

# Update in Glaucoma Management

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## **Lens Opacity, Thickness, and Position in Acute Primary Angle Closure**

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This study was performed to compare lens thickness, lens position, and prevalence of lens opacity between affected and fellow eyes of patients with acute primary angle closure (APAC). This was a prospective observational case series of 62 Asian patients with APAC. Patients who presented with APAC were treated with medical therapy followed by laser iridotomy in both eyes.

Two weeks after iridotomy, central anterior chamber depth, lens thickness, and axial length measurements were made in both eyes using ultrasound pachymetry. Lens position was defined as anterior chamber depth plus half lens thickness and relative lens position was defined as lens position/axial length. A modified version of the Lens Opacity Classification III system was used for grading lens opacity. This system grades nuclear colour, nuclear opalescence, and cortical and posterior sub-capsular cataract according to objective measures of colour, density, and area.

The 62 patients were ethnic Chinese (89%), Malay (8%), or Indian (3%). Women comprised 63% of the sample and the mean age was  $60.2 \pm 10.3$  years. The mean lens thickness was  $5.11 \pm 0.57$  mm and

$5.10 \pm 0.55$  mm in affected and fellow eyes, respectively, ( $p = 0.46$ ) There was no significant difference in lens position or relative lens position. Using paired tests, there was also no significant difference found for lens opacity grades, nuclear opalescence, nuclear colour, and cortical and posterior sub-capsular cataract between attack and fellow eyes.

Two weeks after APAC, there was no significant difference found in lens thickness, lens position, or degree of lens opacity between affected and fellow eyes. The results suggest that factors other than these lens characteristics are significant in triggering APAC.

## **Intraocular Pressure-independent Neuroprotective Ability of Latanoprost**

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Latanoprost, a prostaglandin F<sub>2α</sub> (PGF) analogue, not only has a powerful ocular hypotensive property but also is suggested to have a potential neuroprotective ability. Retinal neurons and glia are known to have PGF receptors. The purpose of this study was to test whether latanoprost exerts an anti-apoptotic ability on retinal neurons and glia in an intraocular pressure (IOP)

-independent fashion in vitro and in vivo.

R28 cells, a model of retinal neurons, were serum-deprived for 24 hours to undergo apoptosis. Varying concentrations of latanoprost acid or vehicle were added with or without inhibitors for phosphatidylinositol 3 kinase (PI3K), mitogen-activated protein kinase (MAPK), protein kinase C (PKC), or cyclic GMP (cGMP). The cells were immunostained against activated caspase 3 and counterstained with Hoechst dye. Male Sprague-Dawley rats were made diabetic by intravenous injection of streptozotocin. After 1 month, latanoprost was instilled into the eyes unilaterally and balanced saline solution (BSS) was given to the contralateral eyes once daily for 5 days. Whole mount retinas were subjected to terminal d-UTP nick end labelling (TUNEL).

Latanoprost acid rescued R28 cells from apoptosis in a dose-dependent fashion. PKC and MAPK, but not cGMP, inhibitors antagonised this effect. Diabetic retinas treated with latanoprost had less TUNEL positive cells ( $12.8 \pm 5.3/0.5$  cm<sup>2</sup>) than those treated with BSS ( $50.9 \pm 21.2/0.5$  cm<sup>2</sup>) [ $p < 0.05$ ]. IOP was not different between the eyes.

In conclusion, latanoprost is neuroprotective in an IOP-independent manner.

## **Melanin in the Trabecular Meshwork Associated with Age and Glaucoma but not Latanoprost**

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The trabecular meshwork is known to become pigmented by phagocytosis of iris-derived melanin granules present within the circulating aqueous humor. This study was performed to determine the distribution of melanin with age and primary open



angle glaucoma (POAG) and to ascertain whether there was an association with latanoprost treatment.

Trabeculectomies (n = 25) from normal enucleated eyes over 40 years and conventional surgical trabeculectomies (n = 62) from Caucasians were selected on the basis of macroscopic examination for the presence of Schlemm's canal and a substantive portion of the trabecular meshwork. Quantitative, masked light, and electron microscopic analysis was conducted on each specimen.

