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Effectiveness of Latanoprost (Xalatan™) Monotherapy in Newly Discovered and Previously Medicamentously Treated Primary Open Angle Glaucoma Patients

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A B S T R A C T

We evaluated the effectiveness of latanoprost (Xalatan™) monotherapy in primary open angle glaucoma (POAG). Latanoprost is a prostaglandin analogue, the pure 15(R) epimer of 13,14-dihydro-17-phenyl-18,19,20-trinor-PGF2α--isopropyl ester. As a prodrug it is being activated by enzymatic hydrolysis in the cornea after which it becomes active acid of latanoprost. Latanoprost is lowering the intraocular pressure (IOP) by increasing the uveoscleral outflow. In this study, latanoprost was used once daily as monotherapy what offers much better compliance for the patients than other combinations of drugs, preserving good IOP control. Based on the significant reduction of the IOP, measured on the day 60 of the trial (mean change in IOP was –5.1 mmHg, with 95% confidence interval in range from –5.6 to –4.5), it is concluded that use of latanoprost is advisable when calculating better IOP control, few side-effects and reductions in costs of potential surgical procedures.

Key words: *latanoprost, Xalatan™, monotherapy, glaucoma, treatment, effectiveness*

Introduction

A glaucoma is the disease characterised in most of the cases by elevated intraocular pressure (IOP) above 21 mm Hg, visual field loss and optic nerve head (ONH) changes[1–4]. In normotensive glaucoma IOP is considered to be »normal« (less than 21 mm Hg). Medicamentous treatment of glaucoma patients has very much changed in the past few years due to appearance.

Latanoprost, i.e., Xalatan™ (Pharmacia & Upjohn; Pfizer group, USA) is a prostaglandin analogue, the pure 15(R) epimer of 13,14-dihydro-17-phenyl-18,19,20--trinor-PGF2α-isopropyl ester. As a prodrug it is being activated by enzymatic hydrolysis in the cornea after which it becomes active acid of latanoprost. Latanoprost is found to be lowering the IOP by increasing the uveoscleral outflow[1,3,5–7], whereby other locally applied medications reduce IOP either by increasing the outflow of fluid through the trabecular drainage system or by reducing the production of fluid in the eye[8]. It is being given once daily in a 0.005 % concentration predominantly in primary open angle glaucoma (POAG), ocular hypertension (OH) and normotensive glaucoma (NTG), but can be used also in other glaucoma types[1,5,9]. As a monotherapy latanoprost lowers IOP by 6–8 mm Hg after 6 months application whereby IOP falls mostly during first 2 weeks and remains stabile in the next period[1,5,10–12]. Latanoprost can be successfully used as the additive therapy of glaucoma patients receiving already maximum tolerated therapy[8], it lowers diurnal varia-

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tions of IOP[14,15] and has been recently accepted as a first-line therapy for some glaucoma types.

The objective of this investigation is to determine whether and in what level latanoprost eye-drops as a monotherapy can substitute single and combined therapy of other antiglaucoma drugs in POAG.

Subjects and Methods

Total number of the patients in the study was 159 (males/females = 72/87). The first group of the patients with glaucoma consisted of 16 newly discovered patients with previously untreated disease (males/females = 5/11).

The second group of the patients (67 men and 76 women), had a glaucoma for the longer period of time. In this group the median of the disease was 4 years, 3 years for males and 5 years for femals (Mann-Whitney U test, $p>0.05$, Table 1).

All patients that participated in the trial had both eyes affected with the same type of glaucoma (POAG). Patients were treated during the 60 days by 0.005% latanoprost monotherapy with one drop per eye daily, applied in the evening. Intraocular pressure was measured by the Goldmann aplanation tonometry. IOP of both eyes was measured and mean of the both values was taken into consideration for the statistics. IOP was measured in both groups of glaucoma patients on three time points: day 0 (initiation of the therapy), day 15 and day 60 (end of the trial). In the group of the patients who had a previous therapy there was no wash out period. Their earlier therapy, presented in Table 2, was changed because of the unsatisfying effectiveness, in several cases combined with poor compliance, local or systemic side effects or poor cooperation of the patient using multiple therapy. The IOP criteria for the change to latanoprost monotherapy were the values of ≥ 22 mmHg.

TABLE 1
DURATION OF THE DISEASE IN PATIENTS WITH PREVIOUSLY TREATED GLAUCOMA

Group	Median (months)	Range (months)
All patients (N = 143)	4	1–36
Males (N = 67)*	3	1–36
Females (N = 76)*	5	1–23

*p > 0.05 Mann-Whitney U test

TABLE 2
THERAPY IN PATIENTS WITH PREVIOUSLY TREATED GLAUCOMA

Previous therapy	Number of patients
Beta blocker	91
Beta blocker + Pilocarpine	28
Beta blocker + Dorzolamide	16
Beta blocker + Pilocarpine + Dorzolamide	8

During the investigation the principles emphasized in the Helsinki Declaration were followed and an informed consent was obtained from the subjects.

