MEDICAL TREATMENT: GENERAL MANAGEMENT,
INDICATION
PREVALENCE OF OCULAR SURFACE DISEASE AND IT’S IMPACT ON QUALITY OF LIFE IN GLAUCOMA PATIENTS
G.C.M. Rossi¹, M. Raimondi¹, M. Bordin¹, A. Mazzone¹, S. Lanteri¹, G. Milano¹, G.M. Pasinetti²
¹University Eye Clinic of Pavia IRCCS Policlinico San Matteo Foundation, Pavia - Italy; ²UO Oculistica, Clinica Beato Palazzolo, Bergamo - Italy

**Purpose.** To examine signs and symptoms of ocular surface disease in treated glaucoma patients. To verify correlations between ocular surface disease and sex, age, number of bottles used and number of instillations pro die.

**Methods.** This prospective observational study enrolled consecutive topically treated open-angle glaucoma or ocular hypertension patients: patients presenting systemic or ocular conditions that could interfere with ocular surface status were excluded. Enrolled patients underwent a complete ophthalmic examination comprehensive of evaluation of tear break up time and fluorescein corneal staining (keratitis punctatae evaluation) and completed the Italian version of both the NEI-VFQ 25 and the Glaucoma Symptom Scale questionnaires.

**Results.** 233 patients adhered to study protocol. Fluorescein corneal staining revealed punctatae keratitis in 90 (38.6%) patients, none had severe staining; abnormal TF-BUT was present in 61 (26.2%) patients. All these alterations were independent from age and sex. The presence of punctatae keratitis was significantly related to the number of used eye drop bottles (p = 0.015) and to the number of eyedrops pro die (p = 0.002). Abnormal TF-BUT was independent from instilled eyedrops (p = 0.95). Both quality of life questionnaires pointed out a worsening trend in total means by increased grade of corneal staining (NS). The NEI ocular pain (OP) subscale was statistically related to number of instillations/die (p = 0.020).

**Conclusions.** Many patients present an ocular surface disease related to the number of instillations and eyedrops a day, and all these can affect their QL. The use of fixed combinations to reduce surface exposition and, better, of BAK-free formulations should be encouraged to try to reduce and contain the onset or worsening of this secondary condition in glaucoma patients.
MEDICAL TREATMENT: ADRENERGIC AGONISTS AND ANTAGONISTS
BILATERAL GRANULOMATOUS UVEITIS ASSOCIATED WITH FIXED-COMBINATION OF BRIMONIDINE-TIMOLOL

M. Carrasco¹, A. Schlaen²

¹Oftalmología, Hospital Universitario de la Universidad Nacional de Cuyo, Mendoza - Argentina; ²Oftalmología, Hospital de Clínicas José de San Martín. Universidad de Buenos Aires, Buenos Aires - Argentina

Background: Ocular allergic reactions are known to occur with chronic brimonidine therapy with a reported incidence of 4.2% to 15.7% of patients, depending on the dosing regimen and duration of therapy. Granulomatous uveitis is a rare adverse effect of brimonidine. Iritis has been mentioned as an adverse reaction in the postmarketing use of brimonidine. A reformulated solution of brimonidine preserved with chlorine dioxide rather than benzalkonium chloride (BAC) and at a reduced concentration of brimonidine (0.15%) was developed in an effort to improve tolerability. However, the fixed-combination of timolol-brimonidine contains brimonidine tartrate 0.2% with BAC 0.005%.

Methods: A 64-year-old man consulted with 12-month history of red eye, foreign body sensation, and photophobia in both eyes (Fig.1). He had a history of myopia, PRK and open-angle glaucoma. Phaco-trabeculectomy was performed on the left eye (OS) two years ago. He had been treated with fixed-combination of brimonidine 0.2%/timolol 0.5% twice daily in both eyes during the previous 16 months. His BCVA was 20/40 OD and 20/60 OS. Slit lamp examination revealed: severe conjunctival injection, papillary conjunctivitis, corneal punctate epithelial erosions, mutton fat keratic precipitates; 3+ cells and 2+ flare and iris nodules in both eyes (Fig. 2-3). The left eye showed a flat bleb and the vitreous was clear in both eyes. Fundus examination showed optic discs with C/D ratios of 0.6 OD and 0.8 OS. His intraocular pressure (IOP) was 12 mm Hg OD and 5 mm Hg OS. Central corneal thicknesses were 487 µm and 490 µm respectively.

Results: Glaucoma medications were ceased, prednisolone 1% every 4 hours and cyclopentolate 1% thrice daily was prescribed. Systemic evaluation comprising full blood count, urea, creatinine and electrolytes, liver function tests, serum angiotensin converting enzyme, ESR, CRP were all normal. Serology for syphilis, HLA-B27, rheumatoid factor, ANA, ANCA, and ENA were negative. Chest and spine x-ray were unremarkable. Marked improvement was noted within 2 days. After 2 weeks both eyes were free of inflammation (Fig. 4-5). Topical steroids were tapered between 3 weeks. The IOP increased to 20 mm Hg OD and 10 mm Hg OS, timolol was added twice daily. Two month after completed resolution of uveitis, the patient agreed to perform a rechallenge with brimonidine in the right eye only. Three days later, he complained of photophobia and showed 1+ cells in the anterior chamber that resolved quickly on topical steroids. A diagnosis of drug-related bilateral anterior uveitis was confirmed.

Conclusion: Drug-induced uveitis has been reported with glaucoma medications, including metipranolol, prostaglandin analogs and miotics. Byles et al proposed that continuing topical administration of brimonidine in eyes with allergic reactions may predispose to the development of uveitis. Patients with dark irides may have more susceptibility to develop uveitis because brimonidine had a higher concentration and cleared more slowly in pigmented tissues than in nonpigmented tissues. In this case the elevation of IOP after treatment could be explained by cessation of glaucoma medications, side effect of steroids and resolution of hypotony secondary to uveitis. Chronic inflammation may have contributed to trabeculectomy failure.
PHASE I STUDY WITH A SYL040012. A SIRNA FOR THE TREATMENT OF GLAUCOMA AND OCULAR HYPERTENSION

V. González¹, V. Ruz², J. Moreno-Montañés³, B. Sádaba⁴, A.I. Jímenez⁵
¹Preclinical Development, ²Regulatory Affairs, ³R&D Department, Sylentis, Madrid - Spain; ⁴Clinica universidad Navarra, Pamplona - Spain; ⁵Clinica Universidad Navarra, Pamplona - Spain

**Background:** SYL040012 is a new topical treatment for ocular hypertension and open angle glaucoma based on RNAi technology. Different doses of the compound were tested in healthy volunteers to evaluate the safety of SYL040012 and explore the effect on intraocular pressure (IOP).

**Methods:** SYL040012 is a new chemical entity targeting beta 2 adrenergic receptors (ADRB2) involved in intraocular pressure (IOP) regulation. SYL040012 siRNA targeting ADRB2 were administered as eye drops in saline solution to 30 healthy volunteers with normal IOP at two different doses (clinical trial Phase I).

The study was set out in two periods; the first period (n = 6 healthy volunteers) is an initial evaluation of safety using a single dose of product; the second period (n = 24 healthy volunteers) is in multiple ascending doses (a single daily administration in one of the eyes during 7 days). For both periods each volunteer was his own IOP control. The eye to receive administration was randomized. Safety evaluation and IOP measurement were performed on both eyes. The ophthalmologist evaluating safety was blind regarding drug administration. The second period began once security and pharmacokinetics of the first period were evaluated.

**Results:** Local tolerance was excellent. No modifications of the ocular surface or iris were detected. The analytical results at final examination did not show differences from those observed during selection. There were statistical differences between area under curve (AUC) of IOP curves on day four with respect to selection day curve (12% decrease) in all volunteers administered with the low level dose of SYL040012 during seven days. Five of them (with an average basal value of IOP higher than the mean value for the whole group) showed reduction higher than 15%. SYL040012 was not detected in blood.

**Conclusions:** The Phase I clinical trial for SYL040012 was completed in 30 healthy volunteers. SYL040012 showed excellent local and systemic tolerance after single and multiple administrations to subjects.
DIURNAL FLUCTUATIONS IN INTRAOCULAR PRESSURE (IOP) CONTROL WITH DIFFERENT FORMULATIONS OF TIMOLOL MALEATE 0.5%: A TWO STAGE COMPARISON STUDY

A. Sudhalkar 1, M. Khamar 1
1M & J Western Regional Institute of Ophthalmology, Ahmedabad - India

Background: Diurnal fluctuations in intraocular pressure (IOP) control in patients with primary open angle glaucoma (POAG) on treatment can further damage the optic nerve head, especially in cases of advanced glaucoma. Recently, OD dosing has been introduced for timolol maleate 0.5%; there are conflicting reports regarding its efficacy in maintaining a persistently low level of IOP in open angle glaucoma patients. We undertook a two stage study, first in normal human volunteers to determine the IOP lowering efficacy and duration of 1 drop of each formulation of timolol maleate and secondly in documented early POAG patients to determine whether the once daily formulations give uniform control throughout the 24 hour period.

Methods: Prospective randomised double blind clinical trial; Applanation tonometry, diurnal variation prior to therapy for dosage adjustment, punctual occlusion and K2 test for normality applied in both stages p < 0.01 considered significant. 1st stage: 60 volunteers randomly assigned to receive a SINGLE DROP of aqueous, semi-aqueous or gel formulations of timolol maleate in one eye (randomized), the other eye acting as a control, 3 groups, twenty in each group. IOP measurements with carried out at 2, 4, 8, 12 and 23 hours post instillation. Unpaired t test was carried out between test and control eye, and paired t test pre instillation and post instillation at each interval for the IOP recorded in the test eye. ANOVA test was used to analyse whether the difference in the IOP in the 3 groups at 23 hours post instillation was statistically significant. 2nd stage: Patients with bilateral early documented POAG (CD < 0.5) randomly assigned to receive timolol maleate (0.5%) semiaqueous (n = 28) or gel forming solution (n = 28) OD in both eyes. Pre instillation peak IOP recorded, therapy initiated and patients called for follow up on day 7 and day 15, two hours after morning dose at 2, 4, 8, 12, 16, 23 hours on day 7 and day 15. Paired t test used to compare differences in IOP at 2 hours with the IOP at 12 and 23 hours on day 7 & 15 in EACH group. Unpaired t test used on day 7 & 15 to compare the IOP at 23 hours post instillation between two groups.

Results: First Stage: Mean age-42.3 years (35-65 years).

<table>
<thead>
<tr>
<th>Mean baseline IOP(mm)</th>
<th>Aqueous</th>
<th>Semi aqueous</th>
<th>Gel Forming Solution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test eye(T)</td>
<td>14.1</td>
<td>13.4</td>
<td>14.8</td>
</tr>
<tr>
<td>Control (C)</td>
<td>14.1</td>
<td>12.2</td>
<td>14.1</td>
</tr>
<tr>
<td>% max reduction (T vs. C)</td>
<td>21.4 (2 hours)</td>
<td>30.6 (4 hours)</td>
<td>25 (at 2 hours)</td>
</tr>
</tbody>
</table>

Duration of effect in all three groups: < 12 hours (p > 0.01 at 12 hours). No significant difference in IOP at 23 hours between 3 groups (p > 0.01). 2nd Stage: Mean age-47.2 years (40-57 years). IOP range- 22-27 mm Hg pre treatment. Difference in IOP on day 7 between 2 and 23 hours post instillation was statistically significant in both groups (p<0.01). At day 15 the difference at same intervals was not significant. No significant difference between two groups at day 7 or 15.

Conclusion: Fluctuations in IOP occur in the first week of therapy with OD dosing of timolol maleate 0.5%. Twice daily dosing might be safer in the first week.
EFFECT OF LONG-ACTING CARTEOLOL HYDROCHLORIDE 2% OPHTHALMIC SOLUTION ON 24- HOUR VARIATION OF INTRAOCULAR PRESSURE IN PRIMARY OPEN ANGLE GLAUCOMA PATIENTS

Y. Nakazawa¹, I. Kimura¹, S. Watanabe¹, A. Mizota², M. Tanaka¹
¹Department of Ophthalmology, Juntendo University Urayasu Hospital, Chiba - Japan; ²Department of Ophthalmology, Teikyo University School of Medicine, Tokyo - Japan

Background: We investigated the effectiveness of long-acting carteolol hydrochloride 2% ophthalmic solution on 24-hour variations in intraocular pressure (IOP) in primary open angle glaucoma (POAG) patients.

Methods: Fourteen POAG patients were treated with long-acting carteolol hydrochloride 2% ophthalmic solution for 6 weeks once daily at 8 o’clock in the morning, and their pretreatment 24-hour IOP variations were compared with those measured after the treatment period. IOP was measured at 1, 4, 7, 10, 13, 16, 19, 22 o’clock.

Results: In the comparison of 24-hour variation of IOP before and after the treatment, IOP values were significantly reduced at 4, 7, 10 o’clock. The reduction of IOP was greater in the morning than in the afternoon or night-time. In the comparison of 24-hour mean IOP before and after the treatment, the mean IOP was reduced by 1.5mmHg from 17.4 mmHg to 15.9 mmHg, and the percent reduction was 8.5% (p < 0.0001).

Conclusions: This study suggests that long-acting carteolol hydrochloride 2% ophthalmic solution lowers IOP especially in the morning, showing similar 24-hour variation of IOP by regular formulation of carteolol hydrochloride ophthalmic solution.
MEDICAL TREATMENT: PROSTAGLANDIN ANALOGUES
COMPARISON OF HUMAN OCULAR DISTRIBUTION OF BIMATOPROST AND LATANOPROST

P. Ichhpujani\textsuperscript{1}, L.J. Katz\textsuperscript{2}, L. Wheeler\textsuperscript{3}, C.L. Shiels\textsuperscript{4}, A. Acheampong\textsuperscript{5}, S. S Wizov\textsuperscript{2}, G. Hollo\textsuperscript{6}, B. Marr\textsuperscript{4}

\textsuperscript{1}Department of Ophthalmology, Govt. Medical College and Hospital, Chandigarh - India; \textsuperscript{2}Glaucoma Service, \textsuperscript{4}Oncology Service, Wills Eye Institute, Philadelphia - USA; \textsuperscript{3}Department of Biological Sciences, \textsuperscript{5}Department of Safety Evaluation, Allergan, Irvine, - USA; \textsuperscript{6}Department of Ophthalmology, Semmelweis University, Budapest - Hungary

Background: To investigate the ocular distribution of bimatoprost, latanoprost and their acid hydrolysis products in the aqueous humor, cornea, sclera, iris and ciliary body of patients treated with a single topical dose of bimatoprost 0.03% or latanoprost 0.005% for understanding concentration-activity relationships.

Methods: Thirty-one patients undergoing enucleation for an intraocular tumor not affecting the anterior part of the globe were randomized to treatment with bimatoprost or latanoprost at 1, 3, 6 or 12 h prior to surgery. Concentrations of bimatoprost, bimatoprost acid, latanoprost and latanoprost acid in the human aqueous and ocular tissues were measured using liquid chromatography tandem-mass spectrometry.

Results: Following topical administration, intact bimatoprost was distributed in human eyes with a rank order of cornea/sclera > iris/ciliary body > aqueous humor. Bimatoprost acid was also detected in these tissues, where its low levels in the cornea relative to that of latanoprost acid indicated that bimatoprost hydrolysis was limited. Latanoprost behaved as a prodrug that entered eyes predominantly via the corneal route. Levels of latanoprost acid were distributed as cornea > aqueous humor > sclera/iris > ciliary body.

Conclusions: The data suggest that bimatoprost reached the target tissues in humans favoring the conjunctival/scleral absorption route. Findings of intact bimatoprost in the ciliary body indicated its involvement in reducing intraocular pressure (IOP). Bimatoprost acid may have only a limited contribution on the basis that bimatoprost has greater/similar IOP lowering efficacy than latanoprost, yet bimatoprost acid levels were a fraction of latanoprost acid levels in the aqueous humor and cornea and only sporadically detectable in the ciliary body.
THE EFFICACY AND SAFETY OF LATANOPROST, TAFLUPROST AND BIMATOPROST IN PATIENTS WITH GLAUCOMA OR OCULAR HYPERTENSION: A 3-MONTH COMPARATIVE CLINICAL TRIAL
S. Nakano¹, T. Kubota¹
¹Department of Ophthalmology, Oita University Faculty of Medicine, Oita - Japan

Background: Intraocular pressure (IOP) reduction is the primary goal for the treatment of patients with primary open-angle glaucoma (POAG), normal-tension glaucoma (NTG) or ocular hypertension (OHT). Many studies have suggested that IOP reduction might prevent the progression of optic nerve damage and visual field deterioration. There are currently 3 commercially available prostaglandin analogs for the primary treatment of glaucoma. The 0.005% latanoprost (LAT, Xalatan®, Pfizer, Inc., New York, NY) is a first prostaglandin analog that is a prototypical FP receptor agonist. The 0.0015% tafluprost (TFU, Tapros®, Santen Pharmaceutical Co. Ltd., Osaka, Japan) is a high affinity and selective FP receptor agonist with a universal design bottle. The 0.03% bimatoprost (BIM, Lumigan®, Allergan, Inc., Irvine, CA) is the first synthetic prostamide analog that lowers the IOP by interaction with the prostaglandin FP receptor and also the FP receptor variant (FP-altFP) complexes.

To the best of our knowledge, no direct comparative study of LAT, TFU and BIM has been published. The purpose of this prospective study was to compare the efficacy and safety of LAT, TFU and BIM as monotherapy and as combination therapy with 0.5% Timolol (TIM, Timoptol®, Santen Pharmaceutical Co. Ltd., Osaka, Japan) in POAG, NTG or OHT patients.

Methods: A 3 month, prospective, open-label, clinical trial was designed. Sixty-nine patients with POAG, NTG or OHT were enrolled. After three baseline visits, the subjects received LAT treatment for a 3 month period starting from December 2007. To take into account the IOP seasonal fluctuation, the TFU examination period began from December 2008, and the BIM examination period began from December 2009. Interview, slit-lamp biomicroscopy, IOP measurement, and funduscopy were performed at the baseline visits and at 1, 2 and 3 months after the starting examination period. The primary outcome measurements were the monthly IOP reduction rate (IOP-RR) and the rate of nonresponders (NR), defined as those with IOP-RR of 20% or less. Safety measures included adverse events, an objective assessment of conjunctival hyperemia, and corneal punctate keratitis. The impressions of treatment were assessed by questionnaires.

Results: Forty-nine patients completed the study. As monotherapy, BIM and TFU had significantly greater IOP-RR than LAT. As combination therapy with 0.5% Timolol, BIM had the strongest hypotensive effect. As monotherapy, the NR rate was 14.8% for BIM, 37.0% for LAT and 29.6% for TFU. The most frequent ocular adverse events were conjunctival hyperemia, reported in 44.4% of BIM patients, 29.6% of LAT patients and 25.9% of TFU patients. The degree of conjunctival hyperemia was greater in patients receiving BIM, however, it led to no discontinuations. The second most common ocular adverse event was corneal punctate keratitis, there were no significant differences among the three treatment groups. The patients preferred TFU for its convenience in the ophthalmic bottle and its good sensation of ophthalmic solution.

Conclusions: All treatments significantly reduced IOP and were well tolerated. BIM had the strongest hypotensive effect and its conjunctival hyperemia led to no discontinuation. TFU had a stronger hypotensive effect than LAT and superior tolerability.
THE INCIDENCE OF DEEPENING OF UPPER EYELID SULCUS CAUSED BY TOPICAL TAFLUPROST OPHTHALMIC SOLUTION

R. Sakata¹, M. Aihara¹, S. Shirato²

¹Department of Ophthalmology, University of Tokyo Graduate School of Medicine, Tokyo - Japan;
²Yotsuya Shirato eye Clinic, Tokyo - Japan

Background: Deepening of upper eyelid sulcus (DUES) has been recently reported as the new side effect caused by prostaglandin (PG)-related ophthalmic solutions, in addition to the conjunctival injection, elongation of eyelashes or pigmentation of eyelid. According to our previous investigation, about 40% patients had expressed DUES by 3 months after switching from latanoprost to bimatoprost. This time, we prospectively investigated the frequency and related risk factors of DUES in glaucoma patients newly started using one of PG analogues, tafluprost.