The percentage of melanin-containing meshwork cell profiles in the control group was 12.9%, while the incidence in the POAG group was significantly higher at 33.2% (p < 0.01). Comparison of eyes with POAG that had not been treated with latanoprost (n = 50) with those that had been treated with latanoprost (n = 12) showed no significant difference, although only 6 of the latter had evidence of iris darkening at the time of surgery. Electron microscopy confirmed that the melanin granules were mostly intracellular and of the larger iris epithelial type, even in the latanoprost-treated specimens.

Meshwork pigmentation was shown to be due to iris epithelial melanin and not iris stromal melanin even in latanoprost-treated eyes. POAG is associated with increased meshwork pigmentation by a mechanism as yet unknown but one that is unlikely to be influenced by prostanoid drugs.

## Post-hoc Analyses of the XLT Study Results

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The purpose of this analysis was to provide additional data in response to queries posed to the authors subsequent to publication of the XLT study. This randomised,

parallel-group study was conducted at 45 sites in the USA over 12 weeks.

Previously treated patients with open-angle glaucoma or ocular hypertension with an intraocular pressure (IOP)  $\geq 23$  mm Hg in 1 or both eyes after washout received latanoprost, bimatoprost, or travoprost once daily (in the evening). At baseline and weeks 6 and 12, IOP was measured in triplicate by masked evaluators at 8:00 am, noon, 4:00 pm, and 8:00 pm. Conjunctival hyperaemia was graded by masked investigators before the 8:00 am IOP measurement at each visit. Patients were also asked whether their red eyes bothered them. Change between baseline and week 12 in 8:00 am IOP measurements was the primary efficacy outcome. Post-hoc analyses of responder rates, power calculations, and hyperaemia gradings were conducted.

Responder rates based on percentages of patients achieving either a 15% or 20% reduction in IOP at week 12 were almost identical for all 3 prostaglandin analogues, as were the proportions of patients reaching specific target IOP levels. At 6 and 12 weeks, no statistically significant difference between treatments was found in the IOP-lowering effect measured at 8:00 am. Post-hoc power calculations indicated a 91% power to detect a difference of 1.5 mm Hg between treatment groups. There was a small but significant increase at all time points after baseline in mean hyperaemia scores in the bimatoprost and travoprost treatment groups, with the bimatoprost group having the largest increase and the latanoprost group the smallest increase. Patient responses to hyperaemia were consistent with investigator gradings.

Mean IOP levels at week 12 were similar across treatment groups at all time points as were the responder rates and proportions of patients reaching specific target pressures. There appears to be no statistical or clinical differences in efficacy among the 3 prostaglandin analogues.

## Factors Determining the Degree of Response to Latanoprost

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This study was performed to identify demographic and clinical factors linked to hyper-response or hyporesponse to latanoprost therapy in everyday practice. This open-label, observational, multicentre study conducted at 124 Spanish centres included patients with primary open angle glaucoma (POAG) or high intraocular pressure (IOP) levels who received latanoprost monotherapy for 1 to 3 months as first-line therapy or following washout of previous therapy. 375 consecutive eligible patients were assigned to 1 of the 2 pre-established groups (hyper-responders had an IOP reduction of  $>30\%$ , n = 284 [76%]; hyporesponders had an IOP reduction of  $<15\%$ , n = 91 [24%]). Data for each patient were collected in a single visit and included IOP, and epidemiological and clinical variables.

Hyporesponders were more likely than hyper-responders to have received ocular hypotensive therapy before latanoprost (37% vs 21%; p = 0.002), have undergone ocular surgery (13% vs 4%; p = 0.002), and have had a longer delay between initial glaucoma diagnosis and latanoprost administration ( $16.7 \pm 29.7$  vs  $9.7 \pm 24.3$  months; p = 0.055). Hyper-responders had a higher IOP at diagnosis ( $27.5 \pm 4.3$  mm Hg vs  $25.4 \pm 3.6$  mm Hg; p = 0.055) and immediately prior to initiating latanoprost therapy (IOP  $>28$  mm Hg; 34% vs 11%; p < 0.0001) No association between responsiveness to latanoprost and clinical features of glaucoma, cup-disk ratio, gonioscopy, eye colour, age, gender, race, previous uveitis, or refractive status was shown.