Statistical analysis was made using Mann-Whitney U test for comparison of independent groups, and Wilcoxon matched pairs test for change in IOP between time points. 95% confidence interval (95% CI) for mean drop in IOP was estimated as more informative parameter of efficacy, in comparison to the simple mean. Friedman test was used to compare the IOP changes within all time points (0, 15 days and 60 days) of the groups of: newly discovered glaucoma patients treated with latanoprost, and previously treated patients that were switched to latanoprost monotherapy. Friedman test is a nonparametric version of the randomized design analysis of variance. It is a generalization of the Wilcoxon test for paired samples to apply to more than two groups. The results of the group measurements at three time points were mutually compared by means of Steel--Dwass test, nonparametric version of Tukey test.

Results

Mean IOP values measured by the aplanation tonometry in the group of the newly discovered patients, on the days 0, 15 and 60 are presented in Table 3. Mean IOP values between the groups of male (24.9 mmHg) and female patients (23.2 mmHg) did not differ, and there were no differences in the male and female IOP at individual time points (Table 3). However, on the day 15 (Table 4) and day 60 (Table 5) we observed significant lowering of IOP following latanoprost monotherapy.

Table 4 shows that on the day 15 of the latanoprost monotherapy IOP difference/drop in the newly discovered glaucoma patients was more pronounced in the females –6.6 (95% CI from –8.8 to –4.5) then in the males –5.9 (95% CI from –11.8 to –0.1). On the day 60 IOP difference/drop in the in the newly discovered glaucoma pa-

TABLE 3
VALUES OF INTRAOCULAR PRESSURE IN PATIENTS WITH NEWLY DISCOVERED GLAUCOMA

Day (X ± SD)	All patients (1)	Males (2)*	Females (3)*
0	23.6 ± 2.4	24.9 ± 2.6	23.2 ± 2.2
15	17.2 ± 2.5	19.0 ± 2.9	16.6 ± 2.0
60	17.0 ± 2.3	18.0 ± 2.8	16.6 ± 2.0

*p > 0.05 Mann-Whitney U Test

TABLE 4
DROP OF OF INTRAOCULAR PRESSURE VALUES IN PATIENTS WITH NEWLY DISCOVERED GLAUCOMA TREATED WITH LATANOPROST MONOTHERAPY (DAY 15 OF THE TRIAL)

All patients (1)	Males (2)	Females (3)
–6.4 mmHg	–5.9 mmHg	–6.6 mmHg
(from –8.2 to –4.6)	(from –11.8 to –0.1)	(from –8.8 to –4.5)

Wilcoxon matched pairs test; means and 95% confidence intervals; $p < 0.05$ (groups 1 and 3); $p = 0.06$ (group 2)

tients was more pronounced in the male patients group –5.8 (95% CI from –6.6 to –5.0) then in the female patients group –4.4 (95% CI from –5.2 to –3.7, Table 5).

Similar results were observed in the group of patients whose earlier therapy, was changed because of the unsatisfying effectiveness, poor compliance, local or systemic side effects and similar reasons. Table 6 presents their IOP values on the days 0, 15 and 60 of the trial. Mean IOP values between the groups of male (22.1 mmHg) and female patients (21.9 mmHg) did not differ, and there were no differences in the male and female IOP at individual time points (Table 6). However, on the day 15 (Table 7) and day 60 (Table 8) we observed significant lowering of IOP following latanoprost monotherapy.

Table 7 shows that on the day 15 of the trial IOP difference/drop in the newly discovered glaucoma patients was more pronounced in the males 4.9 (95% CI from –5.7 to –4.2) then in the females –3.5 (95% CI from –4.9 to –2.1). Table 8 shows an additional drop of IOP on the day 60 of the latanoprost monotherapy. Mean IOP drop was –5.9 mmHg (95% CI from –6.6 to –5.0) in the male glaucoma patients group, and –4.4 mmHg (95% CI from –5.2 to –3.7) in the female patients.

Friedman and Steel-Dwass tests confirmed that latanoprost monotherapy significantly reduced IOP in newly discovered (Table 9) and previously treated glaucoma patients (Table 10) at days 15 and 60 of the trial. There was no statistically significant differences between IOP drop at days 15 and 60 of the latanoprost monotherapy (Table 9–11). IOP values of the groups of newly discovered and previously treated glaucoma patients showed similar patterns, and did not differ at the time points 0, 15 and 60 (Mann-Whitney U test, $p > 0.05$).

No serious side effects or complications were reported during the administration of latanoprost.