Methods: 26 glaucoma patients (13 males, 13 females) who were naïve to PG-related ophthalmic solutions were enrolled. After starting tafluprost eye drop in one eye, face photographs, IOP, and subjective impression of DUES were obtained at start point (0 month), after 2 month, 4 months, and 6 months. The presence of DUES was determined with the unanimous judgment of three examiners by the three photographs after starting medication displayed without chronological order. The relationship between the occurrence of DUES and age, gender, refraction, and IOP reduction were statistically analyzed.

Results: The incidence of DUES was 15% (4/26) at 2 months, 23% (6/26) at 4 months, and there was no increase in the incidence of DUES after 4 months. One patient noticed the subjective symptom of DUES by 2 months, but no one deactivated using this eye drop during this period. The incidence was significantly higher in non-myopic eyes (p = 0.017). There was no significant relationship between DUES and age, gender and IOP reduction.

Conclusion: About 20% patients expressed DUES by 4 months after newly started using tafluprost. When using PG analogues, we should concern about this side effect in addition to the others.
EFFICACY AND SAFETY OF BIMATOPROST 0.03% IN JAPANESE NORMAL TENSION GLAUCOMA
H. Suzumura¹, I. Kimura², S. Sasaki³, T. Kimura⁴, K. Yoshikawa⁵, T. Tsumura⁶
¹Nakano General Hospital, Tokyo - Japan; ²Department of Ophthalmology, Juntendo University
Urayasu Hospital, Chiba - Japan; ³Sasaki Eye Clinic, Tokyo - Japan; ⁴Ueno Eye Clinic, Tokyo -
Japan; Yoshikawa Eye Clinic, Tokyo - Japan; ⁶Fussa Hospital, Tokyo, Japan

Purpose: To evaluate the efficacy and safety of prostaglandin-related drugs, bimatoprost, in
Japanese normal tension glaucoma (NTG).

Participants: Thirty-eight NTG patients with IOP of 18 mmHg or less.

Methods: After approval of the study protocol by the Institutional Review Board, the study
was conducted at six clinical centers. The inclusion criteria were as follows: apparent glaucomatous
optic disc as well as visual filed abnormalities in both eyes; IOP without glaucoma medication was
18 mmHg or less at least consecutive three times measurements; corrected visual acuity ≥0.5;
spherical equivalent refraction ≤-10.0 diopters. Qualified subjects were instructed to begin
treatment with bimatoprost 0.03% ophthalmic solution at night in one eye, which was exhibiting
higher IOP. For the cases with no apparent difference of baseline IOP was observed, the eyes with
lower MD were enrolled for the present study. Time course of IOP and anterior segment findings
(conjunctival hyperemia and superficial punctate keratopathy (SPK) were scored using each
graded standard photogram) were examined at 2, 4, 8 and 12 weeks after treatment of bimatoprost.

Results: While 38 patients (age: 64.1 ± 12.6; 19 males and 19 females) were enrolled in this study,
withdrawal from the study was observed in 6 patients because of presence of side effects or
discontinuance of patient visit. The mean IOP of bimatoprost treated eyes was significantly reduced
from 14.5±2.3mmHg at baseline to 10.9 ± 2.0 mmHg at 2 weeks (p < 0.0001), 10.8 ± 2.0 mmHg at 4
weeks (p < 0.0001), 10.9 ± 1.8 mmHg at 8 weeks (p < 0.0001) and 10.6 ± 1.7 mmHg at 12 weeks (p
< 0.0001) in 32 patients which completed the study. The mean IOP of fellow eyes was not changed
significantly through 12 weeks. The mean score of conjunctival hyperemia of treated eye increase
significantly from 0.3 ± 0.4 at baseline to 0.7 ± 0.6 at 2 weeks (p = 0.0065), 0.8 ± 0.5 at 4 weeks (p
= 0.0001), 0.9 ± 0.6 at 8 weeks (p = 0.0001), and 0.9 ± 0.4 at 12 weeks (p < 0.0001), and the mean
score of SPK of treated eye was not changed from 0.07 ± 0.17 at baseline to 0.09 ± 0.19 at 2 weeks
(p = 0.8125), 0.06 ± 0.13 at 4 weeks (p = 0.7969), 0.05 ± 0.11 at 8 weeks (p = 0.8125), 0.11 ± 0.18
at 12 weeks (p = 0.3398). Patients who experienced eyelash disorder, eyelid pigmentation and
deepening of upper eyelid sulcus were observed in 12 eyes, 5 eyes, 3 eyes, respectively.

Conclusions: While a small number of local side effects was observed, the present study suggests
that bimatoprost has a potent IOP-lowering effect in Japanese NTG patients with IOP of 18 mmHg
or less.
EFFECT OF PROSTAGLANDIN ANALOGUES ON INHIBITION OF ADIPOCYTES DIFFERENTIATION AND ADIPOGENESIS IN 3T3L-1 CELL LINE

Z. Wang¹, R. Yamagishi², T. Fujishiro³, M. Aihara²

¹Department of Ophthalmology, Tokyo University Graduate School of Medicine, Tokyo - Japan; ²Department of Ophthalmology, University of Tokyo Hospital, Tokyo - Japan; ³Saitama Red Cross Hospital, Saitama - Japan

Purpose: Prostaglandin analogues (PGs) are widely used for anti-glaucoma therapy. Recently, deepening of upper eyelid sulcus (DUES) are reported as cosmetic side effects in bimatoprost and travoprost, but not in latanoprost. However, the mechanism of DUES is unclear. We hypothesized orbital fat reduction is one of the causes of DUES, and planned to study the effect of PGs on adipogenesis in vitro.

Methods: 3T3-L1 preadipocytes were cultured and differentiated into adipocytes (day 0). At day 2, unoprostone (UNO), latanoprost acid (LAT-A), travoprost acid (TRA-A), tafluprost acid (TAF-A), bimatoprost (BIM), bimatoprost acid (BIM-A), and prostaglandin F2a (PGF2a) were added at the concentration of 100nM. At day 10, intracellular oil stained with Oil Red O were photographed by a microscopy to measure the area of oil. In one assay using all drugs, 50 areas were counted and 5 independent experiments were repeated in a masked manner. The relative area of oil in the treated culture was calculated in comparison with that in the control culture with DMSO vehicle solution and analyzed by Dunnet test.

Results: The relative oil area of LAT-A, TRA-A, TAF-A, BIM, BIM-A, UNO and PGF2a were 38.7 ± 1.3, 31.4 ± 13.4, 59.6 ± 2.7, 89.7 ± 3.1, 28.3 ± 12.4, 95.5 ± 2.3, and 43.1 ± 2.1%, respectively. All acid form of prost-type PGs, LAT-A, TRA-A, TAF-A, BIM-A, and PGF2a inhibited adipogenesis. TRA-A and BIM-A significantly inhibited adipogenesis (p < 0.05), but BIM and UNO did not. Prost-type PGs with high FP receptor affinity tended to show strong inhibitory effect compared to prostamide-type BIM and prostone-type UNO.

Conclusions: Although DUES were not clarified in all PGs, all acid forms of prost-type FP agonists were more potent than BIM and UNO in interfering adipogenesis in vitro. This result suggests that all prost-type PG analogues may have a potential to induce DUES, probably due to orbital fat reduction.
INCIDENCE OF DEEPENING OF UPPER EYELID SULCUS AFTER TOPICAL USE OF TRAVOPROST IN JAPANESE
K. Maruyama¹, A. Tsuchisaka¹, M. Haneda¹, S. Shirato²
¹Department of Ophthalmology, Tokyo Medical University, Tokyo - Japan; ²Yotsuya Shirato Eye Clinic, Tokyo - Japan

Purpose: To investigate the incidence of deepening of upper eyelid sulcus (DUES) by topical use of travoprost in Japanese glaucoma patients.

Design: Prospective, observer-masked, open label, observational study.

Subjects and Methods: Thirty-one primary open-angle glaucoma patients (22 female and 9 male, 31 eyes) who had been treated with travoprost eye drops in unilateral eye were studied prospectively before and after prescription of travoprost for the fellow eye. The eyes and forehead were photographed and standard ocular examinations were performed before and 2, 4, and 6 months after use of travoprost in the (newly treated) fellow eye. The three post-treatment photographs were compared with the pretreatment photograph to determine if there was DUES. Three examiners assessed each patient independently in a blinded manner. The incidence of DUES and risk factors for DUES were analyzed.

Results: The prevalence of DUES was 35% (11/31), 52% (16/31) and 52% (16/31) at 2, 4 and 6 months, respectively, after use of travoprost was started. No new onset of DUES was found after 4 months of treatment. There were no differences in clinical factors between DUES-positive and -negative groups. Seven of 16 patients (44%) with DUES noticed subjectively changes of the upper eyelid sulcus, but no patient demanded to discontinue travoprost.

Conclusions: Careful examination of the patients revealed that DUES is a common adverse effect of travoprost instillation in Japanese glaucoma patients. Clinicians should pay attention to this complication.
EFFECTS OF GLAUCOMA MEDICATIONS AND PRESERVATIVES ON HUMAN TRABECULAR MESHWORK AND NON-PIGMENTED CILIARY EPITHELIAL CELLS
D.A. Ammar¹, M.Y. Kahook¹
¹Department of Ophthalmology, University of Colorado Denver, Aurora - USA

Background: We investigated the potential cytotoxicity of various topical prostaglandin analogs (PGA) formulations containing different preservatives in cultured human trabecular meshwork (TM) cells and non-pigmented ciliary epithelial (NPCE) cells.

Methods: We tested 0.004% travoprost preserved with either 0.015% benzalkonium chloride (BAK), sofZia®, or 0.001% polyquad® (PQ); and 0.005% latanoprost preserved with 0.020% BAK. Also tested was a range of BAK concentrations (0.001 - 0.020%) in balanced salt solution (BSS). TM cells were treated for 10 minutes at 37°C with solutions diluted 1:10 to mimic the reduced penetration of topical preparations to the anterior chamber. Viability was determined by assaying the uptake of the fluorescent vital dye calcein-AM and normalized to BSS controls.

Results: Exposure to increasing percentages of BAK decreased NPCE viability, although these small changes were statistically insignificant between the 0.0001% BAK (90% ± 3%) and 0.0020% BAK (89% ± 6%) exposure. In contrast, TM cells did show a significant decrease in cell viability when comparing 0.0015% BAK (67% ± 8% live) and 0.0020% BAK (57% ± 6% live, p < 0.05). At all concentrations of BAK tested, there were significantly more live NPCE cells than TM cells (p < 0.05). TM cells exposed to PGAs preserved with BAK had significantly higher number of live cells than their respective concentrations of BAK. In contrast, NPCE cells exposed to latanoprost + BAK, but not travoprost + BAK, performed significantly better than BAK alone (96% ± 3% vs. 89% ± 6% live NPCE cells; p < 0.05). In TM cells, exposure to travoprost + BAK had statistically fewer live cells (83 ± 5%) than both travoprost + sofZia (97 ± 5%) and travoprost + PQ (97 ± 6%; p < 0.05). For NPCE cells exposed to the PGA travoprost, replacement of BAK with PQ or sofZia had no significant effect on cell survival.

Conclusions: In conclusion, our findings argue that replacement of BAK with alternative preservatives (PQ, sofZia) would potentially improve viability of TM cells, which are involved in maintaining the conventional outflow pathway in vivo. The cells responsible for aqueous inflow, NPCE, appear more resilient to BAK-induced damage.
COMPARISON OF FOUR PROSTAGLANDIN ANALOGUES BY BILATERAL TREATMENT IN NORMAL SUBJECTS
I. Kawaguchi1, T. Higashide1, S. Ohkubo1, C. Kawaguchi1, K. Sugiyama1
1Department of Ophthalmology and Visual Science, Kanazawa University Graduate School of Medical Science, Kanazawa - Japan

Background: To investigate the drug efficacy of 4 prostaglandin (PG) analogues by bilateral treatment in normal subjects, in three different study period. (latanoprost vs. travoprost, latanoprost vs.tafluprost, and latanoprost vs.bimatoprost).

Methods: This was a randomized, double-masked, clinical study. Twenty-four normal subjects were recruited in this study. As study 1, “latanoprost vs. travoprost” was examined, and after taking a washout period of over 6 weeks, study 2, “latanoprost vs. tafluprost”, was performed. After a second washout period of over 6 weeks, study 3, “latanoprost vs. bimatoprost”, was done. In each study, 2 drugs were randomly assigned to one eye each. Study subjects instilled the assigned eye drops at 9:00 p.m. everyday for 2 weeks. The same masked investigator measured all intraocular pressure (IOP) using a Goldmann applanation tonometer. IOP measurements were done at 9:00 a.m., 1:00 p.m. and 5:00 p.m. at baseline (day 0), and were repeated on day 7 and 14. The differences in IOP reduction between drugs or subjects were statistically analyzed. Main outcome measurements are the mean diurnal IOP reduction, mean of IOP reduction at three time points, by PG analogues on day 7 and 14 from day 0.

Results: Average of the mean diurnal IOP reduction (mean ± standard deviation, mmHg) on day 14 were latanoprost (3.4 ± 1.4) vs. travoprost (3.5 ± 1.3) in study 1, latanoprost (2.4 ± 1.2 ) vs. tafluprost (2.6 ± 1.3) in study 2, latanoprost (2.8 ± 1.5) vs. bimatoprost (3.7 ± 1.5) in study 3. The mean diurnal IOP reduction on day 14 by latanoprost was similar to that by travoprost and tafluprost, but was significantly smaller than that by bimatoprost. The strength of association of mean diurnal IOP reduction was moderate (r² = 0.55 - 0.71) between latanoprost and other 3 PG analogues on day 7. It was weak between latanoprost and bimatoprost on day 14 (r² = 0.25), which was in remarkable contrast to the strong association between latanoprost and travoprost or between latanoprost and tafluprost (r² = 0.81, 0.82, respectively).

Conclusions: The bilateral treatment protocol revealed a different IOP-lowering efficacy of bimatoprost compared to other PG analogues. Regarding the IOP-lowering mechanism by bimatoprost, FP receptor plays critical role similarly to other PG analogues. However, recent study has shown that the prostamide itself, unhydrolyzed form of bimatoprost, had a distinct pharmacological activity through interaction with the putative prostamide receptor. It may be a reason of dissociated IOP response by bimatoprost compared to latanoprost on day 14. The results of this study indicate that it is reasonable to choose bimatoprost rather than travoprost and tafluprost when considering the switch of medication from latanoprost to other PG analogues.
EFFICACY AND SAFETY OF TAFLUPROST IN NORMAL-TENSION GLAUCOMA WITH INTRAOCULAR PRESSURE OF 16MMHG OR LESS

T. Nakano¹, K. Yoshikawa², T. Kimura³, H. Suzumura⁴, M. Nanno⁵, T. Noro¹

¹Department of Ophthalmology, The Jikei University School of Medicine, Tokyo - Japan; ²Yoshikawa Eye Clinic, Tokyo - Japan; ³Ueno Eye Clinic, Tokyo - Japan, ⁴Department of Ophthalmology, Nakano General Hospital, Tokyo - Japan; ⁵Nihonmatsu Eye Hospital, Tokyo - Japan

Background: Normal-tension glaucoma (NTG) is the most frequently observed glaucoma type in Japan, and accounts for 72% of all glaucoma. Reduction of intraocular pressure (IOP) is the only evidence-based treatment method for glaucoma, and is also recommended for NTG. IOP reduction with the use of ophthalmic solutions as done in other types of glaucoma is also preferred for NTG treatment. Though prostaglandin (PG) analogues are recognized to be mostly effective in reduction of IOP among a variety of glaucoma ophthalmic solutions, efficacy and safety of PG analogues in NTG patients have not been fully investigated. Tafluprost ophthalmic solution (tafluprost), PG F2α derivative launched in 2008, appeared to have comparable IOP reduction effect and safety to latanoprost in primary open-angle glaucoma (POAG) and ocular hypertension. Tafluprost is reported to have significant IOP reduction effect even in NTG patients with IOP of 16mmHg or more. However, no study has investigated on NTG patients with IOP of 16mmHg or less which accounts for 67.5% of NTG according to Tajimi study. In this study, therefore, we evaluated IOP reduction effect and safety of tafluprost in NTG patients with baseline IOP of 16mmHg or less.

Methods: NTG patients with baseline IOP of 16 mmHg or less in either eye were enrolled. The levels and the rate of IOP reduction were measured after tafluprost administration for 12 weeks. Presence of adverse drug reactions and the cumulative incidence rate of adverse events were also investigated.

Results: Forty-one out of 44 eyes of the 44 patients enrolled completed the study. As compared to the levels of baseline IOP (13.2 ± 1.3 mmHg), significant (p < 0.0001) reduction of the levels as well as the rate of IOP was observed at Week 2 (2.5 ± 1.3 mmHg, 19.3% ± 10.2%), 4 (2.9 ± 1.3 mmHg, 22.2% ± 10.4%), 8 (2.8 ± 1.2 mmHg, 21.4% ± 9.0%) and 12 (3.0 ± 1.4 mmHg, 22.7% ± 10.5%) after tafluprost administration, respectively. No apparent adverse drug reactions were observed. The cumulative incidence rate of adverse events was 58.5%. Though ocular itching was most frequently observed (29.3%), all adverse events were clinically tolerable.

Conclusions: Tafluprost demonstrated a significant IOP reduction in NTG patients with baseline IOP of 16 mmHg or less without apparent safety concerns.
APPLANATION TONOMETRY VERSUS DYNAMIC CONTOUR TONOMETRY IN EYES TREATED WITH LATANOPROST

E. Detorakis¹, V. Arvanitaki¹, G. Kymionis¹, I. Pallikaris¹, M. Tsilimbaris¹

¹Department of Ophthalmology, Univ. Hospital of Heraklion, Heraklion - Greece

Background: Previous studies have reported a general agreement between Goldmann Applanation Tonometry (GAT) and Dynamic Contour Tonometry (DCT), with the former providing slightly higher IOP readings than the latter. Nevertheless, an increased disparity in IOP readings between GAT and DCT has been reported for very high or very low central corneal thickness (CCT) scores. Prostaglandin analogues (PGA), such as latanoprost, cause a variety of ocular effects (such as a reduction in CCT), potentially affecting ocular bio-mechanical properties. This study aims at examining differences between GAT and DCT in eyes treated with latanoprost.

Methods: The Latanoprost Group (LG) included 41 eyes (of 24 patients) treated with latanoprost as the only anti-glaucomatous medication. The non-Latanoprost group, (NLG) included 19 eyes (of 11 patients) with glaucoma, receiving antiglaucomatous medications other than prostaglandin analogues. The Control Group (CG) included 40 eyes of 20 non-glaucomatous patients. GAT, DCT, CCT and Axial Length (AL) measurements were performed. The difference between GAT and DCT intraocular pressure (dIOP) was calculated. Differences in dIOP between the 3 groups and correlations of dIOP with other clinical parameters were examined.

Results: dIOP was significantly higher in LG, compared with NLG or CG. The correlations of dIOP with AL was statistically significant in the LG but not in NLG or CG. Correlations of dIOP with CCT, patients’ age and duration of latanoprost use (LG) were statistically not significant.

Conclusions: The fact that dIOP was significantly higher in LG, compared with NLG and CG implies that latanoprost may affect the bio-mechanical properties of the ocular walls. Taking into account the widespread use of latanoprost and other PGA in glaucoma treatment, their potential effects on the accuracy of IOP measurements imply that findings may affect clinical decision making for glaucomatous patients.
EFFECT OF LATANOPROST ON CENTRAL CORNEAL THICKNESS IN UNILATERAL NORMAL-TENSION GLAUCOMA

J.Y. You

Department of Ophthalmology, Konkuk College of Medicine, Seoul - Korea Republic

Background: To evaluate the effects of latanoprost on central corneal thickness (CCT) in patients with unilateral normal tension glaucoma (NTG).

Methods: Thirty-two eyes of 32 patients with unilateral NTG who were being followed in our hospital’s glaucoma clinic and were receiving latanoprost monotherapy were recruited for the study. The data were collected retrospectively from the patients, who were medicated with latanoprost, at the initial diagnosis of glaucoma. Mean CCT and the CCT reduction from baseline were assessed at initial diagnosis, 3 and 6 months after the initiation of the treatment. An unaffected eye without any ocular medication was also evaluated. All the measurements were performed with a commercially available pachymeter.

