Journal of the South East Asia Glaucoma Interest Group

Volume 9 Number 1 February 2007

Safety, Tolerability, and Efficacy of Latanoprost

Reliability of Ultrasound Biomicroscopy Images

Topical Antiglaucoma Drugs and Conjunctival Cell Profile

Cavernous Haemangioma of the Orbit

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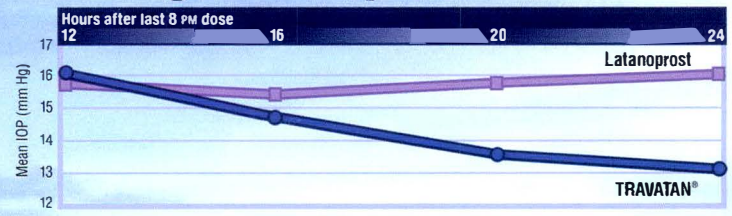
Endurance

TRAVATAN® Solution is still going strong 24 hours post dose.[1]*



TRAVATAN®

(travoprost eye drops solution 0.004%)

Control That Lasts.

TRAVATAN® (travoprost 0.004%) Ophthalmic Solution Sterile **DESCRIPTION** Travoprost is a highly selective, potent agonist for the FP prostanoid receptor. Its chemical name is isopropyl (Z)-7-[(1*R*,2*R*,3*R*,5*S*)-3,5-dihydroxy-2-[(1*E*,3*R*)-3-hydroxy-4-[(α,α,α-trifluoro-*m*-tolyl)oxy]-1-butenyl]cyclopentyl]-5-heptenoate. Its molecular formula is $C_{26}H_{35}F_3O_6$. Travoprost is a clear, colorless to pale yellow oil, which is very soluble in acetonitrile, methanol, octanol, and chloroform. It is practically insoluble in water. TRAVATAN® 0.004% Ophthalmic Solution is supplied as a sterile, buffered aqueous solution of travoprost with a pH of approximately 6.0 and an osmolality of approximately 290 mOsmol/kg. Each mL of TRAVATAN® 0.004% contains 40 µg travoprost. Preservative: benzalkonium chloride 0.015%. Inactive Ingredients: polyoxy 40 hydrogenated castor oil, tromethamine, boric acid, mannitol, edetate disodium, sodium hydroxide and/or hydrochloric acid (to adjust pH) and purified water. **CLINICAL PHARMACOLOGY** Mechanism of Action Travoprost free acid is a highly selective, potent agonist for the FP prostanoid receptor. FP receptor agonists are reported to reduce intraocular pressure by increasing uveoscleral outflow. Pharmacokinetics/Pharmacodynamics Absorption: Travoprost is absorbed through the cornea. Studies in rabbits have shown peak concentrations in aqueous humor were reached one to two hours following topical administration. In humans, peak plasma concentrations of travoprost free acid were low (25 pg/mL or less) and occurred within 30 minutes following topical administration. Elimination from plasma was rapid resulting in concentrations below the limit of quantitation (< 10 pg/mL) by one hour. Metabolism: Travoprost, an isopropyl ester prodrug, is rapidly hydrolyzed by esterases in the cornea to the biologically active free acid. Systemically, travoprost free acid is rapidly and extensively metabolized to inactive metabolites. Biotransformations include beta-oxidation of the α(carboxylic acid) chain to give the 1,2-dinor and 1,2,3,4-tetranor analogs, oxidation of the 15-hydroxyl moiety, as well as reduction of the 13,14 double bond. Excretion: In rats, 95% of a subcutaneous radiolabeled dose was eliminated within 24 hours. The major route of elimination was via the bile (61%) with the remainder excreted by the kidneys. **INDICATIONS AND USAGE** TRAVATAN® Ophthalmic Solution is indicated for the reduction of intraocular pressure in patients with open-angle glaucoma or ocular hypertension. **CLINICAL STUDIES** TRAVATAN® 0.004% Ophthalmic Solution dosed once-daily in patients with open-angle glaucoma or ocular hypertension produced significant reductions in intraocular pressure (IOP) when used either as primary therapy or adjunctively to TIMOPTIC® (timolol maleate ophthalmic solution) 0.5% BID. As primary therapy, TRAVATAN® 0.004%, dosed QD, reduced IOP 7 to 9 mmHg. Stable diurnal IOP reductions were achieved as early as 2 weeks after initiation of therapy and were maintained over the 6 to 12 month treatment periods in three (3) well-controlled studies. The IOP reductions with TRAVATAN® (travoprost 0.004%) Ophthalmic Solution were superior to those obtained with TIMOPTIC® and equal or better than those obtained with XALATAN® (latanoprost ophthalmic solution) 0.005% QD. TRAVATAN® 0.004% demonstrated an earlier stabilization of IOP reduction and better IOP control throughout the day compared to XALATAN® 0.005%. TRAVATAN® 0.004% was significantly more effective (up to 1.4 mmHg) than XALATAN® 0.005% in reducing IOP in black patients. A responder analysis (IOP reduction ≥30% or mean IOP ≤17 mmHg) demonstrated that TRAVATAN® 0.004% had a significantly higher responder rate (56%) compared to XALATAN® 0.005% (50%) and which were both significantly greater than TIMOPTIC® (40%). In a 6-month well-controlled study, TRAVATAN® 0.004% dosed QD adjunctively to TIMOPTIC® 0.5% BID provided additional clinically significant IOP reductions (6 to 7 mmHg). **CONTRAINDICATIONS** Known hypersensitivity to travoprost, benzalkonium chloride or any other ingredients in this product. TRAVATAN® may interfere with the maintenance of pregnancy and should not be used by women during pregnancy or by women attempting to become pregnant. **WARNINGS** TRAVATAN® may gradually change eye color, increasing the amount of brown pigmentation in the iris by increasing the number of melanosomes (pigment granules) in melanocytes. The long term effects on the melanocytes and any consequences thereof are currently unknown. The change in iris color occurs slowly and may not be noticeable for months to years. These changes may be permanent. Periorbital and/or eyelid skin darkening has been reported in association with the use of TRAVATAN®. TRAVATAN® may gradually change eyelashes in the treated eye; these changes include: increased length, thickness, pigmentation, and/or number of lashes. Patients who receive treatment in only one eye may experience increased brown pigmentation of the iris, periorbital and/or eyelid tissue, and eyelashes in the treated eye. They may also experience disparity between the eyes in length, thickness, and/or number of eyelashes. These changes in pigmentation and lash growth may be permanent. **PRECAUTIONS** General There have been reports of bacterial keratitis associated with the use of multiple dose containers of topical ophthalmic products. These containers had been inadvertently contaminated by patients who, in most cases, had a concurrent corneal disease or a disruption of the epithelial surface (see Information for Patients). Patients may slowly develop increased brown pigmentation of the iris. This change may not be noticeable for months to years (see Warnings). This change in eye color has predominantly been seen in patients with mixed colored irides, i.e., blue-brown, grey-brown, yellow-brown and green-brown; however, it has also been observed in patients with brown eyes. Based upon information from the literature, the color change is believed to be due to increased melanin content in the stromal melanocytes of the iris. Typically the brown pigmentation around the pupil spreads concentrically towards the periphery in affected eyes, but the entire iris or parts of it may become more brownish. No further increase in brown iris pigment has been observed after discontinuation of treatment, but the resultant color change may be permanent. TRAVATAN® should be used with caution in patients with active intraocular inflammation (iritis/uveitis). Macular