TABLE 5
DROP OF OF INTRAOCULAR PRESSURE VALUES IN PATIENTS WITH NEWLY DISCOVERED GLAUCOMA TREATED WITH LATANOPROST MONOTHERAPY (DAY 60 OF THE TRIAL)

All patients (1)	Males (2)	Females (3)
–5.1 mmHg (from –5.6 to –4.5)	–5.8 mmHg (from –6.6 to –5.0)	–4.4 mmHg (from –5.2 to –3.7)

$p < 0.05$ Wilcoxon matched pairs test (for all groups); means and 95% confidence interval

TABLE 6
VALUES OF INTRAOCULAR PRESSURE IN PATIENTS WITH PREVIOUSLY TREATED GLAUCOMA

Day	All patients (1)	Males (2)*	Females (3)*
0	22.0 ± 3.6	22.1 ± 3.8	21.9 ± 3.4
15	17.8 ± 4.4	17.2 ± 2.7	18.4 ± 5.7
60	16.9 ± 2.4	16.3 ± 2.3	17.5 ± 2.4

* $p > 0.05$ Mann-Whitney U test (for all groups)

TABLE 7
DROP OF OF INTRAOCULAR PRESSURE VALUES IN PATIENTS WITH PREVIOUSLY TREATED GLAUCOMA FOLLOWING LATANOPROST MONOTHERAPY (DAY 15 OF THE TRIAL)

All patients (1)	Males (2)	Females (3)
–4.2 mmHg (from –5.0 to –3.3)	–4.9 mmHg (from –5.7 to –4.2)	–3.5 mmHg (from –4.9 to –2.1)

$p < 0.05$ Wilcoxon matched pairs test (for all groups); means and 95% confidence interval

TABLE 8
DROP OF OF INTRAOCULAR PRESSURE VALUES IN PATIENTS WITH PREVIOUSLY TREATED GLAUCOMA FOLLOWING LATANOPROST MONOTHERAPY (DAY 60 OF THE TRIAL)

All patients (1)	Males (2)	Females (3)
–5.1 mmHg (from –5.7 to –4.5)	–5.9 mmHg (from –6.6 to –5.0)	–4.4 mmHg (from –5.2 to –3.7)

$p < 0.05$ Wilcoxon matched pairs test (for all groups); means and 95% confidence interval

Discussion

The study shows that latanoprost can be used as a monotherapy in the patients with POAG. It offers a

TABLE 9
DIFFERENCES IN VALUES OF INTRAOCULAR PRESSURE FOR THE GROUPS OF NEWLY DISCOVERED GLAUCOMA PATIENTS AT DIFFERENT TIME POINTS OF LATANOPROST MONOTHERAPY

Day*	15	60
0	4.46 ($p < 0.001$)	4.78 ($p < 0.001$)
15		0.11 ($p > 0.05$)

* Steel-Dwass test; Friedman test: $p < 0.001$

TABLE 10
DIFFERENCES IN VALUES OF INTRAOCULAR PRESSURE FOR THE GROUPS OF PREVIOUSLY TREATED GLAUCOMA PATIENTS AT DIFFERENT TIME POINTS OF LATANOPROST MONOTHERAPY

Day*	15	60
0	9.74 ($p < 0.001$)	11.13 ($p < 0.001$)
15		1.96 ($p > 0.05$)

*Steel-Dwass test; Friedman test: $p < 0.001$

TABLE 11
PERCENTAGE OF PATIENTS WITH REDUCED IOP IN THE GROUPS OF NEWLY DISCOVERED AND PREVIOUSLY TREATED GLAUCOMA PATIENTS AT DIFFERENT TIME POINTS OF LATANOPROST MONOTHERAPY

Day	<22 mm Hg newly discovered	<22 mm Hg previously treated	≥22 mm Hg newly discovered	≥22 mm Hg previously treated
0	31.25%	44.76%	68.75%	55.24%
15	93.75%	91.55%	6.25%	8.45%
60	100%	97.20%	0%	2.80%

Steel-Dwass test: 0 vs.15 ($p < 0.001$); 0 vs. 60 ($p < 0.001$); 15 vs. 60 ($p > 0.05$)

good IOP lowering effects in the newly discovered cases as well as in those which were insufficiently controlled by the other drugs. In the group of patients with newly discovered POAG, latanoprost has significantly lowered the IOP after first 15 days for –6.4 mmHg (95% CI –8.2 to –4.6) (Table 9). The result is comparable to the results of other authors[1,5,10–12,16]. It is clearly noticeable that latanoprost has managed to lower the IOP for minimum of 4.6 mmHg what is still a good result having in mind the fact that mean initial IOP was 23.6 mmHg (± 2.4). After 60 days the mean IOP difference to the day 0 was –5.1 mmHg (95% CI –5.6 to –4.5). This slight rise of IOP is, however, not statistically significant when compared to day 15 values (Table 9). Since the IOP values at day 60 are still significantly below the ones at day 0 of the trial it can still be concluded that the IOP was under control.