Results: Mean age was 54.37 ± 18.43 years old. There were no significant differences between the eyes for baseline IOP and CCT. Mean CCT and CCT changes in the latanoprost-treated eyes (affected eye) and controlateral eyes (unaffected eye) were significantly different at every follow-up (p < 0.05 in each case): Latanoprost-treated eye (n = 32): 529.1 ± 29.6 vs. 524.2 ± 26.6 (p < 0.000) vs. 522.5 ± 32.2 µm (p < 0.000); controlateral eye (n = 32): 530.5 ± 28.3 vs. 530.9 ± 30.6 (p = 0.684) vs. 530.4 ± 28.0 µm (p = 0.688)

Conclusion: Topical therapy with Latanoprost is associated with CCT reduction over a period of 6 months in patients with unilateral normal tension glaucoma.
LONG-TERM EFFECT AND SAFETY OF LATANOPROST MONO-THERAPY ON PRIMARY ANGLE CLOSURE EYES AFTER LASER IRIDOTOMY

S. Sawaguchi¹, Y. Nakamura¹, Y. Arakaki¹, T. Tamashiro¹, E. Teruya¹, H. Sakai¹
¹Department of Ophthalmology, Ryukyu University of Medicine, Nishihara-cho, Okinawa - Japan

Background: We investigated prospectively the long term effect and safety of latanoprost on primary angle closure (PAC) and primary angle closure glaucoma (PACG) after laser iridotomy (LI).

Subjects and methods: Subjects included were PAC/PACG patients over 40 years of age, 18mmHg or higher intraocular pressure (IOP), previous laser iridotomy for longer than 3 months. Right eyes were analyzed in most of cases. Two left eyes were used because of past intraocular surgery. Total of 16 eyes of PAC and 4 eyes of PACG were investigated. IOPs and adverse events were measured and monitored at before and 1, 3, 6, 9, 12 months after initiating evening dose of latanoprost. Humphrey visual field were checked at before and 6, 12 months of instillation of latanoprost.

Results: Base line IOP before treatment was 21.8 ± 2.2 mmHg. Significant IOP reduction was observed at every time points. % reduction of IOP at 12 months was -5.6~35.6% and MD value was unchanged at 12months after treatment. Eye lid pigmentation in 4 cases(20%), conjunctival hyperemia in 3 cases(15%), mild keratitis in 2 cases(10%), and trichiasis(1 case), itching(1 case) were observed, respectively. All adverse events were minimum to mild and none stopped treatment. Conclusion: Latanoprost mono-therapy effectively and safely lowered IOP for PAC/PACG patients for long time period up to 12months.
IOP-LOWERING EFFECT OF TAFLUPROST IN NORMAL TENSION GLAUCOMA: A PROSPECTIVE OBSERVATIONAL POST-MARKETING STUDY IN JAPAN

Y. Kuwayama¹, M. Hashimoto²
¹Fukushima Eye Clinic, Osaka - Japan, ²Santen Pharmaceutical, Clinical Development Center, Osaka - Japan

Background: Tafluprost, a newly developed prostaglandin (PG) analogue, was introduced in Japan in December 2008. In order to evaluate the efficacy and safety of tafluprost in everyday clinical practice, a mandatory post-marketing study is currently being conducted. As shown in epidemiologic studies, most Japanese glaucoma patients have normal tension glaucoma (NTG), and therefore we conducted a subgroup interim analysis focusing on the intraocular pressure (IOP) lowering effect of tafluprost in patients with NTG.

Methods: This is a prospective, multicenter, observational, 2-year follow-up study. Data collection points are at 2, 12, and 24 months after the beginning of the tafluprost therapy. A total of 3038 patients were registered between December 2008 and August 2010 from 422 sites, of which 1256 were NTG patients.

Results: The mean age was 65.9 ± 12.7 years. At baseline, mean IOP was 15.3 ± 2.8 mmHg and 53% of patients had IOP levels of 15 mmHg or less. As for treatment patterns, 787 patients (63%) were received tafluprost as their first medicine and 377 patients (30%) were switched from other drugs, mainly other PGs. In the newly-treated group, the mean IOP was significantly reduced, in both the ‘low-teen’ (≤ 15 mmHg) and the ‘high-teen’ (> 15 mmHg) groups, from 13.4 ± 1.6 mmHg at baseline to 11.5 ± 2.1 mmHg after 2 months of tafluprost (p < 0.001) and from 17.8 ± 1.5 mmHg to 13.9 ± 2.3 mmHg (p < 0.001), respectively, and the percentage of IOP-decrease was 13.7% in the low-teen group and 22.0% in the high-teen group. In the switched-drug group, the mean IOP prior to switching to tafluprost, 14.6 ± 2.7 mmHg, significantly decreased to 13.0 ± 2.6 mmHg at 2 months (p < 0.001).

Conclusion: Tafluprost is effective in NTG patients, both as the first treatment and after switching from another medication.
IMPROVED LOCAL TOLERABILITY AND EFFICACY AFTER SWITCHING TO PRESERVATIVE-FREE TAFLUPROST IN PATIENTS WITH REDUCED TOLERABILITY TO LATANOPROST EYE DROPS

E. Egorov¹, Y. Astakhov², E. Boiko³, A. Doga⁴, O. Kiseleva⁵, V. Sergeev⁴, A. Ryabtseva⁶
¹Department of Ophthalmology, Russian State Medical University, Moscow - Russian Federation; ²Department of Ophthalmology, Saint-Petersburg State Medical University named after acad. I.P.Pavlov, Saint-Petersburg - Russian Federation; ³Military Medical Academy named after S.M. Kirov of Ministry of Defence of Russia, Saint-Petersburg - Russian Federation; ⁴Department of Ophthalmology, Intersectoral Research and Technology Complex, Moscow - Russian Federation; ⁵Moscow Scientific Research Institute of Eye Diseases named by Helmhotz, Moscow - Russian Federation; ⁶Moscow Regional Scientific Research Clinical Institute named after M.F. Vladimirsky, Moscow - Russian Federation

Background: The aim of the study was to investigate whether patients with reduced/poor local tolerability to Xalatan (latanoprost with benzalkonium chloride) benefit from switching to preservative-free Taflotan (tafluprost).

Methods: Open-label, multicenter study including a total of 185 patients with open angle glaucoma or ocular hypertension at 7 centers. To fulfill the inclusion criteria the patients had to exhibit at least 2 symptoms (irritation/burning/stinging, foreign body sensation, tearing, itching or dry eye sensation), or one symptom and one sign (tBUT < 10 sec, significant corneal and conjunctival fluorescein staining, blepharitis, conjunctival hyperemia or poor tear secretion (≤ 10 mm in Schirmer’s test). The patients were switched from Xalatan q.d. treatment to preservative-free Taflotan q.d. treatment for a 12 week period. Xalatan was provided in eye drops bottles whereas preservative-free Taflotan was provided in unit dose pipettes, which necessitated an open-label study design. Primary outcome measures were ocular symptoms and signs at weeks 6 and 12 of preservative-free Taflotan treatment compared to Xalatan treatment at baseline. Intraocular pressure (IOP), drop discomfort, quality of life (COMTOL) as well as safety were also assessed in all patients.

Results: There was a dramatic and statistically highly significant reduction in the number of patients exhibiting ocular symptoms of reduced/poor local tolerability after switching from Xalatan to preservative-free Taflotan both at 6 weeks and 12 weeks of treatment. The same was true for ocular signs. The tear film break-up time (Mean±SEM) increased from 6.4 ± 0.4 sec during Xalatan treatment to 9.5 ± 0.4 sec at week 12 of preservative-free Taflotan treatment (p < 0.001), and the mean conjunctival hyperemia on a scale from 0-4 was reduced from 1.63 ± 0.06 on Xalatan treatment to 0.65 ± 0.05 at week 12 on preservative-free Taflotan treatment (p < 0.001). There was also a marked reduction in the number of patients with drop discomfort and an increase in the number of patients with better quality of life. IOP (Mean±SEM) was reduced from 16.5 ± 0.2 mmHg during Xalatan treatment at baseline to 15.0 ± 0.2 mmHg at week 12 of the preservative-free Taflotan treatment. Throughout the treatment period IOP was lower during the preservative-free Taflotan treatment compared to Xalatan at baseline (p < 0.001; RM ANCOVA). In 20 patients treatment related adverse events were reported, but only 9 patients were withdrawn due to adverse events. Overall preservative-free Taflotan was well tolerated.

Conclusions: Patients with symptoms/signs of reduced/poor local tolerability to Xalatan significantly benefited from switching to preservative-free Taflotan. Thus it is likely that the high concentration of BAC in Xalatan reduces the local tolerability of the drug. In such patients preservative-free Taflotan appears to be a good alternative to avoid local side effects. In addition, after switching from Xalatan to preservative-free Taflotan IOP was further reduced.
EFFECTS OF BENZALKONIUM CHLORIDE- OR POLYQUAD®-PRESERVED COMBINATION GLAUCOMA MEDICATIONS ON HUMAN TRABECULAR MESHWORK CELLS
M.Y. Kahook¹, D.A. Ammar¹
¹Department of Ophthalmology, University of Colorado Denver, Aurora - USA

Background: We investigated the potential short and long-term effects in cultured human trabecular meshwork (TM) cells of various topical combination anti-hypotensive formulations containing different preservatives.

Methods: We tested the combination medication of 0.004% travoprost plus 0.5% timolol preserved with either 0.015% benzalkonium chloride (BAK), or with 0.001% polyquad® (PQ); and 0.005% latanoprost plus 0.5% timolol preserved with 0.020% BAK. Also tested was a range of BAK concentrations (0.001 - 0.020%) in balanced salt solution (BSS). Cells were treated for 25 minutes at 37°C with solutions diluted 1:10 to mimic the reduced penetration of topical preparations to the anterior chamber. The percentage of live cells was determined immediately after treatment through the uptake of the fluorescent vital dye calcein-AM and normalized to BSS controls. To determine any long-term effects, we assayed apoptosis and release of matrix metalloproteinase 9 (MMP-9) 24 hours after exposure to solutions diluted 1:100.

Results: BAK solutions demonstrated a dose-dependent reduction in TM cell viability when assayed immediately after exposure. We observed statistically significant decreases in TM cell viability (p < 0.05) as BAK was increased from 0.0005% (79 ± 7% live) to 0.0020% (33 ± 3% live). In 1:10 dilutions, latanoprost plus timolol preserved with BAK (29 ± 9% live cells) was similar to its corresponding BAK concentration (33 ± 3%). However, diluted travoprost plus timolol preserved in BAK had significantly more live cells (83 ± 12%) than the corresponding amount of BAK (49 ±10%). Travoprost plus timolol preserved with BAK had statistically fewer live TM cells (79 ± 7%) than the same preparation preserved with PQ (93 ± 1%; p < 0.001). When assayed 24 hours after BAK treatments, we found an inverse relationship of BAK concentration to the number of apoptotic TM cells, with 45% ± 8% apoptotic cells after 0.00001% BAK exposure compared to 6% ± 4% apoptotic cells after 0.00020% BAK exposure. We also found that 0.00020% BAK exposure resulted in elevated levels of extracellular MMP-9 at 24 hours.

Conclusions: BAK is toxic to TM cells at concentrations 1/10th of that found in topical combination therapies. Travoprost plus timolol with BAK, but not latanoprost plus timolol with BAK, countered some of the toxic BAK effects. Travoprost plus timolol with PQ had more live TM cells than either travoprost plus timolol with BAK or latanoprost plus timolol with BAK. BAK treatment showed elevated levels of MMP-9, a matrix metalloproteinase implicated in the pathogenesis of glaucoma. Assays of apoptosis in TM cells suggest that low concentrations of BAK, which show no reduction in cell viability in the short term, may nevertheless trigger apoptosis in the long term. These results demonstrate that the substitution or removal of the preservative BAK from topical ophthalmic drugs results in greater viability of TM cells.
Background: A healthy man in age of 20, dedicated to sport activities, complaining of sudden blur on his left eye during skiing. Symptoms were less in the morning and worsening during the day. He has myopia of -4.0Dsph, wears contact lenses and best corrected visual acuity on both eyes is 0.9. The patient’s grand mother is blind on one eye due to glaucoma.

Methods: A patient came to glaucoma department of Clinical center of Vojvodina (Serbia) on January 2011. The IOP was measured with Goldman aplanation (OD = 24 mmHg, OS = 38 mmHg). A Gonioscopy showed the open angle-grade 3 (Shaffer scale) with excessive pigmentation-grade 3 of his right eye and grade 4 of his left eye. The 90D indirect ophthalmoscopy of patient’s right eye showed C/D = 0.5/0.5 and even larger C/D = 0.9/0.9 of his left eye. The additional diagnostic was performed with Humphrey® automated visual field analyzer using Treshold C30-2 and SITA-standard algorythm. The OCT exam of optic nerve head and retinal nerve fibre layer was done on Carl Zeiss Cirrus HD instrument.

Results: A mild visual field damage on the patients right eye showed MD value of -1.4 dB and the advanced damage was found on his left eye with MD value of -14 dB. The OCT confirmed glaucoma damage of patient’s left eye comparing to the right eye, which parameters were in the normal range. The average retinal nerve fiber layer (RNFL) thickness of right eye was 109 µm and RNFL thickness of the left eye was 62 µm. A RNFL symmetry was 64%. A cup volume of the right eye was 0.404 mm$^3$ and the left eye cup volume was 1.306 mm$^3$. The average C/D ratio value measured on OCT was 0.63 for the right eye and 0.86 on the left eye.

Conclusion: There was some of the pigment on corneal endothelium on the slit lamp examination although retro-illumination iris defect was not visible. A therapy started with prostaglandin F2a analogue (Xalatan®, Pfizer). In only 3 days the IOP reduced significantly, with value of 15 mmHg for the right eye and 16 mmHg for the left eye. Comparing to baseline values IOP decrease was 37% on the right eye and 58% on the left eye.
THE LONG-TERM EFFECTS OF TRAVOPROST ON THE BIOMECHANICAL PROPERTIES OF THE CORNEA
C. Altan¹, B. Satana¹, D. Tuzun¹, S. Akar¹, A. Demirok¹, O.F. Yılmaz¹
¹Beyoğlu Eye Training and Research Hospital. Istanbul - Turkey

Background: Travoprost has effects on extracellular matrix and collagen metabolism in the ciliary body. The same mechanisms probably act in cornea. The aim of the current study was to analyze the effects of Travoprost on the corneal biomechanical parameters measured with Ocular Response Analyzer (ORA).

Patients and Methods: Forty-seven eyes of 47 patients with newly diagnosed primary open angle glaucoma, normotensive glaucoma or ocular hypertension were included. Patients were examined before treatment and at the first and sixth months after the onset. Patients who had corneal abnormalities and history of previous ocular surgery or topical medication were excluded. Metrics of corneal biomechanical properties, including corneal hysteresis (CH) and corneal resistance factor (CRF), were measured with the ORA. The ORA also determined the values of intraocular pressure (IOPg) and corneal compensated IOP (IOPcc).

Results: Twenty-eight males and 19 females with a mean age of 57.0 ± 8.9 (41-77) years were included in the study. The mean visual acuity was 0.86 ± 0.26 (Snellen) and the mean CCT measured by ultrasonographic pachimetry was 570.7 ± 49.8 µ. The mean IOP measured by Goldmann applanation tonometry which was 25.2 ± 5.2 mmHg before therapy significantly decreased to 16.9 ± 3.0 mmHg at the first month and 17.0 ± 3.1 at the sixth month (p < 0.001). The pretreatment CH (9.9 ± 2.1 mmHg) increased significantly after treatment at the first month (10.9 ± 1.9 mmHg), but there was no significant difference between pretreatment and sixth month (10.2 ± 2.1 mmHg). There were significant differences of other ORA parameters such as CRF (13.2 ± 2.3; 11.7 ± 2.4; 11.3 ± 2.6 mmHg), IOPg (26.2 ± 6.8; 18.5 ± 4.4; 19.0 ± 5.0 mmHg), IOPcc (25.7 ± 6.7; 18.0 ± 3.6; 19.2 ± 4.3 mmHg) were present between pre-treatment and post-treatment first and sixth months (p < 0.001).

Conclusion: Travoprost is found to be effective in lowering IOP at sixth month. It has CH-increasing effect obtained with ORA after 1 month therapy period. but this effect was not sustained at sixth month. Travoprost also had CRF-decreasing effect during 6 months. Further large-scale studies with longer follow-ups are needed to elucidate effects of travoprost on the corneal biomechanical parameters.
EFFECT OF PROSTAGLANDIN ANALOGUES ON FOveal THICKNESS AFTER PHACoEMULSIFICATION IN PATIENTS WITH OCULAR HYPTERTENSION OR GLAUCOMA

K.G. Sotelo Monge1, A. Antón López1, M. Pazos López1
1Hospital del Mar - Esperanza - Parc de Salut Mar, Instituto Catalán de la Retina ICR, Barcelona - Spain

Background: This is a study to assess the impact on the foveal thickness of discontinuing treatment with prostaglandin analogues prior to cataract surgery in patients with glaucoma or ocular hypertension.

Methods: Prospective and randomized clinical study. We included 86 eyes of 78 patients with ocular hypertension or glaucoma in treatment with prostaglandin analogues, who underwent cataract surgery. Forty three eyes were assigned to group A and discontinued the treatment a week before the surgery and 43 were assigned to group B and instilled the prostaglandin analogue until the day before the surgery. Stratus OCT was performed before macular surgery and 6 weeks postoperatively to quantify the foveal thickness and to determined the appearance of cystoid macular edema (CME).

Results: The mean preoperative foveal thickness was 186.76 ± 17.8 µm in group A and 185 ± 15.7 µm in group B. The mean postoperative foveal thickness at 6 weeks was 197.73 ± 22.9 µm in group A and 195.96 ± 18.7 µm in group B. Foveal thickness increased on average about 10-11 µm after cataract surgery in both groups with no statistically significant difference among them. No difference in the incidence of cystoid macular edema was found among the groups.

Conclusion: Discontinuation of treatment with prostaglandin analogues prior to intraocular surgery does not influence in foveal thickness or postoperative CME after uneventful phacoemulsification in patients with glaucoma or ocular hypertension without other risk factors for postoperative CME.
THE EFFECT OF TRAVOPROST AS INITIAL PROSTAGLANDIN ANALOGUE TREATMENT AND AFTER USE OF LATANOPROST IN JAPANESE GLAUCOMA PATIENTS

K. Tanabe¹, I. Kimura¹, A. Usui¹, M. Tanaka¹
¹Department of Ophthalmology Juntendo University Urayasu Hospital, Chiba - Japan

Background: We investigated the efficacy of travoprost 0.004% benzalkonium chloride free ophthalmic solution compared with 1) treatment without prostaglandin analogues, and 2) previous use of latanoprost 0.005% on intraocular pressure (IOP) lowering effect in Japanese glaucoma patients.

Methods: 1) Comparison with treatment without prostaglandin analogues: nineteen eyes in 11 patients (averaged age: 63.0 ± 14.6 years old) were reviewed retrospectively. Thirteen eyes of primary open angle glaucoma (POAG) (68.4%), 4 eyes of ocular hypertension (21.1%), 1 eye of primary angle closure glaucoma (PACG) (5.3%), and 1 eye of secondary glaucoma (5.3%) comprised the clinical forms of glaucoma. 2) Comparison with previous use of latanoprost 0.005%: Thirty-five eyes in 20 patients (averaged age: 66.0 ± 12.8 years old) were reviewed retrospectively. Thirty eyes of primary open angle glaucoma (POAG) (85.7%), 1 eye of primary angle closure glaucoma (PACG) (2.9%), and 4 eye of secondary glaucoma (11.4%) comprised the clinical forms of glaucoma. IOP values were extracted at 8 ± 4 weeks after treatment of travoprost 0.004%.

Results: 1) Mean IOP was significantly reduced from 18.0 ± 4.4 mmHg at baseline to 13.4 ± 4.6 mmHg (p = 0.0002), and percent reduction was 25.1%. 2) Mean IOP was significantly reduced from 18.8±5.1 mmHg at baseline to 15.9 ± 3.6 mmHg (p = 0.0008), and percent reduction was 8.6%.