Latanoprost response of  $<15\%$  occurred in fewer than one-quarter of patients and



was associated primarily with disease progression and time of latanoprost initiation rather than to patient-related ocular factors.

**Efficacy, Preference, and Compliance of Fixed-combination Latanoprost/Timolol Versus Usual Care**



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This study was performed to compare the intraocular pressure (IOP) lowering effect, therapy preference, and compliance with fixed-combination latanoprost/timolol versus other usual care in patients with insufficient IOP control requiring therapy adjustment. A 3-month observational study conducted at 307 Spanish centres included patients with primary open angle glaucoma (POAG) or high IOP inadequately controlled with previous treatment, who needed a change in therapy and were eligible for latanoprost/timolol according to approved labelling.

Patients received fixed-combination latanoprost 0.005% plus timolol 0.5% once daily (in the morning). IOP was measured at baseline and after 3 months of therapy. The primary efficacy outcome was the difference between groups in mean diurnal IOP reduction. Preference and compliance were evaluated using 2 validated questionnaires.

2787 patients (47% men and 53% women) were included in the final analyses; duration of diagnosis was  $57.6 \pm 51.6$

months. Mean baseline diurnal IOP was 21 mm Hg, which decreased to 18 mm Hg after 3 months of latanoprost/timolol therapy (mean reduction 12.6%;  $p < 0.0001$ ).  $\beta$ -blockers/latanoprost ( $n = 928$ ),  $\beta$ -blockers/carbonic anhydrase inhibitors ( $n = 651$ ), and  $\beta$ -blockers/adrenergic agonists ( $n = 257$ ) were the most frequently administered previous combinations. Some differences were found in baseline IOPs of these groups (18.8 mm Hg, 22.1 mm Hg, and 22.2 mm Hg, respectively), but IOP levels were significantly reduced in all groups ( $p < 0.0001$ ). When only 1 agent was initially given,  $\beta$ -blockers were the most frequently used, and the mean IOP reduction was even greater for this group (21.2%;  $p < 0.0001$ ). When more than 1 therapy was initially given, adequate compliance (excellent and good) increased from 67.6% to 95%, and patient satisfaction with latanoprost/timolol therapy reached 92%. No adverse events were reported by 96.8% of patients.

Fixed-combination latanoprost/timolol administered as a second-line treatment is more effective than previous treatments and increases patient satisfaction and treatment compliance.

**Vaccination as Neuroprotective Therapy for Glaucoma**



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Among the numerous approaches to therapy proposed since the idea of secondary degeneration and neuroprotection in the

context of glaucoma was first introduced, are those based on identifying the physiological mediators of optic nerve degeneration and retinal ganglion cell death. Pharmacological agents are then used to neutralise or circumvent these self-compounds in order to arrest or slow down the progression of degeneration.

An alternative approach targets the local buffering system, which is controlled by non-neuronal cells such as resident microglia. If suitably regulated, the microglia not only buffer threatening self-compounds, but also prevent the formation of noxious compounds such as glutamate and nitrous oxide, or enzymes such as cyclooxygenase-2. One way to control microglial behaviour is by harnessing T cells specific to central nervous system-related self-antigens, thereby obtaining the help needed at the site of injury without risk of autoimmune disease.

Discovery of this control mechanism led to the development of vaccines for arresting or slowing down the progression of degeneration. One such vaccine is Cop-1, a USA Food and Drug Administration-approved synthetic copolymer currently used to treat multiple sclerosis. When used as a vaccine for glaucoma, Cop-1 acts as a weak agonist of a wide range of self-reactive T cells, evoking a systemic T cell response that provides protection at multiple sites inside and outside the visual pathway. The morphological and functional benefit of Cop-1 vaccination has been demonstrated in rodent models of acutely and chronically elevated intraocular pressure. Once the dosage and regimen have been optimised, its efficacy can be tested in clinical trials.