It is interesting to note that the difference between minimum and maximum IOP at day 60 was smaller than at day 15, suggesting the IOP becoming more stable and presumably with less diurnal variations. This is important having in mind that the peaks of the IOP are responsible for the optic nerve and visual field deterioration. We also observed minor differences between IOP changes of males and females, but the reason for this remains unexplained at this time.

The IOP criteria for change to latanoprost monotherapy were the values of ≥ 22 mm Hg. This is a standard preswitch baseline value for IOP studies. To avoid that the observed results of latanoprost monotherapy arise from the regression to the mean effects (i.e., some abnormal values of the first measurement) the second/repeated measurement, done at the beginning of the trial served as a 0 starting point for statistical comparisons[17]. Due to the severity of the disease the patients were switched to latanoprost treatment without stopping medications. However, their IOP was poorly controlled at that time, since there were no statistical differences between IOP values of previously treated and newly discovered glaucoma patients at 0 time point of the trial (Mann-Whitney U test, $p > 0.05$; Results).

The reason for switching the therapy to latanoprost was predominantly motivated by insufficient IOP control with previous medicaments. At the day 15 of the treatment average IOP drop in the switched group was little below the previously untreated group (where the drug has been used as the first line medication). This can be explained with the fact that previous therapy must have had some small effect on IOP at this early point of treatment. After 60 days mean IOP value has remained almost the same as on day 15 and standard deviation of the results is smaller, suggesting again good activity in the average population and presumably less diurnal variations.

The results of the group measurements at three time points were analysed by Friedman and Steel-Dwass tests[18]. The statistical analysis confirmed similar patterns of IOP drop due to latanoprost monotherapy in the groups of newly discovered and previously treated patients suffering from POAG (Table 9–11, Results). It is worth mentioning that in both groups of patients there were no significant differences in the efficacy of latanoprost monotherapy at day 15 and day 60 of the trial (Table 9–11), which indicates that the first evaluation of the latanoprost treatment efficacy could be done on the basis of IOP measurements at day 0 and day 15 of the drug administration. The finding is in agreement with previous observation that IOP falls mostly during first 2 weeks of latanoprost monotherapy and remains stabile in the next period[1,5,10–12].

This investigation confirms data published in last few years showing better IOP control by latanoprost then by some other antiglaucoma medicaments[1,5,16, 19]. It has also been proven that Xalatan™ can be very successfully used as an additive therapy to other medications reducing aqueous production and increasing trabecular outflow (e.g. beta blockers, carbonic anhydrase inhibitors), as it's mechanism of action is primarily increasing the uveoscleral outflow[1,5,20–23]. Therefore it can also be used in other glaucoma types than POAG and ocular hypertension[9] but is not efficient in all[24]. Such results are potentially important also for the visual field preservation due to its effect on increase of the pulsatile blood flow[25].

Latanoprost monotherapy offers much better compliance for the patients than other combinations of drugs, preserving good IOP control. It becomes even more important being aware of the reports saying that persistency with latanoprost is much better comparing to other medicaments[26,27]. This puts different light on the costs of latanoprost therapy which are higher than the ones of timolol and some other antiglaucoma medicaments. Despite this fact use of latanoprost is still advisable when calculating better IOP control, few side-effects and reductions in costs of potential surgical procedures[5,28, 29].

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EFIKASNOST MONOTERAPIJE LATANOPROSTOM (XALATAN™) U NOVOOTKRIVENIH I PRETHODNO MEDIKAMENTOZNO TRETIRANIH BOLESNIKA S PRIMARNIM GLAUKOMOM OTVORENOG KUTA

S A Ž E T A K

U radu je ispitivana učinkovitost monoterapije latanoprostom (Xalatan™) u primarnom glaukomu otvorenog kuta. Latanoprost je prostagladinski analog, čisti 15(R) epimer 13,14-dihydro-17-phenyl-18,19,20-trinor-PGF2α-isopropyl estera. Latanoprost se aktivira enzimskom hidrolizom u rožnici, pri čemu postaje aktivan. Lijek snižava očni tlak povećavajući uveo-skleralno otjecanje. U studiji je utvrđena superiornost monoterapije latanoprostom u odnosu na druge kombinacije antiglaukomatoznih lijekova zbog zadovoljavajuće kontrole očnog tlaka i vrlo dobre prihvatljivosti. Prosječna redukcija intraokularnog tlaka izmjerena na kraju praćenja (dan 60) iznosila je –5,1 mmHg u rasponu od –5,6 do –4,5 (95% intervala pouzdanosti). Zaključeno je da uporaba latanoprosta omogućuje bolju kontrolu intraokularnog tlaka uz manje nuzpojava i moguću redukciju troškova daljnjeg liječenja.