Conclusions: These results suggests that travoprost 0.004% has IOP-lowering effect as initial prostaglandin analogue treatment, or even after use of latanoprost 0.005%.
PROSTAGLANDIN ANALOGUES (PGAS) AND TIMOLOL FIXED COMBINATION (FC) VS. EXTEMPORANEOUS COMBINATION (EC) OR MONOTHERAPY (MT) IN THE TREATMENT OF PRIMARY OPEN-ANGLE GLAUCOMA (POAG) AND OCULAR HYPERTENSION (OHT): A SYSTEMATIC REVIEW AND META-ANALYSIS

L. Quaranta\(^1\), I. Riva\(^1\), A. Russo\(^1\), A. Katsanos\(^1\), I. Floriani\(^2\)

\(^1\)Glaucoma Unit - University of Brescia, Brescia - Italy; \(^2\)Department of Clinical Oncology- Istituto Mario Negri, Milano - Italy

Background: PGAs are the first-choice drugs for the treatment of POAG and OHT. They are administered as Mt or as Fc or Ec with Timolol, a topical beta-blocker. Aim of this meta-analysis was to combine the results of the trials comparing the efficacy of Fc of Timolol and PGAs vs. Ec or vs. Mt.

Methods: MEDLINE and EMBASE were searched for articles published until May 2010. Randomized, controlled trials, comparing treatment with Timolol and PGAs Fc vs. Ec or vs. Mt in patients with POAG or OHT were considered eligible. Quality of studies was assessed using a modified Delphi list, whose score ranges from -15 to +15. The primary efficacy endpoint was the mean difference (MD) between arms of the diurnal intraocular pressure (IOP) reduction from baseline. The pooled estimates were calculated using random effects.

Results: Out of 855 retrieved articles, 15 were eligible accounting for a total of 22 comparisons: 18 assessing Fc vs. Mt, 4 Fc vs. Ec. The median quality score was 12 (range 5-15). Fc was more effective than both its components in Mt: Fc vs. Mt with Timolol (MD = -2.42, 95% CI -2.99,-1.85); Fc vs. Mt with PGAs (MD = -1.22, 95% CI -1.84,-0.59). When considering the type of PGAs given as Mt, the difference in efficacy between Fc and Latanoprost (MD = -1.21, 95% CI -1.75,-0.66) was smaller than in the comparison between Fc and Travoprost (MD = -2.14, 95% CI -3.05,-1.24). The only trial comparing Fc vs. Mt with Bimatoprost showed no significant difference (MD = -0.20, 95% CI -0.69, 0.29). Moreover, the comparison between Fc and Ec showed that Fc is less effective in reducing IOP than Ec (MD = 0.76, 95% CI 0.34, 1.17).

Conclusions: The results of this meta-analysis suggest that Fc are more effective than Mt, and Ec seems to have a greater extent of IOP reduction when compared with Fc.
NONCLINICAL EFFECTS OF TAPRENEPAG ISOPROPYL (PF-04217329), A SELECTIVE EP2 AGONIST, AND ITS ACTIVE METABOLITE ON THE CORNEA
G. Yanochko¹, S. Khoh-Reiter¹, D. Lee¹, R. Schachar², B. Jessen¹
¹Drug Safety Research & Development, ²Clinical, Pfizer, San Diego - USA

Background: To determine the etiology of iritis, photophobia, and increase in corneal thickness observed in a FIH Phase 2 clinical trial of topical taprenepag in ocular hypertensive and primary open angle subjects.

Methods: 1. Monkeys were dosed daily for 28 days in one eye with taprenepag and vehicle control in the other. Recovery following discontinuation of taprenepag was assessed for 28 days in the monkeys in the high dose group. Complete ophthalmic examinations including pachymetry and non contact endothelial cell specular microscopy was performed at baseline and weekly thereafter. The eyes were examined histopathologically and with transmission electron microscopy (TEM). 2. In vitro studies were performed with Skinethic corneal epithelial cultures and HCEC-12 human corneal endothelial cells. Test solutions included clinical formulations of taprenepag, its active metabolite (CP-544326) placebo controls, individual excipients, a structurally distinct EP2 agonist and Xalatan®. Four endpoints were evaluated: cell viability, transepithelial electrical resistance (TEER), histopathology, and TEM. 3. Cytokine induction after HCEC-12 and primary human monocyte exposure was measured with ELISA kits.

Results: Monkeys demonstrated a dose related incidence of iritis and an increase in corneal thickness. These adverse events resolved, as observed in the human clinical studies, within 28 days of discontinuing taprenepag. There was no evidence in vivo of taprenepag toxicity to the corneal endothelium or epithelium. However, TEER decreased after 4 hour exposure to either 0.02% BAC, Xalatan® or taprenepag. Cell viability of Skinethic stratified epithelial cells was affected primarily by excipients and was similar to Xalatan®. Viability of HCEC-12 cells was not affected by taprenepag up to 100μM. CP-544326 induced IL-6 release from HCEC-12 and IL-6 and IL-8 from human monocytes.

Conclusions: The lack of in vivo or in vitro endothelial cytotoxicity and the reversibility of the increase in corneal thickness and iritis in the monkey provide confidence to permit further clinical development of taprenepag.
Efficacy and Safety with the Use of the Fixed Combination of Bimatoprost 0.03%/Timolol 0.5% Versus the Fixed Combination of Latanoprost 0.005%/Timolol 0.5% in Mexican Population

L. Lopez¹, C. Hartleben²
¹Hospital Español de Mexico, Mexico City - Mexico; ²Instituto de Oftalmologia, Mexico City - Mexico

Aim: To evaluate if the fixed combination of bimatoprost 0.03%/timolol 0.5% (Ganfort™) is more effective in lowering the intraocular pressure (IOP), than the fixed combination of latanoprost 0.005%/timolol 0.5% (Xalacom™), in patients with primary open angle glaucoma.

Design: We present a longitudinal, prospective, clinical, comparative, open-label, randomized 3 month study.

Methods: 68 patients were studied. 34 were included in each group. 5 patients of each had a wash out period of 4 weeks before initiating the treatment. The rest were without previous treatment. All were evaluated once a month, for three months, at trough, 8 am before the instillation of that day’s drop, and had a complete eye exam and monitoring of arterial pressure and cardiac rate. All patients concluded the study.

Results: The mean basal IOP of the Xalacom™ group was 26.5 ± 2.59 mmHg, which dropped to 17.9 mmHg (±) at first month, and sustained in 17.06 ± 2.33 mmHg in third month. This represented a mean decrease of 9-57 or 35-9%. The mean of basal IOP for Ganfort™ group was 26.9 ± 2.33 mmHg, which dropped to 16.5 at first month, and continued with 16.03 ± 2.00 mmHg in the second and third months. This decrease was 10.88 mmHg or 40.43% with a statistical difference of p = 0.002.

Conclusion: Once-daily treatment with Ganfort™ was effective in lowering IOP 40.43% or 10-88 mm Hg in patients with POAG or ocular hypertension in this 3 month study versus -9.56 mm Hg or 35-9% in the Xalacom™ group. We found no systemic adverse effects that necessitated removal of patients from study protocol, and local side effects were minimal and similar in both groups.

Key words: Bimatoprost, Latanoprost, Timolol, fixed combination, Primary Open-Angle Glaucoma
MEDICAL TREATMENT: CARBONIC ANHYDRASE INHIBITORS
THE FIXED COMBINATION OF DORZOLAMIDE/TIMOLOL AND THE ADDITION OF A PROSTAGLANDIN ANALOG OR BRIMONIDINE FOR THE TREATMENT OF GLAUCOMA: A 4 YEAR RETROSPECTIVE STUDY
C. Hartleben¹, R. Vences², D. Prada²
¹Instituto de Oftalmología, Mexico Df - Mexico; ²Clinica de Glaucoma, Mexico Df - Mexico

Background: Monotherapy is the recognized initial treatment for the treatment of Glaucoma. It is now a frequent practice to use multiple treatments lowering intraocular pressure if monotherapy, does not succeed in IOP control. However, there is very little long-term evidence of the long term effect of use fixed combinations, such as Cosopt® (fixed combination of Dorzolamide 2% / Timolol 0.5%), with added medication in the form of prostaglandin analogs or Brimonidine.

Methods: In this retrospective, nonrandomized, descriptive clinical study, the long term response of the fixed combination of Dorzolamide/Timolol was evaluated in patients with Primary Open-Angle Glaucoma and the addition of other IOP lowering medications such as prostaglandin analogs and Brimonidine.

Results: 158 patients with POAG were evaluated (280 eyes). Patients were divided into three groups: a group with Cosopt only, a second group with prostaglandin analogs, and a third group with the addition of Brimonidine. IOP was reduced satisfactorily in all three groups. However, a progressive IOP reduction was noted in the group with the fixed combination plus prostaglandin analogs. In this group, a lack of long-term drift and a more homogeneous response of the reduction were also noted in comparison with the other groups.

Conclusions: We concluded that IOP reduction was efficacious in all three groups. The addition of prostaglandin analogs showed progressive IOP reduction and absence of long-term drift. Brimonidine had a similar, but smaller effect.
THE ANTIOXIDANT ACTIVITY OF DORZOLAMIDE AND TIMOLOL IN GLAUCOMA THERAPY
S.C. Saccà¹, A. Izzotti², A. Bagnis³

¹Division of Ophthalmology, St Martino Hospital, Genoa - Italy; ²Department of Health Sciences, ³Department of Neurology, Ophthalmology and Genetics, University of Genoa, Genoa - Italy

Oxidative stress is a driving force for primary open angle glaucoma. We tested the ability of Dorzolamide and Timolol, used in glaucoma therapy, to display antioxidant effects. Antioxidant activity of these two drugs was tested in trabecular meshwork specimens (TM) collected from corneal donors, pure TM cell lines composed of either young or senescent endothelial cells, and in subcellular systems composed of pure DNA and subcellular fractions containing or devoid of mitochondria. Oxidative stress was induced by hydrogen peroxide. Monitored endpoints included DNA fragmentation as evaluated by Halo test, oxidative DNA damage in terms of 8-oxo-2’-deoxyguanosine as evaluated by ³²P postlabelling, mitochondrial function as evaluated by MTT test. The antioxidant effect of Dorzolamide, was observed in TM tissue exposed at high doses of hydrogen peroxide. Timolol exerts a antioxidant activity protecting human endothelial cells, regardless of mitochondria presence. Conversely, the antioxidant effect of Dorzolamide was maximised in presence of mitochondria-containing subcellular fractions and in young endothelial cells, being scanty in senescent TM cells. In the subcellular system, the antioxidant effect of Dorzolamide was maximised in presence of mitochondria-containing subcellular fractions and in young endothelial cells possessing efficient mitochondrial function. Timolol antioxidant effect was direct while Dorzolamide needs the presence of intact mitochondria. Accordingly, Dorzolamide antioxidant effect is likely displayed mainly during early glaucoma phases when the molecular damage in trabecular meshwork is still low. Benzalkonium chloride, used as antiseptic in drug buffer preparation, consistently decreased the antioxidant effect of drugs and was per se able to induced oxidative DNA damage.
SHORT-TERM EFFICACY AND SAFETY OF 1% DORZOLAMIDE HYDROCHLORIDE / 0.5% TIMOLOL MALEATE FIXED COMBINATION FOR LOWERING INTRAOCULAR PRESSURE IN GLAUCOMA PATIENTS

J. Takahashi¹, Y. Ikeda², K. Mori³, M. Ueno³, K. Imai³, K. Tada³, S. Kinoshita³
¹Department of Ophthalmology, Kyoto Minireni Taishimichi Clinic, Kyoto - Japan; ²Oike-Ikeda Eye Clinic, Kyoto - Japan; ³Department of Ophthalmology, Kyoto Prefectural University of Medicine, Kyoto - Japan

Background: To evaluate the short-term efficacy and safety of 1% dorzolamide hydrochloride and 0.5% timolol maleate fixed combination (Cosopt®; MSD, Tokyo, Japan) for lowering intraocular pressure (IOP) in primary open angle glaucoma (POAG) patients.

Methods: A total 31 glaucoma patients who started treating with Cosopt® eye drops from September 2010 to December 2010 at Kyoto Prefectural University Hospital and Oike-Ikeda Eye Clinic were retrospectively reviewed. Of those patients, we enrolled 14 eyes of 14 POAG patients including normal tension glaucoma (NTG) with no history of glaucoma surgery or laser eye operations within 6 months prior to the study (8 female, 6 male; 5 NTG, 9 POAG; mean age 68.5 ± 9.7 years old). Patients were divided into two groups; replacement group whose unfixed combination of beta-blockers and carbonic anhydrase inhibitors (CAIs; dorzolamide or brinzolamide) were replaced to Cosopt® (n = 6; 4 female, 2 male; 3 NTG, 3 POAG; mean age: 69.8 ± 8.0 years old) and add-on group who received Cosopt® as their add-on therapy to their original medication (n = 8; 4 female, 4 male; 2 NTG, 5 POAG; mean age: 67.5 ± 11.3 years old). The beta-blockers or CAIs were stopped when they started Cosopt® if the patients used them in the add-on group. The IOP and the daily frequency of eye drop administrations were compared between the pre- and post-Cosopt® treatment. Right-eye data was analyzed if patients used Cosopt® for both eyes, and the paired-t test was used for the statistical analysis.

Results: The IOP at pre-treatment and at 1 month after the initiation of treatment with Cosopt® were 14.5 ± 4.6, 13.4 ± 3.0 mmHg respectively (p = 0.2116, whole subjects), 13.8 ± 6.2, 13.0 ± 2.2 (p = 0.6904, replacement group), and 15.0 ± 3.2, 13.6 ± 3.6 (p = 0.0543, add-on group). The daily frequency of eye drop administrations decreased significantly from 5.7 ± 2.0 times per day to 3.5 ± 1.8 times per day in replacement group (p = 0.00089), while it increased significantly from 2.0 ± 0.9 to 2.8 ± 0.5 in add-on group (p = 0.0479). Three subjects experienced several side effects such as palpitation (n = 1) and progression of superficial punctate keratitis (n = 2).

Conclusion: The findings of this study showed that Cosopt® has benefits not only in IOP lowering effects equivalent to the unfixed combination, but also in decreasing the frequency of daily eye drop administrations.
MEDICAL TREATMENT: OCULAR PERFUSION
AND BLOOD FLOW
INTRAVITREAL ANTI-VEGF INJECTIONS INDEPENDENTLY DECREASE OCULAR PERFUSION PRESSURE AND INCREASE INTRAOCULAR PRESSURE

F. Falck Jr.

Ophthalmology Section, University of Connecticut School of Medicine, Farmington - USA

Background: Previous studies have found that intravitreal anti-VEGF injections can decrease retinal arteriolar caliber and increase intraocular pressure. Blood flow into the eye is driven by ocular perfusion pressure (OPP). OPP is the difference between mean central artery pressure and intraocular pressure (OPP = MCRAP - IOP). If anti-VEGF agents can alter retinal vessel caliber and increase IOP, what effect are they having on OPP? To answer this question, MCRAP and IOP was measured pre and post anti-VEGF injection.

Methods: In twenty-six eyes of twenty-six patients undergoing intra-vitreal anti-VEGF injections for neovascular macular degeneration, upright ipsilateral mean brachial blood pressure (MBBP), MCRAP and IOP were measured pre and post injection. OPP was calculated. Institutional Review Board and written informed consent were obtained. MCRAP was measured optically using the principle of oscillometry to capture central retinal artery pulsations and blood flow (See Figure 1).

Results: Average age was 79.4 ± 3.6 years. Average upright mean brachial artery blood pressure was 92.4 ± 4.1 mmHg. Post injection the average decrease in MCRAP was 9.3 ± 6 mmHg (p = 0.003), IOP increase 11.6 ± 3.5 mmHg (p < 0.0001) and OPP decrease 13.5 ± 6.1 mmHg (p < 0.0001). There was no significant correlation between the increase in IOP and the decrease in MCRAP ($r^2 = 0.18$). In 18 eyes the IOP increased and the MCRAP decreased. In 2 eyes the OPP decreased to zero. Six eyes with abnormal pre-injection MCRAP and OPP were evaluated for carotid vascular stenosis.

Conclusions: Intra-vitreal anti-VEGF injections can increase IOP and decrease MCRAP causing decreased ocular perfusion. Decreased ocular perfusion post injection in the setting of preexisting vascular stenosis increases the risk of CRAO. The lack of correlation between the post-injection IOP increase and the MCRAP decrease suggest different mechanisms of action. The IOP increase maybe volume related and/or an effect on outflow facility. The decrease in MCRAP is likely due to changes in vessel caliber. The results from this study along with observations from previous studies suggest anti-VEGF agents maybe vasoactive. Because the magnitude of IOP increase and MCRAP decrease are not correlated, monitoring IOP alone is not enough to maximize the safety of injection. If both the IOP increases and MCRAP decreases, aggressive treatment of IOP may be required to restore normal ocular perfusion. This is critical to preserve ocular function in an eye with glaucoma. Use of this technology pre and post injection can identify ocular perfusion abnormalities and monitor the effectivness of treatment to lower IOP and restore normal ocular perfusion.
ASSOCIATION BETWEEN ONH BLOOD FLOW AND MEAN ARTERIAL BLOOD PRESSURE IN PATIENTS WITH GLAUCOMA, OCULAR HYPERTENSION AND HEALTHY CONTROL SUBJECTS
L. Schmetterer

Department of Clinical Pharmacology, Medical University of Vienna, Vienna - Austria

Background: Previous studies have suggested that autoregulation, defined as the ability to keep blood flow constant despite changes in perfusion pressure, is impaired in patients with glaucoma. In the current study we use pressure / flow relationships to investigate the autoregulatory properties of the optic nerve head circulation in patients with treated and untreated glaucoma patients and ocular hypertension and compared them to healthy subjects.

Methods: 136 patients with treated primary open angle glaucoma (POAG), 116 patients with untreated POAG, 138 patients with ocular hypertension and 160 control subjects were included in the study. Optic nerve head blood flow was measured using laser Doppler flowmetry. Mean arterial blood pressure (MAP) was measured non-invasively using automated oscillometry and intraocular pressure (IOP) was measured using applanation tonometry. Ocular perfusion pressure (OPP) in the sitting position was calculated as OPP = 2/3*MAP - IOP.

Results: Optic nerve head blood flow was highest in healthy subjects, followed by ocular hypertensives. Optic nerve head blood flow was significantly reduced in patients with glaucoma compared to patients with ocular hypertension and healthy subjects (p < 0.01). The association between OPP and optic nerve head blood flow was highest in untreated glaucoma patients (r = 0.311) followed by ocular hypertensives (r = 0.241) and treated glaucoma patients (r = 0.212). The lowest correlation between optic nerve head blood flow and OPP was found in healthy subjects (r = 0.165).

Conclusions: The present study confirms previous reports that optic nerve head blood flow is reduced in patients with POAG and patients with ocular hypertension. Correlation coefficients in the glaucoma groups and in the ocular hypertensives indicate a vascular dysregulation in these patients compared to healthy control subjects. Furthermore, our data indicate that this vascular dysregulation may be at least partially caused by increased IOP.
MEDICAL TREATMENT: NEUROPROTECTION
MEMANTINE IN THE TREATMENT OF ADVANCED GLAUCOMA. CLINICAL OBSERVATIONS
C. Erb
¹Schlosspark-Klinik, Department of Ophthalmology, Berlin - Germany

Background: Glaucoma is a neurodegenerative disease characterized by progressive loss of retinal ganglion cells. Excitotoxicity describes the process of neuronal injury by excess stimulation of amino acid receptors. High levels of glutamate can be toxic to retinal ganglion cells. Memantine, an uncompetitive, low-affinity, open-channel calcium blocker, enters the receptor-associated ion channel when it is excessively open.