edema, including cystoid macular edema, has been reported during treatment with prostaglandin $F_{2\alpha}$ analogues. These reports have mainly occurred in aphakic patients, pseudophakic patients with a torn posterior lens capsule, or in patients with known risk factors for macular edema. TRAVATAN® (travoprost 0.004%) Ophthalmic Solution should be used with caution in these patients. Patients should remove contact lenses prior to administration of the solution. Lenses may be reinserted 15 minutes following administration of TRAVATAN®. Information for Patients Patients should be advised concerning all the information contained in the Warnings and Precautions sections. Patients should also be instructed to avoid allowing the tip of the dispensing container to contact the eye or surrounding structures because this could cause the tip to become contaminated by common bacteria known to cause ocular infections. Serious damage to the eye and subsequent loss of vision may result from using contaminated solutions. Patients also should be advised that if they develop an intercurrent ocular condition (e.g., trauma, or infections) or have ocular surgery, they should immediately seek their physician's advice concerning the continued use of the multi-dose container. Patients should be advised that if they develop any ocular reactions, particularly conjunctivitis and lid reactions, they should immediately seek their physician's advice. Patients should also be advised that TRAVATAN® contains benzalkonium chloride which may be absorbed by contact lenses. Contact lenses should be removed prior to administration of the solution. Lenses may be reinserted 15 minutes following administration of TRAVATAN®. If more than one topical ophthalmic drug is being used, the drugs should be administered at least five (5) minutes apart. Carcinogenesis, Mutagenesis, Impairment of Fertility Travoprost was not mutagenic in bacteria, in one mouse lymphoma assay, in the mouse micronucleus tests and in the rat chromosome aberration assay. In another mouse lymphoma assay, higher concentrations of travoprost were slightly mutagenic only in the presence of activation enzymes. In life and early post-mortem evaluations of carcinogenicity studies in rats and mice suggest no evidence of a carcinogenic potential. Travoprost did not affect mating or fertility indices in male or female rats at subcutaneous doses up to 10 µg/kg/day (250 times the recommended human dose). The mean number of corpora lutea was slightly reduced at that dose, and the post-implantation losses were increased, but was not affected at 3 µg/kg/day (75 times the maximum recommended human dose). Pregnancy: Teratogenic Effects Pregnancy Category: C In reproduction studies conducted in pregnant rats and mice, travoprost reduced fetal viability when administered during gestation at doses as low as 1.0 µg/kg/day (25 times the maximum recommended human dose) with the lowest no effect level at 0.3 µg/kg/day (7.5 times the maximum recommended human dose). The incidence of skeletal malformations was increased in fetuses of rat dams receiving travoprost by subcutaneous injection at 10 µg/kg/day (250 times the maximum recommended human dose), but not at 3 µg/kg/day (75 times the maximum recommended human dose). No fetal abnormalities were observed in mice at 1.0 µg/kg/day (25 times the maximum recommended human dose). No adequate and well-controlled studies have been performed in pregnant women. TRAVATAN® may interfere with the maintenance of pregnancy and should not be used by women during pregnancy or by women attempting to become pregnant. Nursing Mothers A study in lactating rats demonstrated that radiolabeled travoprost and/or its metabolites were excreted in milk. It is not known whether this drug or its metabolites are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when TRAVATAN® is administered to a nursing woman. Pediatric Use Safety and effectiveness in pediatric patients have not been established. Geriatric Use No overall differences in safety or effectiveness have been observed between elderly and other adult patients. **ADVERSE REACTIONS** (see Warnings and Precautions) The most common ocular adverse event observed in controlled clinical studies with TRAVATAN® (travoprost 0.004%) Ophthalmic Solution was ocular hyperemia which was reported in 35 to 50% of patients. 95% of the ocular hyperemia observed with TRAVATAN® (travoprost 0.004%) Ophthalmic Solution was mild in intensity and subsided over time without treatment. Approximately 3% of patients discontinued therapy due to conjunctival hyperemia. Ocular adverse events reported at an incidence of 5 to 10% included decreased visual acuity, eye discomfort, foreign body sensation, pain, and pruritus. Ocular adverse events reported at an incidence of 1 to 4% included, abnormal vision, blepharitis, blurred vision, cataract, cells, conjunctivitis, dry eye, eye disorder, flare, iris discoloration, keratitis, lid margin crusting, photophobia, subconjunctival hemorrhage, and tearing. Nonocular adverse events reported at a rate of 1 to 5% were accidental injury, angina pectoris, anxiety, arthritis, back pain, bradycardia, bronchitis, chest pain, cold syndrome, depression, dyspepsia, gastrointestinal disorder, headache, hypercholesterolemia, hypertension, hypotension, infection, pain, prostate disorder, sinusitis, urinary incontinence, and urinary tract infection. **OVERDOSAGE** A single-dose intravenous study in rats was conducted to elucidate maximal acute hazard. The dose employed was 250,000-times the proposed daily clinical exposure and over 5000-times the possible exposure from the entire contents of one product container. No treatment related pharmacotoxic signs were present in the animals receiving Travoprost. If overdosage with TRAVATAN® occurs, treatment should be symptomatic. **DOSAGE AND ADMINISTRATION** The recommended dosage is one drop in the affected eye(s) once daily in the evening. The dosage of TRAVATAN® should not exceed once-daily since it has been shown that more frequent administration may decrease the intraocular pressure lowering effect. Reduction of intraocular pressure starts approximately 2 hours after administration and the maximum effect is reached after 12 hours. TRAVATAN® may be used concomitantly with other topical ophthalmic drug products to lower intraocular pressure. If more than one topical ophthalmic drug is being used, the drugs should be administered at least five (5) minutes apart. **HOW SUPPLIED** TRAVATAN® (travoprost 0.004%) Ophthalmic Solution is a sterile, isotonic, buffered, preserved, aqueous solution supplied in Alcon's oval DROP-TAINER® package system inside a sealed foil pouch. This package system is comprised of a plastic oval shaped dispenser bottle, a dropper tip and tamper evident neck-band which shrinks to conform around the closure and neck area of the package. 0.004%: 2.5 mL fill Storage Store between 2° to 25°C (36° to 77°F). Refrigeration is not required. Rx Only (USA) **CAUTION:** Federal (USA) law prohibits dispensing without prescription.

