21.43±4.16 mmHg (58.40±6.33%) in the ≥21≤30 and >30 mmHg groups, respectively.

In this study, the effect of the drug was evident at the 3rd visit and was nearly constant during the study period. It is known that the action of latanoprost starts within the first 2 weeks, maximizes within the first 6 weeks, and stabilizes thereafter without short or long term drift[14]. This study that showed significant reduction in IOP ($p<0.0001$) from baseline to the end of the 1st month and this reduction was stable to the end of study period and there was insignificant differences ($p=0.36$) in the ≥21 ≤30 mmHg group and ($p=0.94$) in the >30 mmHg group between 1st, 2nd and 3rd month (tested by Anova) in reduction of baseline IOP.

Further, five (14.2 %) patients on latanoprost exhibited a substantial reduction in IOP where baseline IOP was 33.6±6.88 mmHg (mean± SD) and after two weeks on latanoprost, it decreased to 24.4±1.34 mmHg ($P=0.029$); However, this IOP reduction was still short of the therapeutic objective. Hence, timolol 0.5% was added and after one month the IOP decreased to 15.8±3.11 mmHg ($P=0.003$). This inability of latanoprost on its own to achieve the target IOP may be explained by the possibility that in these patients the elevated IOP was due to hypersecretion of aqueous humour which was only effectively reduced by timolol (acting via reduction of production of aqueous humour), as no more operable-drainage mechanisms available for latanoprost to act upon. This view can further be supported by the suggestion made by Kondo *et al* [15] that the inter individual variation in IOP reduction after treatment with latanoprost may be attributed to the differences in substantial change in uveoscleral outflow.

Latanoprost has been shown to reduce intraocular pressure (IOP) by 22-39 % over 1-12 months' treatment in well-controlled trials[16, 17], but in our study, the percentage of reduction in IOP from baseline to the end of 3rd month was higher than what was reported previously by other workers. It is postulated that this higher reduction in IOP may be related to our Iraqi patient's ethnic differences in response to latanoprost and according to our knowledge there is no such study in this country that has been done to show the efficacy of latanoprost in reduction of IOP in Iraqi POAG patients. Furthermore, there is a study Hedman & Larsson[12] reported that the Asian and Mexican patients showed a larger difference in mean diurnal IOP reduction with the use of latanoprost than the European and U.S. patients. The other possible reason is that the absence of the practice of regular eye examinations at least every 2-4 years after age of 40 for those without risk factors and every 1-2 years for those with risk factors[18]. Those who are unchecked and with untreated high IOP which may progress resulting in very high baseline and consequently giving higher reduction upon treatment compared with their western counterpart. The latter view may be supported by the lower overall mean of baseline 24.72±7.01 mmHg[19], while in our study the overall mean IOP was 31.2±6.0 mmHg.

Absolute and percentage IOP reductions were greater in the higher IOP stratum, where it was 45.63±8.26% in the ≥ 21 ≤30

mmHg group vs. 58.40±6.33% in the >30 mmHg group.

Others [20] have observed that higher baseline IOP levels are associated with greater IOP reductions. Nevertheless, significant responses to latanoprost therapy were seen in both IOP strata. IOP levels ≤18 mmHg were achieved by 100% of patients in both ≥ 21 ≤30 and >30 mmHg groups at month 3.

The Collaborative Initial Glaucoma Treatment Study (CIGTS) lowered the IOP by 35%, demonstrated equivalence of medical and surgical treatment[21]. In this study, the reduction of IOP was 45.63±8.26% and 58.40±6.33% in ≥21≤30 and >30 mmHg groups, respectively and none of the patients needed shifting from medical to surgical treatment. Other workers[22, 23] have reported that the decision for ocular surgery may be delayed or obviated and the frequency of surgeries for OAG has been markedly decreased since the introduction of latanoprost in 1996.

In patients required a change from timolol 0.5 % twice daily to latanoprost 0.005% once daily; Latanoprost reduced IOP from 22.00 ±4.15mm Hg (baseline on timolol) to 14.00±1.12 mmHg at month 3 and the percentage of reduction was 34.88±10.02 ($p<0.001$). This reduction was stable to the end of the study period and there were insignificant differences ($p=0.68$) between 1st, 2nd and 3rd month in reduction of baseline IOP. Many trials have shown latanoprost instilled once daily to be at least as effective and as generally superior to timolol administered twice daily[24].

Latanoprost is generally well tolerated and induces minimal systemic adverse events. The most common reported side effect of the prostaglandin analogs was conjunctival hyperemia[25] which is shared by all compounds of this class, with its highest incidence seen in patients on bimatoprost[26]. In this present study there were three (18.75%) incidence of conjunctival hyperemia in the 21 to ≤30 and four (28.5%) in >30 mmHg group at the end of week 12. It was higher in 2nd group in which the reduction of IOP was higher and correlation was found between a change in intraocular pressure and conjunctival hyperemia severity induced by latanoprost[27].

Iris pigmentation has been reported following latanoprost treatment[28, 29]. In this study, there were no signs of increased iris pigmentation in any patients in the two treatment groups.

This may be related to the short duration of treatment and most of the participated patients had homogeneously brown iris colour.

It is worth noting that slit-lamp examinations were performed regularly to detect any cells or flare in the anterior chamber as a sign of increased permeability of the blood-aqueous barrier. No cells or flare in the anterior chamber were reported for any patient during the study. In several clinical studies[30, 31] no signs of breakdown of the blood-aqueous barrier were observed.

It is concluded that the use of latanoprost as 1st line monotherapy is highly justified in POAG naive patients and in patients whose IOP is insufficiently controlled on β-blocker monotherapy (timolol) by shifting them to latanoprost.

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