Methods: At our hospital patients with advanced glaucoma damage and increasing visual field loss were treated with memantine. The intraocular pressure must be stable (≤ 15 mmHg) with or without local medications. The therapy with memantine starts with a dosage by 5mg/d at the first week and will increased on 10 mg 2 x daily within 4 weeks. All patients underwent ophthalmologic examinations (visual acuity, refraction, slit lamp and fundus examination), achromatic perimetry and visually evoked potentials before treatment with memantine and every three month during the therapy. The statistic analysis took place with the Wilcoxon- test (side comparison).

Results: We found a stabilisation in visual fields in one year. The statistic analysis of the parameter Mean deviation as well as Loss Variance after 3 months, 6 months, 9 months as well as after 12 months therapy took place. We found no statistically significant change (no worsening) of the parameters at each time points (p > 0.05). The therapy was well tolerated by most patients (90%).

Conclusion: A systemic therapy with memantine seems to slow progression of the visual field defects in patients with advanced glaucoma.
IDEBENONE PREVENTS HUMAN OPTIC NERVE HEAD ASTROCYTES FROM OXIDATIVE STRESS, APOPTOSIS, AND SENESCENCE BY STABILIZING BAX/BCL-2 RATIO
M. Kernt¹, A. Kampik¹, C. Hirneiss¹
¹Department of Ophthalmology, Ludwig Maximilian University, Munich - Germany

Purpose: Primary open-angle glaucoma is one of the leading causes of blindness. Oxidative stress plays an important role in the pathogenesis of this neurodegenerative disease. This study investigates the possible anti-apoptotic and cytoprotective effects of idebenone on optic nerve head astrocytes (ONHA) under oxidative stress.

Methods: ONHA were treated with 1 to 150 µM idebenone. Cell viability (tetrazolium dye-reduction assay and live-dead assay), induction of intracellular reactive oxygen species (ROS), senescence-associated β-galactosidase (SA β-Gal) activity, apoptosis (detection of histone-associated DNA fragmentation), and expression of BAX and Bcl-2, two key modulators of apoptosis, and their mRNA were determined after 48 h and after H₂O₂ treatment.

Results: Idebenone concentrations from 1 to 50 µM showed no toxic effects on ONHA. Pretreatment with 7.5 to 15 µM idebenone led to an increase in viability of ONHA after H₂O₂ treatment. In addition, idebenone pretreatment significantly attenuated the increase of histone-associated DNA fragmentation, induction of SA β-Gal, and intracellular ROS after treatment with H₂O₂. When ONHA cells were treated with idebenone and H₂O₂, RT-PCR and Western blot analysis yielded an increased expression of Bcl-2 and a decrease of BAX compared to those cells that were treated with H₂O₂ only.

Conclusion: In this study idebenone reduced senescence, oxidative stress, and apoptotic cell death in cultured ONHA in vitro. Our results suggest that idebenone may help to protect ONHA in vivo, and therefore might be helpful in preventing the progression of glaucomatous degeneration.
THE SEARCH FOR POTENTIAL NEUROPROTECTIVE AGENTS IN GLAUCOMA THERAPY: IS AYURVEDA’S CURCUMIN IN A COMPLEX WITH OMEGA-3 EPA/DHA AND PHOSPHOLIPIDS ONE FUTURE DIRECTION?
A. Bayer
1
Private Practice, Weilheim - Germany

Background: While reduction of intraocular pressure (IOP) remains the clinician’s principal method to treat glaucoma, such treatment is often partly effective. Neuroprotective agents would allow therapy at a common endpoint of this neurodegenerative disease by rescuing dying cells no matter the nature of the primary insults, and by protecting as yet unaffected neurons from that insult. Since the time of Ayurveda (1900 BC), numerous therapeutic activities have been assigned to Tumeric (Curcuma Xanth. L.). Extensive research within the last half century has proven that most of these activities are due to Curcumin.

Methods: A systematic search of the Medline database using Pubmed Web site for the years 1970 through December 2010, was conducted. In addition, the concentration of Curcumin in the serum after oral intake of 500 mg Curcumin95 and 2 capsules of Neuroprotekt™ (complex of 250 mg Curcumin 95, 250 mg Omega-3 DHA/EPA, phospholipid Eucerit200™) have been measured.

Results: Ongoing clinical trials with Curcumin in patients with Alzheimer Disease, a neurodegenerative disease which has been linked to glaucoma, show borderline significant efficacies. In addition, in more than 80 studies on animal models of different neurodegenerative diseases, Curcumin enhanced neuronal survival by its potential to influence the different mechanisms of neuronal cell loss. Thereby, Curcumin has shown beneficial effects in most of the mechanisms which are involved in the development and progression of glaucoma that could be targets for pharmacological interventions. Reported targets with which Curcumin directly or indirectly interacts or binds are β-amyloid, cyclooxgenase (COX)-2, xanthine oxidase, DNA polymerase, glutathione, albumin, tubulin, metal ions, transcription factors, glutathione reductase, growth factors, antiapoptotic proteins, inflammatory mediators, and angiogenesis biomarkers. Curcumin is a strong antioxidant and free-radical scavenger, an upregulator of defensive genes and proteins, and a nitric oxide synthase inhibitor. Curcumin is effective in the NMDA-induced damage of cultured retinal cells and is effective on the pro-inflammatory cytokines and against glutamate toxicity, attributed to increased brain-derived neurotropic factor (BDNF) levels. Curcumin inhibits lipid peroxidation and secretion of cytokines such as TNF-α. Curcumin attenuates mitochondrial dysfunction and is reducing reperfusion injury in focal cerebral and retinal ischemia and modulates the cell survival and death signalling pathways by involving Bcl-2, cytochrome-c and caspase-activity. Curcumin has a selective growth-inhibitory effect on glial cell modulation and affects β-amyloid, suppressing oxidative damage and inflammatory signaling pathways. Our lab results showed, that bioavailability of Curcumin could be significantly increased by making complexes with Omega-3 and phospholipids.

Conclusions: Curcumin could be considered as a neuroprotective candidate in glaucoma, since Curcumin: binds to specific and relevant molecules on the target tissue - has adequate penetration to reach the target tissue in pharmacologically effective concentrations, and - enhance neuronal survival and decrease neuronal damage in animal models. With so much potential, the argument for Curcumin’s development for glaucoma is compelling. In Germany, Neuroprotect™ (Nutrition, Science & Health, Munich, Germany) is being used in addition to IOP reduction by more than 80 Ophthalmologists so far. A clinical trial on patients with glaucoma is on its way.
PROTEIN KINASE INHIBITORS AS NEUROPROTECTIVE AGENTS FOR THE TREATMENT OF GLAUCOMA

D. Zack¹, Z. Yang¹, T. Vojkovsky¹, Y. Ge¹, D. Welsbie¹, C. Berlinicke¹, D. Ferraris², B. Slusher², H. Quigley¹

¹Department of Ophthalmology, Wilmer Eye Institute, Johns Hopkins University, Baltimore - USA; ²Department of Ophthalmology, Brain Science Institute, Johns Hopkins University, Baltimore - USA

Background: Although lowering IOP is often effective in slowing down or preventing further optic nerve damage in glaucoma, sometimes it is not possible to lower the IOP sufficiently, and sometimes even with significant IOP lowering retinal ganglion cell (RGC) loss continues. In an effort to complement IOP-based therapies, we have been working to develop neuroprotective strategies for glaucoma treatment. We have performed a high-content screen (HCS) to identify small molecules that can promote RGC survival and neurite outgrowth.

Methods: Primary murine RGCs were purified with anti-Thy1.2 immunopanning, and used to screen various compound libraries with an image-based assay. Identified compounds were investigated by gene expression profiling and phospho-protein analysis. Structural analogs of drug leads were synthesized to study structure-function relationships. RGC survival promoting activity in vivo was tested using animal models of optic nerve injury.

Results: Of the molecules identified by the HCS, one of the most potent at promoting RGC survival and neurite outgrowth is the broad-spectrum receptor tyrosine kinase inhibitor sunitinib, an FDA approved drug that is used for the treatment of a variety of cancers. Sunitinib strongly promotes RGC survival in vitro, and protects RGCs from NMDA excitotoxicity and axon injury-associated degeneration in vivo. Sunitinib can induce changes in the phospho-protein signaling network that favors the inhibition of cell death pathway and stimulation of pro-surviving pathway simultaneously. Screening for additional neuroprotective compounds is continuing, as are further studies designed to define the neuroprotective mechanism(s) by which sunitinib and related kinase inhibitors promote RGC survival.

Conclusions: Protein kinase inhibitors appear to be promising leads for the development of possible neuroprotective drugs for the treatment of glaucoma and other optic nerve diseases.
MELATONIN INCREASES RETINAL GANGLION CELL SURVIVAL IN ISCHEMIC RAT RETINA
S.W. Park¹, H.G. Kim¹
¹Department of Ophthalmology, Chonnam National University Medical School, Gwangju - Korea Republic

Purpose. To determine whether melatonin increase retinal ganglion cell (RGC) survival in ischemic rat retina.
Methods. Sprague-Dawley rats received intraperitoneal injections of melatonin (5 mg/kg) or vehicle and then transient retinal ischemia was induced by acute IOP elevation. RGC survival was measured after Fluoro-Gold labeling. Glial fibrillary acidic protein (GFAP) protein expression and distribution were assessed at 12 hours after ischemia-reperfusion by Western blot and immunohistochemistry.
Results: GFAP protein expression was significantly increased in the early neurodegenerative events (within 12 hours) of ischemic rat retina. The treatment of ischemic rat retina with melatonin resulted in a decrease in the GFAP protein expression and an increase of RGC survival at 2 weeks after ischemia.
Conclusions: These findings suggest that altered GFAP activity following acute IOP elevation may be an important component of a biochemical cascade leading to RGC death in ischemic retina. Thus, these results support further studies to determine whether decreased activity of müller cells by melatonin may provide a novel mechanism to protect RGCs against pressure-related ischemic damage.
NEUROPROTECTIVE EFFECTS OF EXOENZYME C3 TRANSFERASE IN EXCITOTOXIC OPTIC NEUROPATHY

X. Liu¹, Q. Yang¹, L. Guo¹, G. Liu¹, J. Zhu¹, W. Yu¹, P. Kaufman²

¹Ophthalmic Laboratories & Department of Ophthalmology, West China Hospital, Sichuan University, Chengdu - China; ²Department of Ophthalmology & Visual Sciences, University of Wisconsin-Madison, School of Medicine & Public Health, Madison, WI - USA

Background: To evaluate the neuroprotective effects of exoenzyme C3 transferase (C3) on N-methyl-D-aspartate (NMDA)-induced neurotoxicity in the rats.

Methods: C3 was expressed in E.coli, purified by affinity chromatography, and injected intravitreally into rat eyes treated with or without NMDA. At various time points after injection, eyes were nucleated. Western blot analysis of Rho levels was performed on homogenized retinas to confirm Rho inhibition by C3. Terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL) and cresyl violet staining were performed on retina flat-mounts. TUNEL positive cells or cresyl violet-stained cells were counted. Hematoxylin/eosin (HE) staining was also performed on retina cross-sections for morphological analysis.

Results: Western blot showed that Rho expression in rat retinas was inhibited for 2 days after intravitreal injection of C3. Intravitreal injection of NMDA induced apoptosis of neurons within the ganglion cell layer (GCL), accompanied by reduction of cell density in the GCL and decrease in inner plexiform layer (IPL) thickness. Co-injection of C3 reduced retinal ganglion cell (RGC) apoptosis, and increased neuronal density in the GCL and IPL thickness.

Conclusions: C3 protected the retina from excitotoxicitic damages induced by NMDA. C3 might be used in glaucoma treatment, not only for its IOP lowering effects, but also for its neuroprotective potential.

Keywords: glaucoma; retinal ganglion cell; C3; excitotoxicity; neuroprotection
NEUROPROTECTIVE EFFECT OF FASUDIL FOR RETINAL GANGLION CELLS AND ITS MECHANISM RESEARCH IN RAT ACUTE ELEVATED INTRAOCULAR PRESSURE
J. Zhang¹, Z. An²
¹Department of Ophthalmology, Wuhan Union Hospital, Tongji Medical College of Huazhong University of Science and Technology, Hubei Province, China, Wuhan, Hubei Province - China; ²Department of Ophthalmology, Qinghai Traditional Hospital, Xining - China

Backgrounds: To investigate the neuroprotective effect of fasudil for retinal ganglion cells (RGCs) and its mechanism research in rat acute elevated intraocular pressure (IOP).

Methods: 24 SD rats were divided into 4 groups at random: N group (normal), M group(model), MP group (model+PBS: began PBS i.p. 300mg*kg⁻¹ Q.d. a week before the operation) and F group (model+Fasudil: began Fasudil i.p. 300mg*kg⁻¹ Q.d. a week before the operation). Excavating their eyeballs and collecting blood from their hearts 7th day after the operation, TUNEL was employed to observe apoptosis of RGCs, immuno-histological assay to carry out on paraffin sections of retina and to research the distribution and expression of ROCK-2 and ET-1, western blotting to view the expression of p-MYTP-1, radio-immunity assay to survey the content of ET-1 in blood plasma, and blood rheometer to measure the blood viscosities, blood cell aggregation index (BCAI) and hematocrit (HCT).

Results: In N group, ROCK-2 or ET-1 was only distributed in ganglion cells layer (GCL) and not found in other layers. The distribution of ROCK-2 in M or MP group was in GCL, inner plexiform layer (IPL), inner nuclear layer (INL), outer plexiform layer (OPL) and outer nuclear layer (ONL), and ET-1 was in GCL, IPL, INL, OPL but not ONL. In M or MP group, the average optical density (AOD) of ROCK-2 and ET-1 in retina, the expression of p-MYTP-1 in retina and ET-1 in blood plasma, and the blood viscosities, BCAI and HCT were all obviously increased compared with N group (p < 0.05), but there was no significant difference between them (p > 0.05). In F group, the distribution of ROCK-2 and ET-1 was the same as M or MP group, but their AOD in retina, the expression of p-MYTP-1 in retina and ET-1 in blood plasma, and the blood viscosities, BCAI and HCT, and RGCs apoptosis index (AI) were all prominently decreased compared with M or MP group (p < 0.05).

Conclusion: Fasudil could produce neuroprotective effect probably owing to inhibiting ROCK-2, decreasing p-MYTP-1, reducing actin-miosin cross link, restraining smooth muscle contraction, diminishing ET-1, suppressing vasoconstriction, depressing blood viscosity, raising blood flow, enhancing blood and oxygen quantity within eye balls and lessening the apoptosis of RGCs.
Fig. 1 Expression of TUNEL in rats retina of W, MP and F groups (Fig A, N group; Fig B, MP group; Fig C, F group; the positive RGCs in GCL are directed by arrowheads). The positive rate of RGCs in GCL in N or MP group was markedly more than in F group (P<0.05). And there was no prominently difference between W and MP groups (P>0.05).

Fig. 2 Expression of ROCK-2 in rats retina of N, W, MP and F groups (positive RGCs in GCL are directed by arrowheads). In N group (Fig D), ROCK-2 was only distributed in GCL and not found in other layers. The distribution of ROCK-2 in W (Fig E), MP (Fig F) or F (Fig G) group was in GCL, IPL, INL, OPL and ONL. But the positive RGCs in GCL of W or MP group was markedly more than N group (P<0.01). And the positive RGCs in GCL of F group was obviously lesser than N or MP group (P<0.05), but more than N group (P>0.05).

Fig. 3 Expression of ET-1 in rats retina of N, W, MP and F groups (positive RGCs in GCL are directed by arrowheads). In N group (Fig H), ET-1 was only distributed in GCL and not found in other layers. The distribution of ET-1 in W (Fig I), MP (Fig J) or F (Fig K) group was in GCL, IPL, INL and OPL, but not ONL. But the positive RGCs in GCL of W or MP group was markedly more than N group (P<0.01). And the positive RGCs in GCL of F group was obviously lesser than W or MP group (P<0.05), but more than N group (P>0.05).
Fig. 4 Expression of p-MYTP-1 with Western blotting in rat retina of N, M, MP and F groups after acute elevated IOP. Molecular size standards are shown on the right.

Fig. 5 Expression of p-MYTP-1 in rat retina of N, M, MP and F group (grey scale)
MEDICAL TREATMENT: GENE THERAPY
INCREASED RESISTANCE TO OXIDATIVE DNA DAMAGE OF TRABECULAR MESHWORK CELLS BY E. COLI FPG GENE TRANSFECTION

S.C. Saccà, A. Izzotti

1Division of Ophthalmology, St. Martino Hospital, Genoa - Italy, 2Department of Health Sciences, University of Genoa, Genoa - Italy

Oxidative damage plays a pathogenic role in various chronic degenerative diseases. Oxidative damage targeting trabecular meshwork (TM) cells as a consequence of mitochondrial damage is a pathogenic mechanism for glaucoma, the most common cause of irreversible blindness worldwide. Consequences of oxidative damage are attenuated by endocellular activities involved in scavenging reactive oxidative species and DNA repair. Selected bacterial genes are highly efficient at protecting cells from oxidative DNA damage. This situation occurs for *Escherichia coli* formamidopyrimidine DNA glycosylase (FPG), a major DNA glycosylase that repairs oxidatively damaged DNA. Accordingly, we initiated this study aimed at transfecting TM cells with Fpg in order to increase their resistance to oxidative damage. TM cells were transfected with pEGFP-C1-FPG vectors by lipofectamine. Transfected cells were identified and collected by FACS. Oxidative DNA damage was evaluated in FPG-transfected as compared to vector only-transfected TM cells by endonuclease digestion at abasic sites, alkali denaturation and biochip capillary electrophoresis. TM cells were found to be quite resistant to gene transfection as compared to other cell types. FPG-transfected TM cells have a significantly decreased amount of oxidative DNA damage as compared to their wild-type counterparts. In fact, DNA fragmentation resulting from apurinic site formation was 36% lower in Fpg+ than in Fpg- cells (p < 0.05). This study demonstrates that it is feasible to increase resistance of TM cells to endogenous oxidative damage by gene transfection. These findings bear relevance for primary and secondary prevention of degenerative glaucomas and other degenerative diseases where oxidative damage plays a pathogenic role.
MEDICAL TREATMENT: INVESTIGATIONAL DRUGS; PHARMACOLOGICAL EXPERIMENTS
IOP-LOWERING EFFECT OF PROSTANOID EP RECEPTOR AGONIST IN COMBINATION WITH FP RECEPTOR AGONIST

R. Yamagishi\(^1\), M. Aihara\(^1\)

\(^1\)Department of Ophthalmology, University of Tokyo, Tokyo - Japan

**Purpose:** Prostanoid EP2 and EP4 receptor agonists have been reported to lower intraocular pressure (IOP). We also reported that selective agonists of EP2 and EP4 receptor reduced IOP in a dose-dependent manner in mice. However, combined effect of EP receptor agonists on IOP reduction with other ocular hypotensive agents has not been clarified. The purpose of this study is to investigate combined effect on IOP reduction by EP receptor agonists and a first-line drug, FP receptor agonist, in mouse eyes.

**Method:** A single drop with 3 microL aliquots of 0.1% ONO-AE1-259 (EP2 agonist; EP2), 0.1% ONO-AE1-329 (EP4 agonist; EP4), 0.005% latanoprost (FP agonist; LAT) and 5% DMSO as a vehicle solution (DMSO) were topically applied into randomly selected one of two eyes in ddY mouse. To clarify combined effect of EP2 and EP4 with LAT, LAT or DMSO was concomitantly applied 30 min before application of DMSO, LAT, EP2 or EP4. Two hours later, IOP was measured with a microneedle method and IOP reduction was evaluated by the difference between IOP of the treated eye and that of the contralateral control eye.

**Result:** IOP reduction by a single application of DMSO, EP2, EP4 and LAT were -0.8%, 9.8%, 7.8%, and 17.3%, respectively. EP2, EP4 and LAT significantly reduced IOP (p < 0.01 v.s. DMSO by Dunnett test, n = 10). IOP reduction by a concomitant administration of LAT/EP2, LAT/EP4, LAT/LAT, LAT/DMSO and DMSO/DMSO were 17.1%, 23.8%, 18.3%, 15.2%, and 1.4%, respectively. Among them, LAT/EP4 showed significant more IOP reduction than LAT/DMSO (p < 0.05).