*TIMOPTIC is a registered trademark of Merck & Co.Inc. *XALATAN is a registered trademark of Pharmacia Corp. U.S. Patent Nos. 5,631,287; 5,849,792; 5,889,052; 6,011,062 and 6,235,781.

* A washout period of 4 weeks was followed by 2 weeks of TRAVATAN® Solution (n=16) or latanoprost monotherapy (n=18). At day 14, the final dose was administered at 8 pm and IOP measurements were taken. Baseline values for the two treatment groups were not significantly different. The standard deviations for the TRAVATAN® group were 3.9 mm Hg (12 hours), 2.9 mm Hg (16 hours), 3.2 mm Hg (20 hours), and 2.1 mm Hg (24 hours). For the latanoprost group, the standard deviations were 3.8 mm Hg (12 hours), 3.0 mm Hg (16 hours), 3.2 mm Hg (20hours), and 3.1 mm Hg (24 hours). The difference between the two groups at 24 hours post dose was statistically significant ($p=0.0117$).

Reference 1. Dubiner HB, Sircy MD, Landry T, et al. Comparison of the diurnal ocular hypotensive efficacy of travoprost and latanoprost over a 44-hour period in patients with elevated intraocular pressure. Clin Ther. 2004;26:84-91.

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SEAGIG
South East Asia Glaucoma Interest Group

Asian Journal of OPHTHALMOLOGY is the official peer-reviewed journal of the South East Asia Glaucoma Interest Group (SEAGIG) and is indexed in EMBASE/Excerpta Medica. The website of *Asian Journal of OPHTHALMOLOGY* and SEAGIG membership details can be found at **www.seagig.org**.

As new technologies and therapeutic interventions are continually being developed, ophthalmology has become a field of rapid change, particularly in the Asia-Pacific region, where disease patterns and health care delivery differ greatly from those seen in the West. *Asian Journal of OPHTHALMOLOGY* was established in 1998 and became the official journal of SEAGIG in 2003, with the aim of disseminating information relevant to ophthalmology and glaucoma throughout Asia and to interested groups worldwide. The objectives of *Asian Journal of OPHTHALMOLOGY* are as follows:

- to provide a platform for the publication of information with a focus on ophthalmology in Asia
- to disseminate information that will improve the care of patients with all types of ophthalmological disorders, with a special focus on glaucoma
- to increase the understanding of such disorders through reporting of educational activities
- to publish the results of research programmes to expand knowledge about the causes, prevention, and treatment of ophthalmological disorders
- to work closely with Asian and international researchers to achieve these aims
- to provide a forum for young and relatively inexperienced researchers to present their research results as Original Articles via an international platform
- to maintain and promote relationships with any organisation with similar goals.

Although the focus of *Asian Journal of OPHTHALMOLOGY* is on glaucoma, other topics relevant to the region will not be ignored, and submissions on all aspects of ophthalmology are welcome.

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International Limited
Suite C, 10/F, Wo On Building
10 Wo On Lane, Central, Hong Kong
Tel: (852) 2868 9171
Fax: (852) 2868 9269
E-mail: editor@seagig.org

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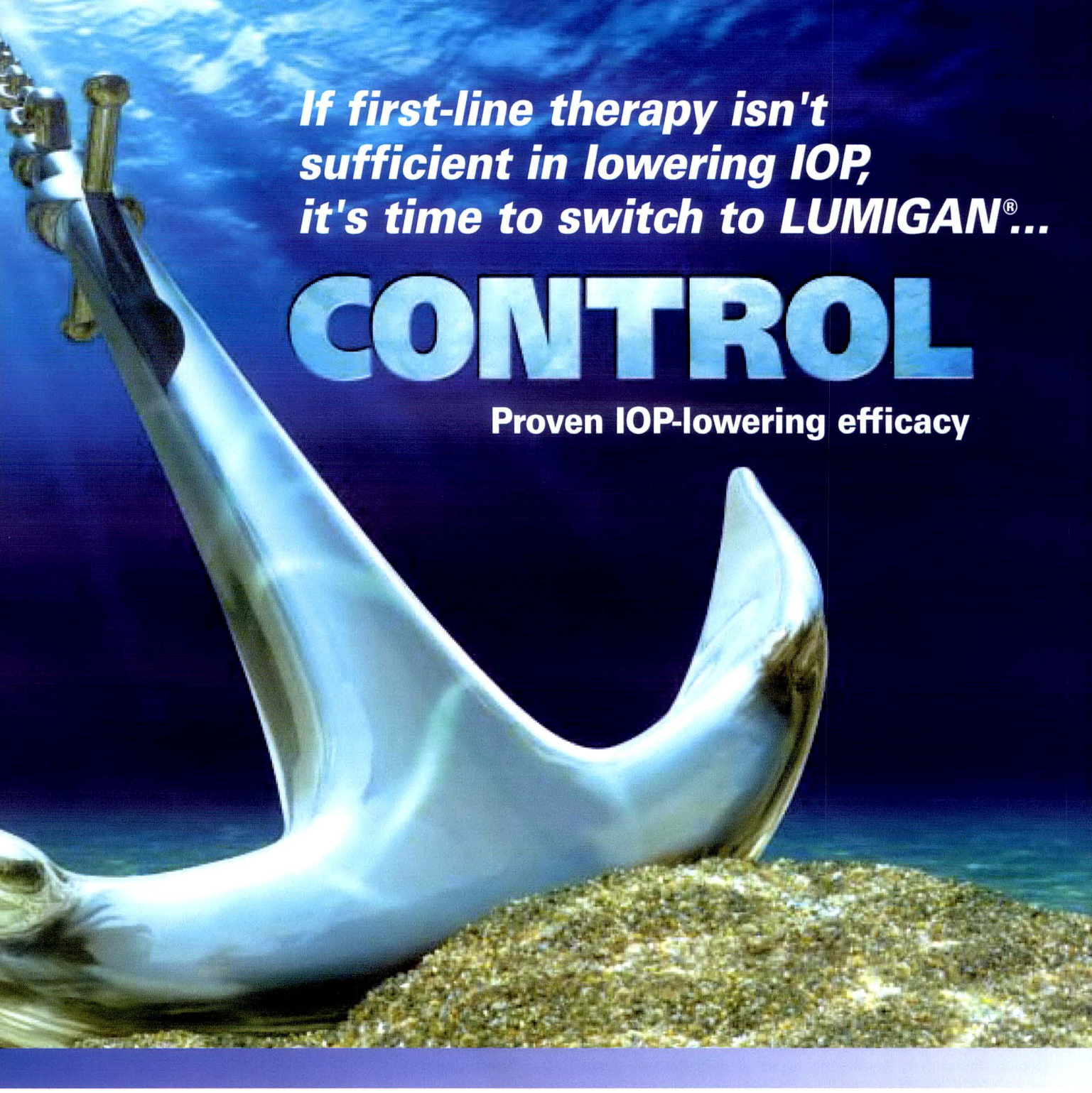

LUMIGAN® (bimatoprost ophthalmic solution) 0.03% is indicated for the reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension who are intolerant of other IOP-lowering medications or insufficiently responsive (failed to achieve target IOP determined after multiple measurements over time) to another IOP-lowering medication.

IMPORTANT SAFETY INFORMATION

LUMIGAN® (bimatoprost ophthalmic solution) 0.03% has been reported to cause changes to pigmented tissues. These reports include increased pigmentation and growth of eyelashes and increased pigmentation of the iris and periorbital tissue (eyelid). These changes may be permanent.

The most frequently reported adverse events occurring in approximately 15% to 45% of patients dosed once daily, in descending order of incidence, were conjunctival hyperemia, growth of eyelashes, and ocular pruritus.

See LUMIGAN® Prescribing Information.

LUMIGAN®
(bimatoprost ophthalmic solution) 0.03%

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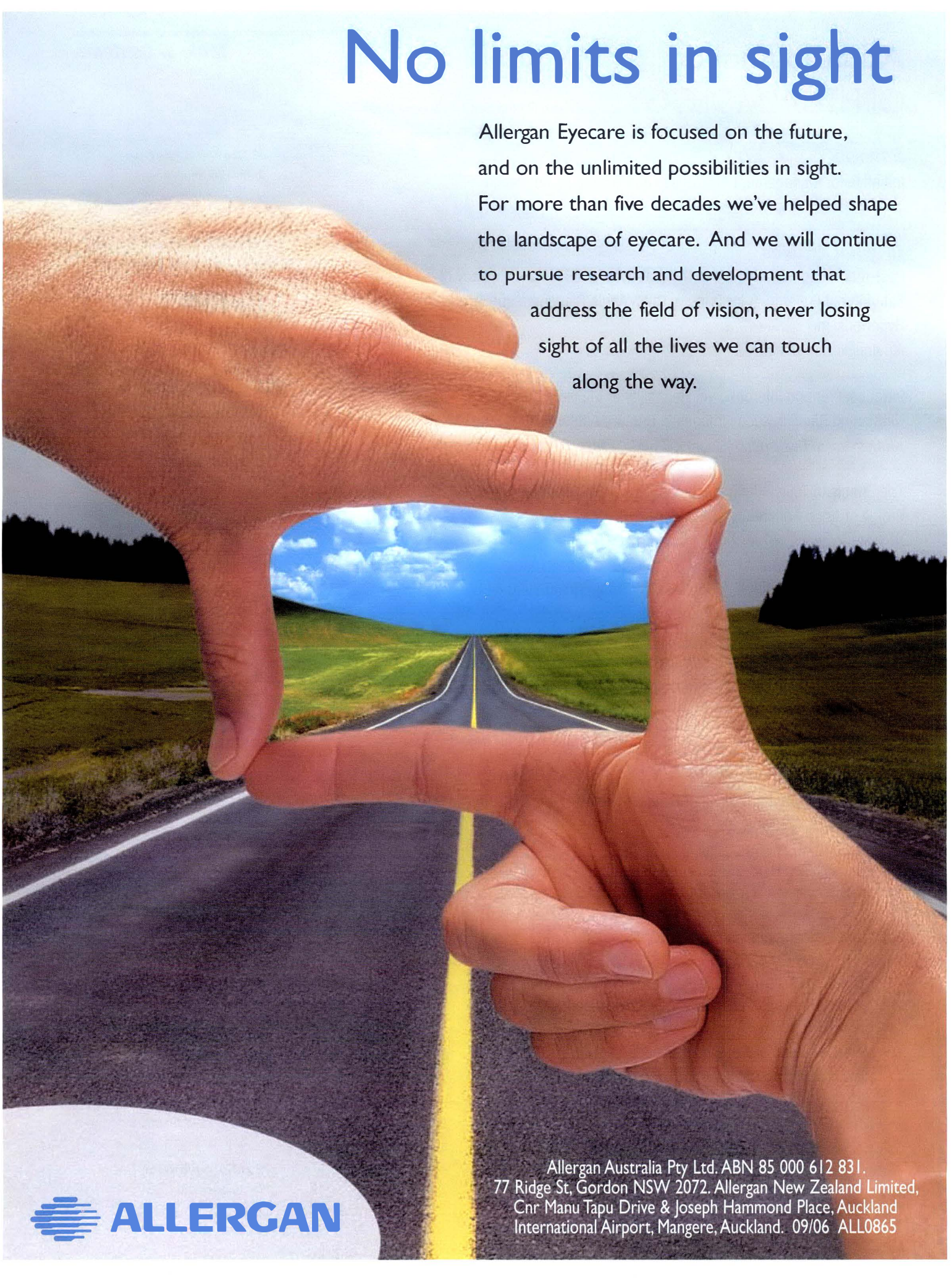

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Initiative for Management, Awareness and Glaucoma Education

SEAGIG-IMAGE Project Working Group

The South East Asia Glaucoma Interest Group (SEAGIG) is proud to launch the educational resource that has emerged from our Initiative for Management, Awareness and Glaucoma Education (IMAGE) project. Aiming to enhance glaucoma management throughout the region, this comprehensive slide and video kit is the result of contributions from more than 50 leading experts from 7 Asian countries. The resource covers the spectrum of glaucoma management, from diagnosis to follow-up, using the Asia-Pacific Glaucoma Guidelines as its curriculum basis. SEAGIG is grateful to Allergan for their sponsorship of this project through an unrestricted educational grant.