**Conclusion:** Additive effect on FP agonist-induced IOP reduction was induced by EP4 agonist, but not by EP2 agonist in mice. EP4 agonist may be expected to be a useful therapeutic agent for IOP reduction in combination with FP agonist.
INTRAMUSCULAR CITICOLINE (CITIDIN-5-PHOSPHOCHOLINE) IS ABLE TO REDUCE PERIMETRIC DEFECTS IN PRIMARY OPEN-ANGLE GLAUCOMA PATIENTS WITH PHARMACOLOGICALLY CONTROLLED INTRAOCULAR PRESSURE. STUDIES ON MECHANISM OF ACTION

M. Virno, J. Pecori-Giraldi

1Department of Ophthalmological Sciences, University of Rome, Rome - Italy

Background: Citicoline represents a passage in the formation of some classes of phospholipids fundamental for the structure and function of neuronic membranes. It has been favorably employed as an anti-ischemic agent in processes of cerebral ageing and in the treatment of both acute and chronic vasculopathies. The action of citicoline in reducing perimetric defects in Primary Open-Angle Glaucoma (POAG) patients was evidenced by Virno et al. in 1988 at the Department of Glaucoma and Ocular Physiopharmacology of the University of Rome “La Sapienza”. Aim of the present study was to investigate on the mechanism of action by which citicoline affects the visual field by means of both clinical and experimental techniques.

Methods: Clinical investigation: 98 patients (196 eyes), range 55-82 years, suffering from POAG, whose intraocular pressure was pharmacologically controlled (within 18 mmHg) but showed a progression of perimetric defects, were treated intramuscularly for 15 consecutive days with 1000 mg citicoline. Humphrey 30-2 full threshold test was performed at baseline (at least 2 to 3 tests) and after 15, 30, 60, 120 and 180 days from beginning of treatment. A double-blind study versus placebo (physiological saline) was performed in 45 POAG patients prior to and after 15 days of the treatment. Moreover, 20 POAG patients were submitted to the “Blue Field” endoptic technique after intravenous administration of 1000 mg citicoline and prior to and after the treatment blood systemic pressure and retinal blood flow were measured. Experimental investigation: a continuous electromanometric recording of both intraocular pressure (IOP) and systemic blood pressure was performed in 22 anesthetized animals (rabbits) following the intravenous administration of 50 mg/Kg of body weight of citicoline.

Results: Clinical investigation After 30 days of intramuscular treatment with 1000 mg citicoline a statistically significant (p = 0.01) improvement of Mean Deviation (MD) was observed in 183 POAG lasting 3 to 6 months: The citicoline administration was repeated every 3 to 6 months according to the response obtained. The double-blind study versus placebo evidenced a statistically significant (p > 0.005) improvement in MD in 22 citicoline treated POAG patients versus 23 untreated POAG patients. The intravenous administration of 1000 mg citicoline in 20 POAG patients induced a statistically significant (p < 0.05) mean increase both of retinal blood flow and systemic blood pressure. Experimental investigation: the continuous electromanometric recording of both IOP and systemic blood pressure in 22 anesthetized rabbits evidenced a mean increase (10 ± 1.88 mmHg) in mean systemic blood pressure following the intravenous administration of 50 mg/Kg body weight of citicoline.

Conclusion: The intramuscular administration of citicoline at the dose of 1000 mg for 15 consecutive days, repeated every 4 to 6 months is able to reduce perimetric defects in POAG patients with pharmacologically controlled IOP but showing a progression of the disease. On the basis of both clinical and experimental data the mechanism of action by which the drug intervenes in restoring part of the visual field in POAG is referable to an increase in perfusion pressure at the level of the intraocular microcirculation “anti-ischemic action".
THE EFFECT OF INTRA-OPERATIVE USE OF TOPICAL MITOMYCIN-C ON INTRA-OCULAR PRESSURE IN PATIENTS WITH PTERYGIUM EXCISION
P.S. Mahar

Section of Ophthalmology, Department of Surgery, Aga Khan University Hospital, Karachi - Pakistan

Background: Topical Mitomycin-C (MMC) is utilized in both glaucoma filtering and pterygium excision surgeries. However, hypotony is an important effect observed in the former, while there is scarcity of evidence to the effect in the latter. The aim of the present study was to determine the effect on Intra-ocular Pressure (IOP) in patients undergoing pterygium excision with intraoperative use of adjunctive topical MMC.

Methods: This was a descriptive, interventional case series of 102 patients (118 eyes) with different grades of pterygium. All patients were assisted at the Ophthalmology Department from 1995 up to 2008 that, having met other inclusion criteria, underwent pterygium excision with adjunctive MMC. Intra-operative topical MMC in a dosage of 0.2 mg/ml was administered between 1 and 5 minutes and changes in IOP were noted on day1, day7 and 3 months. Data were analyzed using proportion, group means, standard deviations, and analysis of variance (ANOVA) and paired student t test.

Results: There was no significant decline in IOP in patients throughout the follow-up period (p = 0.435, student t test). After 3 months post-operatively, 109 eyes (92.4%) had no change in IOP of greater than 5 mmHg. Seventy-eight eyes (72%) experienced minimal change in IOP which was not considered statistically significant followed by 31 eyes (28%) that experienced no change in IOP at 3 months.

Conclusion: Intra-operative topical administration of MMC has minimal effect in lowering IOP in pterygium patients. These results do not seem to support a transscleral effect of MMC on the ciliary body as an IOP lowering mechanism, suggested in the glaucoma filtering surgery.
NEW THERAPIES FOR GLAUCOMA TREATMENT BASED ON TOPICALLY ADMINISTERED siRNAs
A.I. Jiménez1, V. González2, T. Martínez1
1R&D Department, 2Preclinical Department, Sylentis, Madrid - Spain

Background: To find a new treatment for ocular hypertension and open angle glaucoma based on topical administration of small interference RNAs (iRNAs) targeting different genes involved in control of intraocular pressure (IOP). Different siRNAs were designed to target 24 genes involved in intraocular pressure (IOP) regulation. Efficacy of these siRNAs was demonstrated in several validated in vitro and in vivo models.

Methods: Several siRNA sequences, previously validated by in vitro assays, were tested in vivo in normotensive and hypertensive models of New Zealand White rabbit to analyze their effect on IOP. The siRNAs were administered daily as eye drops. Different experiments were performed to evaluate: maximal IOP reduction, longest-lasting time effect, potential for long term treatments, dose-response studies, optimal administration pattern, analysis of in vivo downregulation and preliminary toxicology studies. As controls for in vivo studies, both commercial drugs and scrambled siRNAs, were analyzed.

Results: Different siRNA sequences were demonstrated to effectively reduce elevated IOP and to exhibit much longer lasting effect than commercial drugs. Targeted genes in these studies included carbonic anhydrases, Adrenergic receptors (ADRs), Acetyl-cholinesterase, ELAM-1, Cyclooxygenase, Angiotensin receptors, angiotensin converting enzyme (ACE), renin, Cochlin, ATPases and 11-Hydroxysteroid dehydrogenase (HSD). IOP decrease depends on the targeted gene and the siRNA sequence used, causing an IOP decrease of between 10 and 30 %, with the effect lasting between 30 and 110 hours. The siRNA sequences targeting ADRs, carbonic anhydrases, ATPases and Cochlin genes achieved the highest IOP reduction and longer-lasting effects whereas the siRNAs with lower efficacies were those targeting Angiotensin receptors. Rabbits were treated daily with several siRNAs during one month of and the IOP decrease was maintained with no rebound effect on discontinuation. No side-effects were observed after or during treatment. The in vivo analysis of gene expression of some of these sequences showed a clear reduction of mRNA levels in the ciliary body of treated animals. On the other hand, the preliminary toxicology experiments showed no toxicological effects resulting from siRNA administration.

Conclusions: These results postulate topically administered siRNAs targeting several genes as potential new therapeutic treatments for ocular hypertension and open angle glaucoma. The IOP decrease obtained with specific siRNAs is similar to that produced by commercial drugs but siRNA treatment shows a generalized longer lasting effect when compared to commercials.
PYM50018 AND PYM50028, ORALLY ACTIVE NEUROTROPHIC FACTOR MODULATORS, PROTECTS RAT RETINAL GANGLION CELLS FROM GLUTAMATE-INDUCED NEURONAL DAMAGE IN VITRO
P. Howson¹, C. Ward¹, N. Meyers¹, R. Steinschneider², N. Callizot²
¹Phytopharm plc, Huntingdon - United Kingdom; ²Neuron Experts, Marseille - France

**Background:** Glaucoma is a neurodegenerative disorder characterised by the progressive death of retinal ganglion cells (RGCs) and, in animal models, this loss can be prevented by application of neurotrophic factors, including brain-derived and glial cell line-derived neurotrophic factor (BDNF and GDNF). PYM50018 and PYM50028 are orally active neurotrophic factor modulators. In addition, PYM50028 is currently being evaluated in a Phase II clinical study in Parkinson’s disease patients. PYM50018 and PYM50028 are neuroprotective in a range of neuronal cell types including dopaminergic, cortical and motor neurones and are active in preclinical models of Parkinson’s disease, Alzheimer’s disease and amyotrophic lateral sclerosis, suggesting a potential therapeutic benefit in several neurodegenerative conditions. However, their effect in glaucoma has not been evaluated to-date. This study investigated the neuroprotective effect of PYM50018 and PYM50028 in rat RGCs exposed to glutamate, a model of glaucoma in vitro.

**Methods:** Cultured RGCs were prepared from 7-day old Long Evans rat pup retinas. Dissociated RGCs were cultured at a density of 200000 cells/well in 96 well-plates (pre-coated with poly-L-lysine) at 37°C in a humidified air (95%)/CO₂ (5%) atmosphere in Neurobasal medium supplemented with B27 (2%), L-glutamine (0.2 mM), penicillin/streptomycin solution (1%), ciliary neurotrophic factor (40 ng/ml), BDNF (10 ng/ml) and fibroblast growth factor basic (10 ng/ml). Every two days, half of the medium was replaced with fresh medium. After 3 days, cultures were exposed to glutamate (40 µM, 20 min). Cultures were incubated for 24 h with PYM50018 and PYM50028 either immediately before glutamate exposure (prevention) or immediately after glutamate exposure (reversion). BDNF (50 ng/ml) was used as a reference compound. Twenty-four hours after glutamate exposure cells were fixed in paraformaldehyde (3%) and permeabilised with saponin. Neurones were stained with mouse monoclonal primary β-tubulin followed by Alexa Fluor 488 goat anti-mouse IgG to visualise them. Nuclei of neurones were labelled using Hoechst solution. Six wells per condition per culture were used and 3 independent cultures performed. Neuronal survival was assessed using 10 pictures/well with an InCell Analyzer™ 1000 with 20x magnification. Statistical analysis was performed using a one-way ANOVA followed by Fisher’s PLSD post-hoc test.

**Results:** Glutamate (40 µM, 20 min) significantly reduced RGC survival by ~25% (p < 0.001). Pretreatment of RGCs for 24 h with PYM50018 (300 nM), PYM50028 (300 nM) or BDNF (50 ng/ml) significantly increased cell survival to 92%, 90% and 96% of control respectively (all p < 0.001). Treatment with PYM50018 (3 and 30 nM) for 24 h after glutamate exposure significantly increased cell survival to 88% and 90% of control respectively (both p < 0.001). Treatment with PYM50028 (3, 30 and 300 nM) or BDNF (50 ng/ml) for 24 h after glutamate exposure all significantly increased cell survival to 83% of control (all p < 0.05). PYM50018 (300 nM) increased cell survival to 79% of control but this was not statistically significant (p = 0.126).

**Conclusion:** PYM50018 and PYM50028 significantly reduced glutamate-induced neuronal damage in rat RGCs and were neuroprotective when applied either before or after glutamate exposure. These results support the development of these compounds as a treatment for glaucoma.
EVALUATION OF NEWLY DEVELOPED CATIOPROST®, A PRESERVATIVE-FREE CATIONIC EMULSION OF LATANOPROST IN AN IN VITRO CORNEAL WOUND HEALING MODEL

H. Liang1,2,3,4, C. Baudouin1,2,3,4, P. Daull5, J.-S. Garrigue5, F. Brignole-Baudouin1,2,3,4
1INSERM, UMR_S968, Vision Institute, Paris, France; 2UPMC University, Vision Institute, Paris, France; 3Paris Descartes University, Faculty of Pharmaceutical and Biological Sciences, Toxicology Department, Paris, France; 4Quinze-Vingts National Hospital of Ophthalmology, Paris, France; 5Novagali Pharma, Evry, France

Background: Ocular Surface Disease (OSD) negatively impacts life quality and jeopardizes long-term glaucoma therapy of approximately 60% of glaucoma patients. Therefore, there is a need for preservative-free anti-glaucoma therapies to avoid triggering or worsening of OSD upon treatment. Ideally, such therapies should also possess ocular surface (OS) protection properties to treat OSD. Therefore, Catioprost®, a benzalkonium chloride (BAC)-free cationic emulsion of 0.005% latanoprost was developed. Indeed, cationic emulsions (e. g., Cationorm®) were shown to have OS protection properties improving signs and symptoms of dry eye in clinical trials. Previous preclinical data demonstrated the ocular safety, efficacy and healing properties of Catioprost® and confirmed the deleterious effects of BAC-containing glaucoma therapies. The goal of this study was to investigate and compare Catioprost® to other glaucoma therapies in an established in vitro corneal wound healing model.

Methods: A wound was created by mechanically scraping through a monolayer of confluent immortalized human corneal epithelial (HCE) cells. Cytotoxicity, cell migration and proliferation were analyzed 2h and 1, 3, 6 days after a 30min exposure to either phosphate buffered saline (PBS), 0.02%BAC+latanoprost, 0.01%BAC+tafluprost, 0.015%BAC+travoprost, 0.005%BAC+bimatoprost, Catioprost® and its emulsion vehicle. Immunostaining was performed for Ki67 and Occludin, and TUNEL was assessed to detect apoptosis.

Results: Preserved antiglaucoma eye drops delayed corneal healing primarily related to the concentrations of their common BAC preservative (0.02%BAC+latanoprost > 0.01%BAC+tafluprost > 0.015%BAC+travoprost > 0.005%BAC+bimatoprost), especially from 1 day. The delayed healing observed with all of the BAC-containing solutions was accompanied by the loss of dividing cells (i.e. Ki67-positive cells) and an increased number of apoptotic cells. In contrast, Catioprost® favored the healing process and maintained the capacity of cells to divide. Moreover, when compared to PBS-treated cells, Catioprost® increased rate of wound closure.

Conclusions: This in vitro scraping model allowed us to compare the cytotoxicity and dynamic wound healing capacity of commonly prescribed IOP lowering ophthalmic preparations. We demonstrated that one application of a BAC-containing prostaglandin analogue blocked the wound healing process, and induced apoptosis in a HCE cells monolayer, whereas, BAC-free Catioprost® protected the viability of the HCE cells and accelerated the healing process. Catioprost® appears to have important advantages over existing prostaglandin analogue eye drops and should be of particular interest for the management of glaucoma patients with and without OSD.
A 28-DAY ACTIVE-CONTROLLED, PHASE 2B STUDY ASSESSING THE SAFETY AND OCULAR HYPOTENSIVE EFFICACY OF AR-12286 IN PATIENTS WITH ELEVATED INTRAOCULAR PRESSURE

J. Serle1, G. Novack2, T. Van Haarlem3, C. Kopczynski3
1Mount Sinai School of Medicine, New York - USA; 2PharmLogic Development Development INC, San Rafael - USA; 3Aerie Pharmaceuticals, Inc, Bridgewater - USA

Background: To evaluate the ocular hypotensive efficacy and safety of AR-12286 0.25% and 0.5% Ophthalmic Solutions in comparison to latanoprost in patients previously treated for ocular hypertension or glaucoma. AR-12286 is a selective Rho kinase inhibitor that lowers intraocular pressure (IOP) by increasing trabecular outflow.

Methods: Double-masked, active-controlled, randomized clinical trial. Subjects (n = 217) were randomly assigned to receive AR-12286 0.25% b.i.d., AR-12286 0.5% q.d. PM, or latanoprost q.d. PM for 28 days. Primary and secondary efficacy endpoints were mean IOP at each diurnal time point (8 am, 10 am, 12 pm, and 4 pm) on days 14 and 28 and mean change in IOP from diurnal baseline, respectively.

Results: Both concentrations of AR-12286 produced statistically and clinically significant reductions in mean IOP at all time points across days 14 and 28. Mean IOP ranged from 18.0 to 21.8 mmHg (-6.0 to -3.9 mmHg) for AR-12286 0.25% b.i.d., 18.0 to 20.4 mmHg (-6.1 to -2.9 mmHg) for AR-12286 0.5% q.d., and 17.5 to 19.0 mmHg (-7.0 to -4.4 mmHg) for latanoprost q.d. AR-12286 0.5% provided a superior diurnal IOP profile compared to AR-12286 0.25% due to better control of IOP at 8 am (12 hours after pm dosing). The overall difference in mean diurnal IOP between AR-12286 0.5% and latanoprost was +0.9 mmHg (p = 0.002) in favor of latanoprost. This difference was +0.5 mmHg (p = 0.051) when responder sub-groups (mean IOP reduction > 5%) were compared. The only adverse events of note for AR-12286 0.5% were conjunctival hyperemia, which typically resolved during sleep, and mild stinging upon instillation. Two out of 140 AR-12286 patients were discontinued for hyperemia (1 -0.25%, 1 - 0.5%).

Conclusions: AR-12286 0.5% dosed q.d. PM provided better control of diurnal IOP than AR-12286 0.25% dosed b.i.d., was slightly less efficacious than latanoprost, and was well tolerated. There were no drug-related serious adverse events in the study.
A TWELVE-MONTH OPEN-LABEL SAFETY STUDY OF POLYQUATERNIUM-PRESERVED DUOTRAV
I. Stalmans
1Adjunct Clinic Head, Ophthalmology Department, University Hospitals Leuven, Leuven - Belgium

Background: DuoTrav, preserved with benzalkonium chloride (BAK), is a combination eye drop containing a topical prostaglandin analogue, travoprost 40 µg/mL, and a topical beta-adrenergic receptor blocking agent, timolol 5 mg/mL. DuoTrav is indicated for the reduction of IOP in adult patients with open-angle glaucoma or ocular hypertension who are insufficiently responsive to topical beta-blockers or prostaglandin analogues. A new formulation of DuoTrav has been developed which uses polyquaternium-1 (PQ) as the preservative. The primary objective of this clinical trial was to evaluate the long-term safety of DuoTrav (PQ-preserved) in patients with open-angle glaucoma or ocular hypertension.

Methods: One hundred fifty-four patients (18 to 85 years of age) with open-angle glaucoma or ocular hypertension were enrolled in this 12-month open-label safety study. Patients received DuoTrav (PQ-preserved) once daily at 9 AM for 12 months and returned for follow-up examinations at 6 weeks, 3 months, 6 months, 9 months, and 12 months. Safety assessments included best-corrected visual acuity, ocular signs (eyelids/conjunctiva, cornea, iris/anterior chamber, lens), pachymetry, automated perimetry, tonometry, ophthalmoscopy (vitreous, retina/macula/choroid, optic nerve, cup/disc ratio), cardiovascular parameters (pulse and blood pressure), and adverse events.

Results: No safety issues with DuoTrav (PQ-preserved) were identified based upon a review of changes from baseline for best-corrected visual acuity, ocular signs, IOP, ophthalmoscopy, corneal thickness, visual fields, and pulse and blood pressure. No serious adverse events assessed as related to the use of DuoTrav (PQ-preserved) were reported during the study. Twelve patients reported serious adverse events unrelated to the use of DuoTrav (PQ-preserved). Adverse events reported in this trial were consistent with the established safety profile of DuoTrav (BAK-preserved) or its individual components.

Conclusions: The overall safety profile of DuoTrav (PQ-preserved) administered for 12 months was consistent with the established safety profile of DuoTrav (BAK-preserved) or its individual components. Further studies are required to confirm the benefits of the BAK-free formulation on ocular surface of patients with open-angle glaucoma or ocular hypertension.
Background: Taprenepag is an investigational EP2 agonist under evaluation as monotherapy and in combination with latanoprost for reduction of elevated IOP.