Intended for use by ophthalmologists for their own educational advancement, as well as to facilitate educational programmes, the slides have been prepared by SEAGIG/IMAGE members along the following lines:

- are the topics clinically relevant to glaucoma care in the region?
- do the slides have educational value relevant to the region?

All modules will be available on the SEAGIG website, at www.seagig.org. Thumbnails will be freely visible by all visitors, with the full slide sets freely accessible by SEAGIG members. The first 2 modules, covering *Glaucoma Assessment* and *Setting IOP Targets,* will be launched in January 2007, followed by another 2 modules per issue of SEAGIG's official publication, *Asian Journal of Ophthalmology*, which is released every 2 months.

The *Glaucoma Assessment* module provides an overview of objectives and components of an initial assessment, including patient histories, examination, and development of a management plan based on findings.

The *Setting IOP Targets* module covers the rationale for setting target intraocular pressure and outlines data from important glaucoma clinical trials with their implications for patient management.

Glaucoma Assessment

This presentation aims to provide the practicing ophthalmologist with an updated understanding of the assessment of patients with glaucoma or those suspected of having glaucoma. Following the concepts outlined here can translate into improved detection and evaluation of glaucoma and, ultimately, more effective prevention of visual loss and blindness.

This module introduces the aims and 2 key phases of initial glaucoma assessment, followed by separate sections dedicated to history and examination/investigations. At the end of the presentation, participating clinicians should be able to:

- list the 2 phases of initial glaucoma assessment (Figures 1 and 2)
- obtain a patient's history in a logical, organised and thorough manner (Figure 3)
- identify points in the history that may be relevant to the diagnosis and treatment of glaucoma (Figure 4)
- consider other factors that may impact on glaucoma management (Figure 5)
- describe the clinical work-up in the diagnosis of glaucoma (Figure 6)
- understand the concepts behind the different tests and procedures used to diagnose and evaluate glaucoma (Figures 7 and 8).

The final slide lists key take-home messages from the presentation (Figure 9).

Setting IOP Targets

Reducing the intraocular pressure (IOP) level is an important goal when treating patients with glaucoma, as several clinical trials have shown that most glaucoma-induced damage is pressure-dependent. Keeping IOP in check benefits patients by protecting the optic nerve from damage and preserving the visual field. However, determining the specific level to which IOP should be lowered to achieve optimal glaucoma management in every patient is a challenge.

The first part of this presentation discusses the rationale behind setting IOP targets and is designed to aid the practising ophthalmologist in establishing an IOP range for each patient that will help preserve vision and quality of life. In-depth evidence from landmark trials in glaucoma, covering major findings that impact clinical care, is reviewed in the second portion of this module.

Correspondence: Dr Prin RojanaPongpun, Department of Ophthalmology, Chulalongkorn University, Bangkok, Thailand.
Fax: (662) 256 4425;
E-mail: rprin@chula.ac.th

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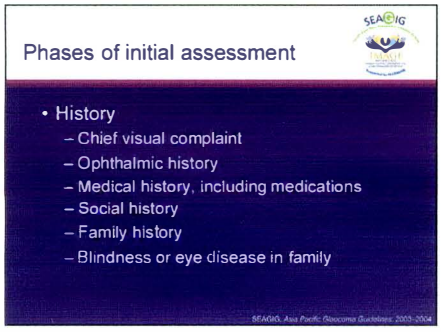
Figure 1.



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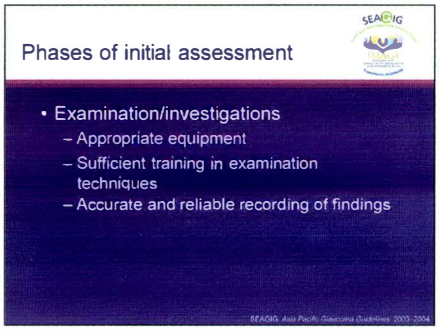

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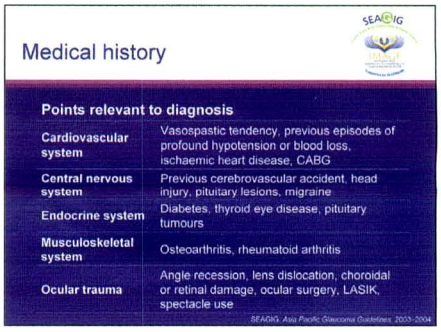

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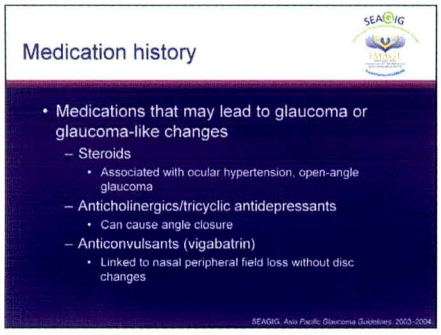

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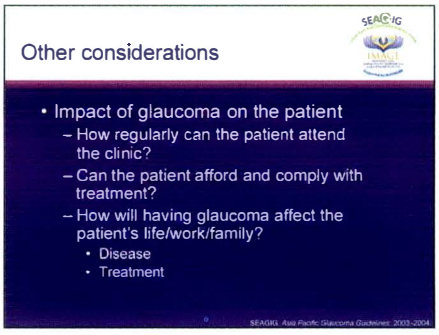

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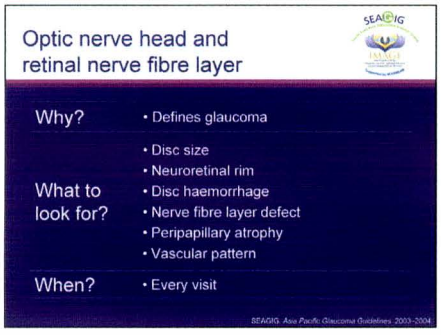

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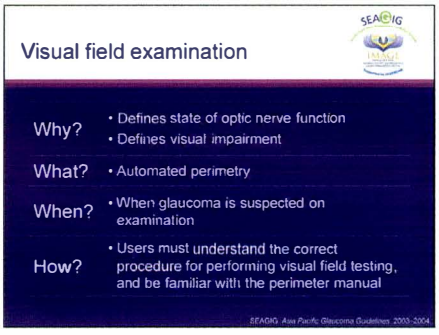

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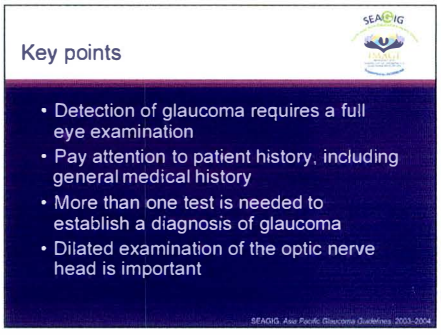

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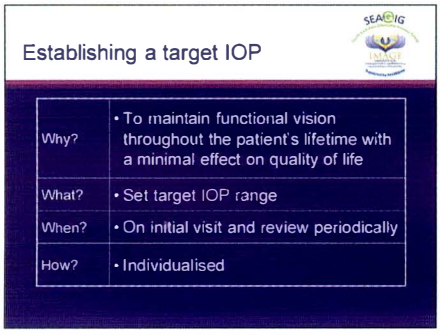


Figure 11.

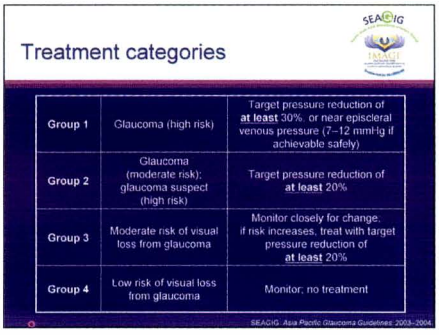
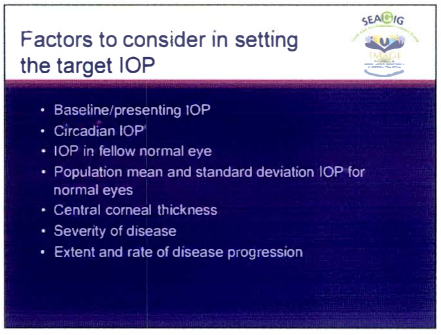


Figure 12.



At the end of the presentation, participating clinicians should be able to:

- understand the importance of establishing and maintaining consistently low target IOP ranges (Figure 10)
- list the different treatment categories for glaucoma based on the SEAGIG guidelines[1] (Figure 11)
- confidently set a target IOP range based on the treatment categories and individual patient factors (Figures 12 and 13)
- describe the outcomes and implications of key clinical trials demonstrating the role of IOP lowering in preventing disease

Figure 13.

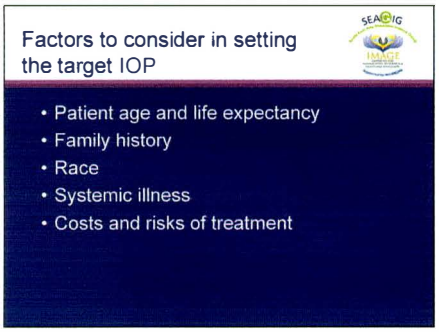


Figure 14.

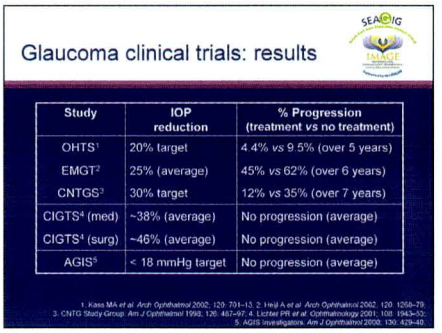
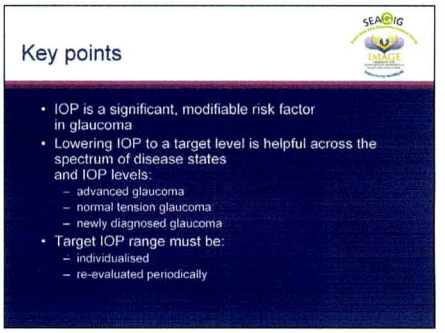


Figure 15.



progression (Figure 14).

The final slide lists key take-home messages from the presentation (Figure 15).

Acknowledgement

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Reference

1. South East Asia Glaucoma Interest Group. Asia Pacific Glaucoma Guidelines. Singapore: SEAGIG, 2003-2004. Available at: www.seagig.org/pdf/APGGuidelinesNMview.pdf.

Comments and Suggestions

The SEAGIG-IMAGE Project Working Group has endeavoured to make this educational resource as comprehensive as possible. It is intended to be user-friendly and responsive to the challenges faced by ophthalmologists and glaucomatologists today. Your feedback will be welcomed, including any suggestions for improvement. Please contact the SEAGIG-IMAGE Project Working Group, via *Asian Journal of Ophthalmology*, at: editor@seagig.org.

Post-marketing Surveillance of the Safety, Tolerability, and Efficacy of Latanoprost (Xalatan™) for Primary Open Angle Glaucoma and Ocular Hypertension

Norman A Aquino,[1] Joan Catherine P Manalo[2]
[1]American Eye Center, Mandaluyong City, and [2]Pfizer Philippines Inc, Makati City, The Philippines

Aim: This non-interventional, open-label, multicentre, post-marketing surveillance study was conducted to evaluate the overall safety, tolerability, and efficacy of latanoprost (Xalatan™) for the treatment of Filipino patients with glaucoma and/or intraocular hypertension.
Methods: Patients were Filipinos with unilateral or bilateral open angle glaucoma. 721 patients were recruited and assessed, 425 of whom had elevated intraocular pressure or ocular hypertension of ≥22 mm Hg. Each patient was carefully instructed to instil one drop of latanoprost in the affected eye(s) once daily as prescribed in the product insert. If more than one topical ophthalmic drug was being used, the drugs were administered at least 5 minutes apart. Patients received latanoprost for 4 weeks and were assessed weekly during this period.
Results: Most patients (91.7%) responded to latanoprost treatment. A reduction in intraocular pressure of ≥30% occurred in 62.1% of patients. The overall mean percentage reduction in intraocular pressure at the end of the study was 40.8%. A statistically significant reduction in intraocular pressure was sustained throughout the treatment period. The results of this study compared favourably with those of previous clinical trials performed under more rigorous conditions. Side effects were reported for 47 patients, and were mainly conjunctival redness/hyperaemia. No systemic or serious adverse events were reported.
Conclusion: The study has shown that latanoprost given once daily has significant and sustained ocular hypotensive efficacy and is relatively safe for use by patients with open angle glaucoma and/or ocular hypertension.