Methods: Safety, efficacy, and dose-response of taprenepag once-daily topical ocular solution was assessed in preclinical models (rabbits, dogs, nonhuman primates) and in 2 Phase II trials in subjects with open angle glaucoma or ocular hypertension. In 30 subjects, serial corneal staining and pachymetry were assessed in addition to full 24-hour IOP evaluation in habitual body position.

Results: Taprenepag significantly lowered IOP and provided 24-hour control in normotensive and glaucomatous dogs and in ocular hypertensive nonhuman primates. Taprenepag induced dose-dependent conjunctival hyperemia in dogs and rabbits. At high doses in the primate, taprenepag induced iritis, severe conjunctival hyperemia, and increased corneal thickness. There was no specular microscopic, histological, or transmission electron microscopic evidence of toxicity to the cornea or its endothelium. The adverse events resolved with discontinuation of the medication. A total of 347 ocular hypertensive and open angle glaucoma subjects were treated with taprenepag alone or in an unfixed combination with latanoprost 0.005% once daily for a maximum of 28 days. Taprenepag significantly lowered IOP during both day and night-time hours. IOP reduction with monotherapy was comparable to latanoprost; combination therapy produced mean diurnal IOP reduction ~ 2 mmHg greater than latanoprost alone. The taprenepag related emergent adverse events were mild to moderate conjunctival hyperemia, photophobia, corneal staining and increased corneal thickness. There was no evidence of taprenepag toxicity to the corneal endothelium, stromal kerocytes or basal cell epithelium on confocal microscopy (Nidek ConfoScan 4). Mild corneal staining and disturbance of the superficial corneal epithelium may explain the observed increase in anterior stromal reflectivity.

Conclusions: Taprenepag significantly reduces IOP and maintains control for at least 24 hours. Treatment-related adverse events were mild to moderate and resolved without sequelae. Because of its novel mechanism of action, taprenepag is additive to the IOP-reducing effect of latanoprost 0.005% and may show similar additivity to other ocular antihypertensive medications.
MEDICAL TREATMENT: OTHER DRUGS IN RELATION TO GLAUCOMA
OCULAR HYPERTENSION AFTER INTRAVITREAL APPLICATION OF TRIAMCINOLON- ACETONIDE IN THE TREATMENT OF MACULAR EDEMA

M. Janićijević-Petrović¹, T. Sarenac¹, S. Srećković¹, N. Petrović¹, M. Simeunović¹, D. Vučović²
¹Clinic of Ophthalmology, Clinical Centre Kragujevac, Kragujevac - Serbia; ²Medical Faculty, University of Kragujevac, Kragujevac - Serbia

Background: The aim of our study was to investigate frequency of ocular hypertension at the patients, who were treated with intravitreal triamcinolone- acetonide for the treatment of macular edema.

Methods: We examined 60 eyes (60 patients) with diffuse diabetic macular edema, who were not treated with laserphotocoagulation before. We applied 25 mg triamcinolone-acetonide intravitreal. We examined the results in the period of three years of: visual acuity, intraocular pressure (IOP) and biomicroscopic examination of the anterior and posterior segment of the eye.

Results: We noticed increasing of IOP (more than 22mmHg) at 34 eyes (56.7%). The period when we notified this increasing was about 1.55 ± 1.63 months after intravitreal application of triamcinolone-acetonide. At 33 patients (97.1%), where we noticed increased IOP, we regulated IOP of our patients with local medicament therapy. At one patient filtrating surgery was necessary. Regulating of the IOP without medicament therapy was achieved 9.41 ± 2.51 months after intravitreal application of triamcinolone-acetonide.

Conclusion: We notified significant increasing of IOP after intravitreal application of triamcinolone-acetonide, even if we got good results with reduction of macular edema and increasing of visual acuity.
EFFICACY AND SAFETY OF THE FIXED COMBINATION TRAVOPROST/TIMOLOL VERSUS DORZOLAMIDE/TIMOLOL IN PATIENTS WITH OPEN-ANGLE GLAUCOMA OR OCULAR HYPERTENSION

N. Babic1, V. Andreic1, A. Miljkovic1
1Eye Clinic, Clinical Center Vojvodina, Novi Sad - Serbia

Background: To compare the efficacy and safety of the fixed combination travoprost 0.004%/timolol 0.5% versus fixed combination dorzolamide 2%/timolol 0.5% in patients with open-angle glaucoma or ocular hypertension.

Methods: Three-month, prospective clinical study included 60 patients with open-angle glaucoma or ocular hypertension who were randomized into 2 groups to receive fixed combination travoprost/timolol once daily in the morning and fixed combination dorzolamide/timolol twice daily. Follow-up was done at 14 and 45 days and 3 months. Intraocular pressure measurements were taken at each follow-up examination at 8 am, 10 am and 4 pm.

Results: Both fixed combination reduced intraocular pressure significantly at all follow-up and times of day (p < 0.001). For all visits the mean diurnal IOP was 16.13 mmHg for the travoprost/timolol group and 16.15 mmHg for dorzolamide/timolol group. The mean intraocular pressure reduction from baseline was greater for travoprost/timolol fixed group -8.96 mmHg (-7.46 mmHg to -9.92 mmHg) than for dorzolamide/timolol fixed group -8.07 mmHg (-6.93 mmHg to -8.93 mmHg) [p = 0.196]. The most frequent treatment related adverse events were conjunctival hyperemia in travoprost/timolol fixed group and dry eye and foreign body sensation in dorzolamide/timolol fixed group.

Conclusions: Travoprost/timolol fixed combination was slightly more effective than dorzolamide/timolol fixed combination in reducing mean diurnal intraocular pressure. Travoprost/timolol fixed combination resulted in an intraocular pressure reduction up to 1.07 mmHg greater that dorzolamide/timolol fixed group. Both fixed combination were well tolerated and safe.
THE PROTECTIVE EFFECT OF STATINS AND COMPARISON OF SEVERITY OF GLAUCOMA AMONG PATIENTS ON STATINS AND WITHOUT STATINS IN A COMMUNITY BASED GLAUCOMA PRACTICE

S. Sonty

1Dept of Ophthalmology UIC Eye Center Chicago, Chicago - USA

Background: Studies have shown lower prevalence of primary open angle glaucoma and slowed progression of optic nerve head parameters in glaucoma suspects on oral statin therapy. The purpose of this study is to determine the protective effect of the oral statin therapy on the severity of glaucoma in primary open angle glaucoma patients.

Materials and Methods: A retrospective study of 287 primary open angle glaucoma (POAG) patients, classified by race, gender, and age, was conducted. POAG patients are identified by statin use (CWS, &AABS) and without statin use (CNS & AABNS). POAG was stratified by severity of nerve damage and visual field loss by GDX/OCT imaging, HVF perimetry, and CD ratios. Duration of statin use was classified as short (1-5 yrs), medium (6-10 yrs), and long (11+ yrs).

Results: 176 African Americans (AAB) and 110 Caucasians (CW) were analyzed and classified as normal (N), early (E), intermediate (I), and severe (S) for each test using normative databases by color coding white/green (N), blue (E), yellow (I), and red (S) on (GDX/OCT), CD ratios by 0.0-0.3 (N), 0.4-0.5 (E), 0.6-0.7 (I), and 0.8-1.0 (S) values, and HVF (MD) values. +1.0-1.0 (N), -1.1-5.9 (E), -6.0-10.9 (I), and > -11 (S). The patients were grouped N & E and I & S. Combined AA & W analyses of more severe eyes in each patient showed less prevalence of severe glaucoma in the statin group. HVF p = 0.04, GDX/OCT p = 0.21, CDR p = 0.39, and when both eyes were analyzed, CW patients showed more significant protection to severity than AAB. HVF p = 0.005 vs p = 0.13, GDX/OCT p = 0.03 vs p = 0.82, and CDR p = 0.18 vs p = 0.9. In CW, statin therapy was less frequent in the I & S group than AAB.

Conclusions: This study showed in patients on statin therapy, CW patients have less prevalence of I & S and higher prevalence of N & E level than AAB. The duration of statin use affected CW patients more positively (25% vs 33%) than AAB patients.

![Graph showing percentages of N & E and I & S for Statin and Nonstatin groups among African American and Caucasian patients.](image-url)
Severity vs. Duration of Statin Use for GDX - OCT

Severity vs. Duration of Statin Use for HVF
COMPARISON OF THE EFFECT OF BIMATOPROST-TIMOLOL FIXED COMBINATION AND TRAVOPROST-TIMOLOL FIXED COMBINATION ON INTRAOCULAR PRESSURE IN PATIENTS WITH PRIMARY OPEN ANGLE GLAUCOMA OR OCULAR HYPERTENSION

L. Ming Yueh

Department of Ophthalmology, Kuala Lumpur Hospital, Kuala Lumpur - Malaysia

**Background:** Fixed combination of glaucoma medicines improves compliance and adherence to treatment. Nevertheless, the current available fixed combination of Latanoprost and Timolol was showed to be less effective than the non-fixed combination of their counterpart. Thus it was not widely prescribed. This study was designed to identify a fixed combination of Prostaglandin & Timolol to replace a non-fixed combination of Latanoprost & Timolol which are commonly used in our setting. It has a secondary objective to increase compliance and adherence and to cut cost on glaucoma medicine expenditure. We compared the effect of fixed combination of Bimatoprost & Timolol (BTFC) and fixed combination of Travaprost & Timolol (TTFC) on intraocular pressure (IOP) in patients with primary open angle glaucoma (POAG) or ocular hypertension (OHT) after they were switched from a non-fixed combination of Latanoprost & Timolol (LTNFC).

**Methods:** It was a prospective, randomized, observer-masked, crossover comparison study. 41 consecutive patients with POAG or OHT patients whose IOP were controlled (IOP ≤ 21mmHg) on LTNFC for at least 3 months before baseline visit were randomized to either BTFC or TTFC for a 8-weeks treatment period. IOP was measured at baseline and at the end of 8-weeks for each drug at 8AM, 12PM, 4PM and 8PM. After the first treatment with either BTFC or TTFC for a period of 8 weeks, diurnal IOP measurement was performed. The patients were then switched to the opposite drug without a medication-free period. Diurnal IOP measurement was again performed at the end of the second 8-weeks treatment period. The main outcome measure was the mean IOP of the 12-hour IOP curve and mean baseline IOP at each time point (8AM, 12PM, 4PM and 8PM) at baseline, compared to BTFC and TTFC after 8-weeks of treatment. Conjunctiva hyperaemia and Superficial Punctate Keratopathy (SPK) at baseline and after 8-weeks of treatment with BTFC and TTFC were graded and analyzed.

**Results:** There were no statistically significant differences in IOP lowering between BTFC and TTFC at all time-points after a period of 8-weeks treatment. However, both BTFC and TTFC reduced the mean IOP from baseline (LTNFC). BTFC reduced the mean IOP at baseline significantly statistically from 17.3 mmHg (95% CI) to 16.4 mmHg (p = 0.036). The IOP was lower at all time-points compared to baseline and statistical significance were achieved at 4 PM and 8 PM. TTFC lowered the IOP to 17.1 mmHg but it was not statistically significant. TTFC reduced the IOP at 12 PM, 4 PM and 8 PM but showed increased level at 8 AM. Both BTFC and TTFC had no significance difference effect in term of conjunctiva hyperaemia compared to baseline. However there was significantly less SPK after 8-weeks treatment with TTFC (p = 0.012). Both treatments showed similar tolerability profile.

**Conclusions:** Both BTFC and TTFC are comparable in IOP lowering effect. BTFC had showed significant reduction of mean IOP from baseline and at 4 PM and 8 PM. Both BTFC and TTFC showed good tolerability and TTFC had demonstrated significant less effect of SPK.
COMPARATIVE STUDY OF THE EFFICACY AND SAFETY OF A FIXED COMBINATION OF DORZOLAMIDE-TIMOLOL AND BRIMONIDINE-TIMOLOL IN PATIENTS WITH OPEN ANGLE GLAUCOMA AND OCULAR HYPERTENSION
T. Gil-Martinez¹, R. Castellanos¹, M. Boissiere¹, M. Vargas¹, A. Bruzual¹, J.C. Vieira¹
¹Glaucoma Service, Caracas - Venezuela

Background: To evaluate the efficacy and safety between Fixed combination of Dorzolamide-Timolol and Brimonidine-Timolol in patients with Open Angle Glaucoma (OAG) and Ocular hypertension (OH).

Methods: A prospective, multicentric, randomized, and simple blind clinic study with 3 months of follow-up in patients with OAG and OH. Patients were randomized in two groups: Group A Dorzolamide-timolol and group B Brimonidine-timolol twice a day. Intraocular pressure (IOP) was measured at the beginning of treatment and 4, 8 and 12 weeks after. Arterial pressure, heart beat and local side effects survey were also registered. Statistical analysis was made using Student Test for non pared samples.

Results: Forty-eight patients (48 eyes), 26 in group A and 22 in group B were treated. A reduction of IOP from basal was -8.92 mmHg, -9.35 mmHg and -9.08 mmHg in group A and -7.64 mmHG, -7.82 mmHG and -8.86 mmHG in group B at 4.8 and 12 weeks respectively. These values were not statistically different. No changes were seen in arterial pressure and heart beat. Local side effects as itching and burning were more frequent in group B so as pain was in group A.

Conclusions: Both medical treatments showed the same efficacy and safety in patients with OAG and OH. Nevertheless, IOP reduction was clinically more significant in group A.
MEDICAL TREATMENT: VEHICLES, DELIVERY SYSTEMS, PHARMACOKINETICS, FORMULATION
NONCLINICAL ASSESSMENT OF THE EFFECT OF TAPRENEPAG ISOPROPYL (PF-04217329) DOSES AND FORMULATIONS ON INTRAOCULAR EXPOSURE OF THE ACTIVE METABOLITE OF TAPRENEPAG (CP-544326)

M.H. I. Shiue1, B. Jessen2, S. Raber3, R.A. Schachar4, J. Shah5, D. Arenson5, T. Zhou5

1Pharmacokinetics, 2Drug Safety R&D, Dynamic & Drug Metabolism, 3Clinical Pharmacology, 4Ophthalmology, 5Pharmaceutical Sciences, Pfizer Global R&D, San Diego, CA - USA

Background: The current investigation elucidates potential effects of topical administration of taprenepag (PF-04217329) formulation strength and composition on the ocular pharmacokinetic profile of its active metabolite, CP-544326. The results help inform a minimum taprenepag (PF-04217329) dose and formulation required for achieving maximum intraocular CP-544326 exposure and/or clinical efficacy for reducing intraocular pressure (IOP).

Methods: Dutch belted pigmented rabbits (N = 70) were dosed topically with taprenepag (PF-04217329) solutions prepared in formulations A and B used in the Phase 2 clinical trials, or multiple variations of formulation B with different taprenepag (PF-04217329) and solubilizing agent concentrations resulting in different solution saturation levels. The rabbits were sacrificed at predetermined time points within 12 hours following the application of the eye drops, and the exposure levels of CP-544326 were measured in cornea, aqueous humor, and iris/ciliary body (ICB). The collected samples were analyzed using LC-MS/MS methods. All rabbit studies were conducted in accordance with the Animal Welfare Act, the Guide for the Care and Use of Laboratory Animals and the Office of Animal Welfare.

Results: In all formulations, the descending order of exposure to CP-544326 in rabbit ocular tissues was cornea > aqueous humor > ICB. Taprenepag (PF-04217329) prepared in formulation B and its variations resulted in 2-3 fold higher bioavailability of CP-544326 in all rabbit ocular tissues compared to administration of taprenepag (PF-04217329) prepared in formulation A. Among formulation B and its variations, intraocular CP-544326 exposure was driven mainly by taprenepag (PF-04217329) concentration and was not significantly affected by the amount of solubilizing agent or degree of saturation.

Conclusions: The current investigation suggests that ocular exposure of CP-544326 appears to be influenced mainly by taprenepag (PF-04217329) concentration. Other formulation components such as osmolarity, buffering, and chelating agents and pH may have contributed to ocular CP-544326 bioavailability as well.
MEDICAL TREATMENT: COOPERATION WITH MEDICAL THERAPY E.G. PERSISTENCY, COMPLIANCE, ADHERENCE
MULTICENTER STUDY OF COMPLIANCE AND VIDEO-TAPED EVALUATION OF EYE DROP INSTILLATION IN GLAUCOMA PATIENTS

Z. Mandic

1University Eye Clinic, Zagreb - Croatia

Purpose: To assess the prevalence of noncompliance and evaluate improper administration single drop onto their eye among the glaucoma patients

Methods: 120 glaucoma patients from 4 different hospitals were evaluated using a carefully prepared questionnaires. Noncompliance was defined as missing at least 1 drop of medication per week. Patients were asked to indicate the most common reason for missing medication. Instillation of one eye drop into their eye were video-recorded and analyzed.

Results: 120 patients with glaucoma participated in the study. Of these, 41 (33.1%) reported missing at least 1 drop of medication per week and 7 (5.8%) were unable to accurately describe their medication regime. Forgetfulness, unavailability of eye drops were the most cited reasons for non-adherence. With regard to drop administration 18 (15.0%) missed their eye, and 32 (26.6%) contaminated the bottle tip. Factors associated with improper administration technique were 60 years and older, but there were no association between non adherence and sex, level of education and family history of glaucoma.

Conclusion: Non-adherence to topical glaucoma medication is fairly common and patients demonstrated improper administration technique. They should be educated on the importance of compliance and instructed on proper drop administration.
ADHERENCE TO MEDICATION AND CO-RELATION TO KNOWLEDGE OF GLAUCOMA AND MULTIDIMENTIONAL HEALTH LOCUS OF CONTROL

A. Niranjan¹, G. Murthy¹
¹Glaucoma Service, Vittala International Institute of Ophthalmology, Bangalore - India

Background: In Glaucoma, the nature of the disorder and lack of an immediate perceptible benefit with daily therapy might well foster nonadherence. There is no single determinant of nonadherence. Patients are the final health decision makers and their inherent beliefs about what controls and affects their health are crucial in their adherence behavior. Psychological assessment questionnaires are used to classify patients’ attitude towards their illnesses. Little is known if such classification can help predict patient adherence behavior.

Aims: 1. To estimate the awareness and knowledge about glaucoma in patients diagnosed with glaucoma; 2. To determine self reported adherence/non adherence to glaucoma medications; 3. To evaluate Multidimensional Locus of Control in patients and co-relate with reported adherence to medication.

Design: Clinic based cross sectional study.

Methods: This cross sectional analysis examined 164 consecutive patients. All glaucoma patients who had been prescribed one or more topical anti-glaucoma medications at least for the past 6 months were included in the study. Self reported adherence was assessed using Morisky’s self-report questionnaire. Basic knowledge about glaucoma was tested using 6 questions. The Multidimensional Locus of Control (MHLC) questionnaire measured three dimensions of locus of control of reinforcement as it pertains to health - internal, chance, and external powerful and others. The questionnaires were administered either in a glaucoma information meeting with small groups of 10-20 patients, or by face to face interviews by a single interviewer. In addition to the questionnaire based assessment of adherence, an objective assessment was attempted by collecting the medication bottles in a subset of the sample to determine the number of drops used in a specified time. The two methods of classification, namely questionnaire based, and drop counting methods of adherence were compared for agreement.

Results: 60 (36.6%) were classified as adherent, 62 (37.8%) were moderately adherent, and 42 (25.6%) were non adherent by the self-reported questionnaire. 60.6% of the nonadherers were males. Adherers did not differ significantly from nonadherers in age, education or number of glaucoma medications. Patients with other pre-existing co-morbid conditions were found to be significantly more adherent than others (p = 0.038). 74 (45.1%) patients had good knowledge about glaucoma, but this was not statistically significant when co-related to adherence. Of the nonadherers (n = 104), 43.3% had a predominantly ‘chance’ LOC, 34.6% had a predominantly ‘Internal’ LOC and 22.1% had an ‘external’ LOC. But none of these could predict adherence behaviour. By the drop counting method, 77.3% (N = 58) were classified as adherent and 22.7% (N = 17) were found to be nonadherent. People who claimed to be adherent in the questionnaire were also likely found to be adherent by the drop counting method.