Key words: Clinical trials, Latanoprost, Ocular hypertension, Open angle glaucoma, Treatment outcome

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Introduction

Glaucoma is a group of ocular diseases characterised by progressive optic nerve damage. The condition is usually chronic and may lead to disabling visual field loss and even blindness. A high intraocular pressure (IOP) is a major risk factor for development of glaucoma. Glaucoma may be categorised as open angle or closed angle. As IOP is the primary treatable risk factor for glaucoma, the treatment aim is to reduce IOP to a level that may prevent optic nerve damage and help preserve the patient's visual field. The current mainstay of medical management of glaucoma is the use of eye drops, which act on aqueous humour dynamics to lower IOP in 3 ways: decrease aqueous humour production in the ciliary processes, increase aqueous humour outflow through the trabecular meshwork, or increase aqueous humour outflow through the uveoscleral pathway. These pressure-reducing mechanisms are additive in terms of IOP-lowering effects. Eyedrops used for the management of glaucoma include prostaglandin analogues, β-adrenergic antagonists, adrenergic agonists, cholinergic agonists, or carbonic anhydrase inhibitors.[1]

Latanoprost (Xalatan™) is an $F2_{\alpha}$ prostaglandin that reduces IOP by acting as an agonist for the F-prostanoid receptor. Latanoprost reduces IOP primarily by increasing uveoscleral outflow and does not alter aqueous humour production to a clinically significant extent.[2] Latanoprost has been found to reduce IOP and maintain the reduction in IOP over 1 to 2 years of treatment with no evidence of IOP drift.[3] Systemically absorbed latanoprost is rapidly

Correspondence: Joan Catherine P Manalo, Pfizer Philippines Inc, 23F Ayala Life FGU Center, 6811 Ayala Avenue, Makati City, The Philippines.
Tel: (63 2) 888 6001; Fax: (63 2) 864 3780;
E-mail: JoanCatherine.P.Manalo@pfizer.com

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metabolised.[1] The plasma elimination half-life of the acid of latanoprost is 17 minutes after both intravenous and topical administration. Latanoprost is rapidly hydrolyzed to this biologically active acid form in the eye. Since latanoprost has a long residence time in ocular tissue, a short plasma half-life, and is completely cleared by hepatic metabolism to inactive metabolites, it has almost ideal pharmacokinetic properties for a topical drug for the treatment of glaucoma.[1]

This study was conducted to evaluate the overall safety and tolerability of latanoprost for treatment of patients with glaucoma or intraocular hypertension based on the incidence of adverse events. Also included was the evaluation of the IOP-lowering efficacy of latanoprost in these patients, in terms of the mean change from baseline IOP, and the physicians' and patients' global assessment of satisfaction with the drug.

Methods

This 2-year, non-interventional, open-label, multicentre, post-marketing surveillance study was conducted in private practices in The Philippines. The study was conducted in compliance with regulatory authority requirements.

Patients

The study included 425 patients with a diagnosis of unilateral or bilateral open angle glaucoma associated with elevated IOP or ocular hypertension (defined as IOP of ≥22 mm Hg). Also included were 296 participants with baseline IOPs ranging from 7 to 21 mm Hg (mean, 16 mm Hg). Patients were excluded from the study if they had known hypersensitivity to latanoprost, benzalkonium chloride or related compounds, a diagnosis of closed angle glaucoma, or were pregnant or lactating.

Treatment Protocol

Each patient was carefully instructed to instil one drop of latanoprost in the affected eye(s) once daily as prescribed in the product insert. If more than one topical ophthalmic drug was being used, the drugs were administered at least 5 minutes apart. All patients enrolled were treated with latanoprost for a minimum of 4 weeks and concomitant medications were allowed during the study period. Table 1 indicates the schedule of visits and examinations and the specific assessments carried out at each visit.

Outcome Measures and Analyses

All patients who received at least one dose of latanoprost were included in the following safety analysis. All observed or reported adverse events, regardless of the treatment group or suspected causal relationship to the study drug, were recorded on the adverse event page(s) of the case report form. These reports were based on self-reported symptoms and physician-reported signs. Safety was evaluated by generating frequency distributions of patients reporting at least one specific adverse event (incidence table), the total number of episodes for each event reported (frequency table), and the severity and possible relationship of each episode to the study drug (severity and attribution tables). Listings of adverse events by patient and by event included the duration of each event, severity, and whether it caused withdrawal, as well as both investigators' opinions of whether it was related to the study medication.

The efficacy variable assessed was a significant reduction in IOP from baseline. Repeated measures ANOVA was used to analyse the change from baseline. Global Efficacy Assessment was used to determine the patients' and physicians' assessment of the study medication.

Results

Demographics

721 patients were recruited to provide efficacy and safety data for latanoprost in a Filipino population. Demographic assessment revealed a mean age of 61.5 years with a predominance of females (Table 2). Most patients (97.8%) completed the study. The reasons for withdrawal of 16 patients (2.2%) were as follows: 2 (0.3%) due to adverse events, 2 (0.1%) due to lack of efficacy, 3 (0.4%) due to

Table 1. Schedule of examinations and procedures.

Procedure	Initial visit	Visit 1, week 1	Visit 2, week 2	Visit 3, week 3	Visit 4, week 4
Demographics	x				
Medical history	x				
Prescribe study medication	x				
Concomitant drugs	x	x	x	x	x
Physical examination	x				x
Efficacy, intraocular pressure determination	x	x	x	x	x
Adverse event/tolerability assessment	x	x	x	x	x
Physician's assessment					x
Patient's assessment					x
Patient status at end of study					x

Table 2. Demographic characteristics.

	Number of patients (%)		
	Male	Female	Total
All patients	304 (42.1)	417 (57.8)	721 (100.0)
Age (years)			
<18	1 (0.3)	0	1 (0.1)
18-44	35 (11.5)	34 (8.2)	69 (9.6)
45-64	133 (43.8)	151 (36.2)	284 (39.4)
≥65	102 (33.2)	168 (40.3)	269 (37.3)
Unspecified	34 (11,2)	64 (15.3)	98 (13.6)
Total, age specified	271 (88.8)	353 (84.7)	623 (86.0)
Mean age (SD) [years]	60 (13)	62.4 (13.5)	61.5 (13.5)
Range (years)	15-90	20-94	15-94

Table 3. Distribution of patients according to type of glaucoma and laterality of the affected eye.