Conclusion: In a country like India, there is no scope for assessing adherence by pharmacy data or use of electronic devices. It is difficult to get a true estimate of adherence. Even an indirect estimate by counting the drops in the medication bottles could not easily pick up non-adherers. The Locus Of control has been useful in predicting adherence behavior in other systemic illnesses, however in Glaucoma; this relation could not be demonstrated.
EASE OF ADMINISTRATION OF ANTIGLAUCOMA MEDICATION: MONODOSE VERSUS MULTIDOSE VIALS

T. Shaarawy¹
¹Clinique d'Ophthalmologie, Hopitaux Universitaire, Geneve, Switzerland

Background: There is evidence that between 28 to 58% patients do not use their anti glaucoma medication as prescribed, with non compliance ranging from 30-40%. This is a serious limiting factor in glaucoma therapy as patients require long term care for a disease which is largely asymptomatic. The reasons for non compliance are varied, ranging from economics, lack of understanding of the nature of disease, and poor access to medication. Patient factors like forgetfulness and side effects of the medication, both ocular and systemic, are also important considerations. With an aging population demographics worldwide, the patients inability to use the medication assumes great importance. This study aims to evaluate the ease of administration of antiglaucoma medication and correlates it to the use of monodose and multidose vials.

Methods: 65 patients on anti glaucoma therapy for a mean duration of 105.2 ± 91.2 months (range 2-360; median 120 months) were included in this questionnaire based non interventional study. A four point questionnaire with binary end points was completed by patients and evaluated subsequently. The level of statistical significance was set as p < 0.05.

Results: Out of the 65 patients recruited for the study, 29 were using monodose vials, while 36 used the multidose conventional bottles. The mean age of the patients enrolled in this study was 73.7 ± 8.8 years (75, range 52-93 years); with 37 males and 28 females. The age distribution in the multidose and monodose groups were not found to be statistically significant, and were 74.6 ± 9.9 years (median 75.5, range 52-93) and 72.5 ± 7.2 years (median 73, range 54-89) respectively (p = 0.33). 26 out of 65 (40%) were unable to put the drops themselves, and required external assistance. No patients below the age of 68 years need assistance for administration of eyedrops. A significant correlation was noticed between age and difficulty of administration of eyedrops (p < 0.02). Number of women needing assistance was found to be 13/28; as against 13/37 men, but the difference was not found to be statistically significant. The need for assistance as well as difficulty in administration were found to be significantly dependent on the number of glaucoma medications instilled.

The difficulty in administration, as well as the need for a caregiver for administer the drops, were not correlated with gender, duration of disease or the vial used. The patients on monodoses were not found to be more likely (Mann Whitney Rank Sum Test, p = 0.56) to request a change in their medication depending on ease of administration, in comparison to the patient on multidoses. Patient satisfaction with the monodose vial was not found to be more than that with the multidose vial (Mann Whitney Rank Sum Test, p = 0.560.54).

Conclusion: As many as forty percent patients require external assistance in using their antiglaucoma medication, and this can potentially affect compliance. This becomes increasingly relevant in an ageing population, as disease severity and the use of multiple medications becomes more frequent. Patients do not report a difference in the ease of administration using monodose or multidose vials.
WHICH ONE IS MORE EFFECTIVE AND SAFE?
T. Tuna¹, M. Unal¹, G. Koklu¹, A.G. Kocak Altintas¹
¹Ministry of Health Ulucanlar Eye Research and Education Hospital, Ankara - Turkey

Background: To compare the reducing effect of intraocular pressure (IOP) and the safety of the fixed combination (FC) of dorzolamid/timolol, FC of latanoprost/timolol, and FC of travoprost/timolol administered in POAG patients.

Methods: 60 POAG patients, where monotherapy is inadequate, were separated 3 groups. First group received once-daily morning dose of the fixed combination latanoprost and timolol. Second group received twice-daily dose of the fixed combination of the dorzolamid and timolol and last group received once-daily evening dose of the fixed combination of the travoprost and timolol for months. The IOP was measured at 08:00, 12:00, and 16:00 at baselines at the end of first month and third month. Adverse events were recorded at each visit.

Results: All 60 patients were included in observed cases analyses. Mean IOP at baseline was 27.3 mmHg in all groups. With respect to baseline, mean reductions in day time IOP at the end of 3 months were 9.5 mmHg, 9.7 mmHg and 9.7 mmHg respectively in all groups. All treatments were well-tolerated.

Conclusion: The study showed that when monotherapy is inadequate, all of the FC treatments result in significant decreases both clinically and statistically, in post-baseline IOP levels and are well tolerated.
Background: A number of studies have reported poor persistence with glaucoma medications. However, biases induced by the use of pharmacy databases and short study durations have raised questions concerning the accuracy of this data. This study assessed persistence with and adherence to glaucoma therapy in a highly inclusive national population over at least 4 years.

Methods: Data was drawn from Australia's universal Pharmaceutical Benefits Scheme (PBS). The dataset consists of random 1 in 10 dispensed claims in the period June 2002 to March 2010. Estimates were validated against the independently published PBS website statistics for each product. Persistence was measured using a 6 month initiation period of no therapy, 3 and 6 month cessation periods for all patients and a long term concessional cohort in the initiation window from October 2005 to September 2009. All glaucoma medications where tested using proportional hazards ratio with Latanoprost as the comparator. Persistence by patient gender, age, patient concessional status and prescriber type was also measured using both cessation rulings.

Results: During this period 17,442 patients were initiated on glaucoma medications. Using the 3 month cessation ruling, patient persistence at 6 months was 47.6%, at 12 months 39.4%, at 48 months 23.7% with a median persistence of 9 months. Using the 6 month cessation ruling patient persistence at 6 months was 55.7%, at 12 months 47.8% and at 48 months 30.2% with a median persistence of 9 months. The mean periods of therapy from initiation to censorship for both groups were 5.14 and 5.31 months respectively. Latanoprost showed significant differences in patient persistence with therapy compared to other medications.

Conclusions: Persistence with glaucoma therapy in this inclusive long term study was poor and similar to estimates in previous studies. This suggests a substantial disconnect between prescribers intentions and patient behaviour. Loss to follow-up may be a major reason for poor persistence and with glaucoma medications.
MEDICAL TREATMENT: OTHER
AN EVALUATION OF THE USEFULNESS OF A UNILOCAL TRIAL OF TOPICAL GLAUCOMA MEDICATION WHEN INITIATING THERAPY

S. Uppal, A. Lakshmanan, A. Abedin, E. Henry, A. Rotchford, A. King

1Department of Ophthalmology, Queen’s Medical Centre, Nottingham - United Kingdom

Purpose: To assess the value of a uniocular trial.

Methods: Twenty eight phakic patients with untreated open angle glaucoma or ocular hypertension and IOP > 21 mmHg in both eyes were included. IOP was measured at 8 am, 11 am and 4 pm on one day a week for three weeks. On the third week travoprost was started in the eye with the higher IOP, on week 4 treatment was started in the second eye and measurements were made over the following 3 weeks.

Results: 28 patients recruited. 392 separate measurements at 11 am. Regression to mean demonstrated in both eyes (V0 - mean V1, V2, V3). Difference noted between adjusted and unadjusted IOP values for first eye. Significant reduction in IOP for both eyes with Travatan (true effect). First eye = 8.5 mmHg [(mean V1, V2, V3) - (mean V5, V6, V7)]. Second eye = 6.8 mmHg [(mean V1, V2, V3) - (mean V5, V6, V7)]. No significant difference between adjusted IOP and true mean effect in first eye

Discussion: The value of a uniocular trial of topical glaucoma medication in predicting a response to medication is a controversial approach to commencement of therapy and the results in the literature are inconclusive. Our study shows that a uniocular trial of topical glaucoma medication results in a measurable reduction of pressure in the treated eye which remains when adjustment for regression to the mean is made.

Conclusion: A uniocular trial is a useful clinical indicator of an individual’s response to a glaucoma drop.
COMPARATION OF TEAR FILM STATUS OF PATIENTS WITH GLAUCOMA AND CONTROL GROUP
S. Jandrokovic¹, I. Petriček¹, S. Peric¹
¹Clinical Hospital Center Zagreb, Department of Ophthalmology, Zagreb - Croatia

Background: To determine the condition of the tear film glaucoma patients. Compare the result with the control group. Establish a connection tests results with the subjective symptoms, the duration of glaucoma treatment and with amount of off drugs in the treatment of glaucoma therapy.

Methods: A prospective study which involved 31 respondents (statistically 62), older than 40 years, divided into two groups: Glaucomatous patients. Control group. In assessing the state of the tear film were used to search: Slit lamp examination TBUT Schirmer test 1 Standardized questionnaire on subjective symptoms.

Results and Conclusion: The amount of drugs affect the condition of the tear film by TBUT. What's more drugs in the treatment to the poorer tear film. Patients in the first year of treatment had a worse state of the tear film. Duration of therapy has no effect on tear film. General therapy may have an impact on the tear film, especially therapy for cardiovascular disease.
ELEVATED SYSTOLIC BLOOD PRESSURE ASSOCIATED TO THE USE OF LATANOPROST
L. Palmero-Fernández¹, E. Santos-Bueso¹, F. Sáenz-Francés-San-Baldomero¹, Ana Fernández-Vidal¹, J.-M. Martínez-de-la-Casa¹, C.-D. Méndez-Hernández¹, J. García-Feijóo¹, J. García-Sánchez¹
¹Department of Ophthalmology, Hospital Clínico San Carlos, Madrid - Spain

Background: a case of elevated blood pressure (BP) associated with the use of latanoprost.

Methods: the daughter of a patient diagnosed with primary open-angle glaucoma, and who controlled her mother’s BP at home, reported an increase in both systolic (ST) and diastolic (DT) blood pressures after beginning treatment with latanoprost. We decided to stop the treatment for 6 weeks and afterwards to monitor her BP without any ocular hypotensive medication for one month (every 3 days, measuring the BP at 9 AM, 3 PM and 9 PM). After that, we prescribed latanoprost one drop per day on both eyes at 8 PM and, after 6 weeks, we monitored again her BP every 3 days - again three times a day - for one month.

Results: Saphiro-Wilk test did not reveal any violation of normality for all the variables considered. We obtained both systolic and diastolic mean pressures for each of the days registered, and then calculated the mean pressure for the entire period with and without the presence of latanoprost. Mean ST and DT at baseline were 140.24 mmHg (CI 95%: 133.03-147.46) and 69.45 mmHg (CI 95%: 67.72-71.19), respectively. Mean ST and DT under latanoprost were 159.9 mmHg (CI 95%: 150.54-167.25) and 73.97 mmHg (CI 95%: 71.49-76.45), respectively. A T test revealed a significant difference between baseline and latanoprost for ST (mean difference of 18.66 mmHg; CI 95%: 8.42-28.89). DT difference between baseline and latanoprost was statistically significant but clinically irrelevant (mean difference of 4.51 mmHg CI 95%: 1.74-7.35).

Conclusions: we report a case of significant increase in systolic blood pressure associated with the use of latanoprost. To the best of our knowledge, this effect has not been previously reported.
EVALUATION OF OCULAR SURFACE DISEASE IN PATIENTS OF PRIMARY GLAUCOMA
S. Sharma¹, A. Dave¹, T. Arora¹, A. Panda¹, M. Vanathi¹, L. Tejwani¹, T. Dada¹
¹Glaucoma Services, Dr R.P. Centre for Ophthalmic Sciences, AIIMS, New Delhi - India

Background: Glaucoma patients often have undiagnosed ocular surface disease due to use of topical anti-glaucoma medications which can impact the quality of life and adherence to therapy. We evaluated the prevalence of ocular surface disease (OSD) in glaucoma patients on chronic topical ocular hypotensive therapy.

Methods: Sixty four eyes of 64 cases with of primary glaucomas (POAG 30, PACG 34) on chronic topical therapy for more than 6 months were included. All patients underwent a detailed ocular surface evaluation (tear break-up time, schirmer, corneal and conjunctival rose bengal dye staining). Patients with secondary glaucoma or any other form of topical therapy were excluded.

Results: Mean age of the patients was 56.4 ± 8.2 years. A decreased schirmer's value (< 10 mm) was seen in 54.7% of cases with 6.25% showing severe (< 5 mm) tear deficiency. Early tear break up (< 10 seconds) was found in 68.75% patients with 15.6% showing severe tear film (< 5 seconds) abnormality on TBUT. Corneal/conjunctival vital staining was seen in 51.6% cases with 2 patients having severe OSD. Mean schirmer score was 12.43 ± 5.05 mm in eyes on 1 medication and 9.64 ± 3.58 mm in eyes on 2 medications (p = 0.02).

Conclusion: Ocular surface disease was found in more than half of the patients with primary adult glaucomas on chronical topical medical therapy. Evaluation of the tear film and ocular surface should be incorporated in the work up of glaucoma patients.
COMPARISON OF THE EFFECT OF TRAVOPROST AND DORZOLAMIDUM/TIMOLOL FIXED COMBINATION ON 24 HOUR IOP IN OPEN ANGLE GLAUCOMA
D. Costin¹, M.P. Bucatariu², A.R. al Mousa¹, A.D. Moraru², M. Dogaru²
¹University of Medicine and Pharmacy “Gr. T. Popa”, Iasi - Romania; ²Clinical Emergency, Neurosurgical Hospital, Iasi - Romania

Background: To compare the efficiency of travoprost/dorzolamidum/timolol fixed combination therapy on 24 hour IOP in open angle glaucoma.

Methods: The study was retrospective on 22 patients with primary open angle glaucoma. The 24 hour IOP was measured in sitting position with a Goldmann tonometer at 9:00, 12:00, 15:00 and 18:00. The 24 hour variation was measured at baseline and measured again at 3 months. The mean age of patients was 57.64 ± 8.81 years. The patients was randomly selected in two groups, the first group was treated with travoprost and the other group was treated with dorzolamidum/timolol fixed combination.

Results: IOP was lowered significantly statistic (p < 0.05%) in both groups. At baseline the mean IOP was 22.63 ± 2.68 mmHg for the group treated with travoprost and 22.67 ± 2.64 mmHg for the group treated with dorzolamidum/timolol fixed combination. The mean IOP after 3 months was 18.02 ± 1.64 mmHg (20.37% reduction rate) for the group treated with travoprost and 17.03 ± 1.33 mmHg (24.87% reduction rate) for the group treated with dorzolamidum/timolol fixed combination. The IOP was lowered significantly below the target IOP. p = 3.68 E-08 for the first group and p = 5.74 E-11 for the second group.

Conclusions: The 24 hour reduction was better in the group treated with the fixed combination than the 24 hour reduction in the group treated with travoprost even if the mean IOP at baseline was almost the same. The fixed combination had a significantly better IOP reduction at all measurement time points.
BACKGROUND: Primary aim of Glaucoma treatment is to lower intraocular pressure and preserve visual functions. Several evidence based studies have shown that lowering intraocular pressure (IOP) effectively slows optic nerve damage and visual field loss progression. The treatment options available for lowering IOP include medications, Laser surgery, and incisional surgery. Our study is aimed at evaluating the outcome of Primary adult Glaucoma treatment at the Eye clinic of a tertiary health institution in Lagos.

METHODS: A comparative non-randomised retrospective study of consecutive adult patients diagnosed and treated for Glaucoma at Guinness Eye Centre of Lagos University Teaching Hospital, Idi-Araba Lagos from May 2007-April 2010. Chart review of the patients was done. Details of age, sex, type of glaucoma (defined by Shaffer's grading into Open and angle closure, severity of disease defined by Mean deviation on Humphrey's Visual Field Analyser and cup to disc ratio measurements, intraocular pressure (IOP), Pattern Standard deviation (PSD) on visual field (VF) and modality of treatment were extracted from the case records and analyzed. Main outcome measures were mean IOP measurements at baseline, 6, 12, 18, 24, 30 and 36 months follow-up and VF measurement of the mean PSD at baseline, 6, 12, 18 and 24 months follow-up. Data analysis was done using Statistical Package for Social Sciences Software (SPSS14). A p value of < 0.05 was accepted as indicative of statistical significance.

RESULTS: Medical records of 300 patients were reviewed. Male constituted 58.3% (176) while female was 124 (41.3%). 83.9% of the patient had open angle and 16.7% had angle closure. Mild disease constituted 37.2%, Moderate 24.3% and Advanced 38.7%. The number of patients on medical treatment was 167 (55.7%) while only 64 (21.3%) had surgery (Trabeculectomy + 5 Fluorouracil) and 69 (23%) defaulted after first visit. At 1 year, for medical treatment, 78.5% of patients had IOP less than 21 mmHg while for surgical intervention 88% of the patients had IOP less than 21 mmHg (p = 0.04). 21.5% of patients on medical treatment had IOP greater than 21 mmHg while 12% of patients with surgical intervention had IOP greater than 21 mmHg with significant difference p < 0.05 (p = 0.04). The visual field deteriorated significantly from 3.14 dB to 4.55 dB for medical treatment compared to 5.32 dB to 5.40 dB for surgical intervention p < 0.05.

CONCLUSION: Surgical intervention of Trabeculectomy with adjunct 5 Fluorouracil resulted in a better treatment outcome with remarkable reduction in progression of the disease as revealed on the visual field assessment. Increase in uptake of trabeculectomy would help reduce the burden of blindness from glaucoma.
FREQUENCY AND RISK FACTORS FOR OCULAR SURFACE DISEASE AMONG PATIENTS SUFFERING FROM CHRONIC OPEN-ANGLE GLAUCOMA (COAG) IN FRANCE
C. Baudouin¹, J.P. Renard², S. Korsia³, V. Jeanbat⁴, S. Bouee⁴
¹Chno des Quinze Vingts, Paris - France; ²H.I.A. du Val de Grace, Paris - France;
³Alcon, Rueil Malmaison - France; ⁴CEMKA-EVAL, Bourg la Reine - France

Background: There is a large body of evidence from experimental and clinical studies showing that the long-term use of topical drugs for POAG may induce ocular surface changes, causing ocular discomfort, tear film instability, conjunctival inflammation, subconjunctival fibrosis, epithelial cell apoptosis, corneal surface impairment, and the potential risk of failure for further glaucoma surgery. The aim of this study was to describe ocular surface diseases and identify its risk factors in French patients treated for COAG.

Methods: An observational cross-sectional study describing ocular surface disease in patients treated for their COAG. Patients were recruited by ophthalmologists involved in the management of POAG. Were included in this study: 1) Patients aged 18 or older, 2) Patients presenting with OAG or OHT and treated with a topical IOP-lowering treatment. Sociodemographic features, clinical features, treatment and side effects were collected in a web-based standardized case report form. An ocular surface disease intensity score was calculated after answering 10 questions regarding ocular surface symptoms (5 questions) and ocular surface signs (5 questions) with a 4-grade scale. Patients were classified into three groups according to this total score: group A: score = [1 – 4], group B: score = ]4 – 10[ and group C: score = ]10 – 30]. After bivariate analysis, a multinomial logistic regression was performed in order to identify risk factors for surface disease.

Results: In the overall sample of 516 included patients by 50 ophthalmologists, 49% belonged to group A (ocular surface disease intensity score 1 to 4), 30% to group B (5 to 10), and 21% to group C (11 to 30). The frequencies of the symptoms were: burning (47%), eye dryness (44%), foreign body (40%), itching (39%) and tearing (32%). The frequencies of the signs were: conjunctival hyperemia (60%), eyelid margin redness (47%), positive corneal fluorescein staining (35%) and positive conjunctival staining (28%), eyelid swelling (24%). 75% of patients had one history of change in the past, in their topical medication. According to bivariate analysis, ocular surface disease severity was positively correlated with the following factors: patient’s age, time since the topical treatment was initiated, number of topical drugs, number of daily drops, number of eyedrop, changes of topical treatment in the past, intraocular pressure and severity of the POAG (as defined by the ophthalmologist). Once the multivariate analysis was performed, the following factors were still correlated with the severity of ocular surface disease: patient’s age, number of topical drugs, changes of topical treatment in the past, intraocular pressure, glaucoma severity.

Conclusion: Patients treated for POAG or OHT often suffer from ocular surface diseases: the prevalence of clinical signs and symptoms vary between 24% and 60%. These high prevalence values may have consequences on the burden of the disease in terms of adherence to the medication and quality of life. Physicians should take into account ocular surface involvement more carefully and discuss possible alternatives to reduce side effects and improve further outcome of the disease.