Characteristic	Number (%)
Type of glaucoma	
Primary open angle glaucoma	523 (72.5)
Exfoliation (capsular)	18 (2.5)
Pigmentary	14 (1.9)
Other*	98 (13.6)
No information	68 (9.4)
Laterality	
Right	79 (11.0)
Left	98 (13.6)
Bilateral	544 (75.5)

* Other diagnoses included secondary open angle, wide narrow angle, acute angle closure, angle recession, aphakic, chronic angle closure, combined mechanism, intermittent angle closure, low tension, mixed mechanism, narrow angle, neovascular, normal tension, ocular hypertension, pseudophakic and steroid-induced glaucoma, central blood vessel occlusion, optic atrophy, glaucoma suspect, immature cataract.

Table 4. Concomitant medical conditions.

Condition	Percent of patients (n = 295)
Hypertension	46.0
Diabetes mellitus	26.4
Asthma	5.5
Cataract and post-surgery	2.1
Thyroid and post-thyroidectomy	1.5
Heart disease, unspecified	1.2
Allergy, unspecified	1.2
Blurred vision	0.6
Breast cancer (female)	0.6
Gall stones	0.6
Hypercholesterolaemia	0.6
Other	13.5

poor compliance, 6 (0.8%) lost to follow-up, and 3 (0.4%) for financial reasons or because the patient required surgery. Only 188 patients (26%) had or reported a family history of glaucoma. Table 3 shows that the diagnosis for most patients (72.5%) was primary open angle glaucoma and that both eyes were affected in 3 of 4 patients. A pertinent medical history was reported for 295 patients (40.9%), most commonly hypertension or diabetes mellitus (Table 4). Approximately half the patients received concomitant medication during the study period (Table 5).

Table 5. Concomitant medications.

Medication	Percent of patients (n = 345)
Timolol	33.9
Alphagan	12.8
Betaxolol	11.6
Dorzolamide	11.3
Cosopt	10.1
Brinzolamide	7.8
Betoptic	6.9
Diamox	5.5
Pilocarpine 2%	4.3
Brimonide tartrate	2.9
Brimonidine	2.9
Norvasc	2.6
Travoprost	2.6

Efficacy

IOP measurements of both eyes of each patient were included. The overall mean IOPs decreased throughout the treatment period (Figure 1). This is shown as an increasing change from baseline IOP in Table 6. There was a significant effect on the IOP at succeeding visits ($p < 0.001$) and in each patient ($p < 0.001$), as shown by repeated measures ANOVA analysis.

The overall mean percentage reduction in IOP at the end of the study was 40.8%. The percentage of patients who achieved specific percentage reductions in IOP at the end of the study is shown in Figure 2. A mean IOP reduction from baseline of ≥30% was observed in 62% of patients. Responders were defined as those having a reduction of IOP of ≥10 mm Hg from baseline at the final visit. In this study, 91.7% of patients were responders. A mean IOP of 15 mm Hg or less was achieved by 60.5% of the patients. Assessments of physicians and patients were comparable, with 31.1% and 28.0% of the latter groups, respectively, rating the drug as 'excellent' and 53.4% and 52.7% rating the drug as 'very good'.

Figure 1. Mean intraocular pressure measured weekly during treatment.

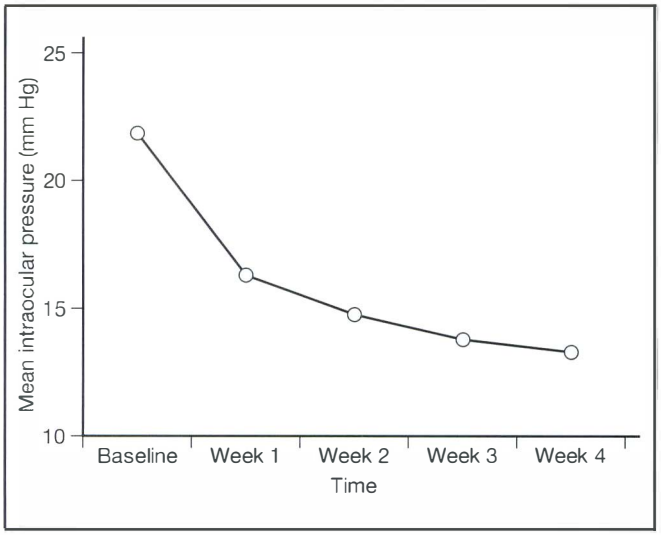


Table 6. Mean intraocular pressure (IOP) change from baseline at each weekly visit.

IOP change (mm Hg)	Visit 1	Visit 2	Visit 3	Visit 4
Mean (SD)	5.8 (6.1)	7.3 (7.3)	8.3 (7.7}	8.8 (7.9)
Median	5.0	6.0	7.0	8.0
Range	26-38	24-38	22-38	23-43

Overall, 84.5% of physicians and 80.7% of patients rated the drug as either excellent or very good.

Safety

Most patients (93.8%) reported no adverse event during the study and no serious adverse event was reported over the entire duration of the study. Table 7 presents a summary of all ocular and systemic adverse events reported by the 47 patients (6.5%) who experienced such events. The most common adverse events reported were conjunctivitis, rashes, and vasodilation. Only 65.9% of adverse events were considered related to the study drug and 72.3% were of mild severity. Three patients temporarily discontinued treatment and 2 patients permanently discontinued treatment due to adverse events experienced, which were all reported to be of moderate severity. Approximately 50% of the adverse effects had cleared by the end of the study period.

Table 7. Number of patients with ocular or systemic adverse events reported at least once during the study.

Variable	Number of patients (%)
Signs and symptoms (n = 721)	
Conjunctivitis	27 (3.7)
Rashes	4 (0.6)
Vasodilation	4 (0.6)
Other	12 (1.7)
Severity (n = 47)	
Mild	34 (72,3)
Moderate	13 (27.6)
Relation to treatment (n = 47)	
Related	31 (65.9)
Unknown	4 (8.5)
Unspecified	12 (25.5)
Action on study medication (n = 47)	
No action	30 (63.8)
Temporarily discontinued	3 (6.4)
Permanently discontinued	6 (12.8)
Unspecified	8 (17.0)
Outcome of adverse event (n = 47)	
Cleared	25 (53.2)
Still present	9 (19.1)
Unknown	2 (4.3)
Unspecified	11 (23.4)

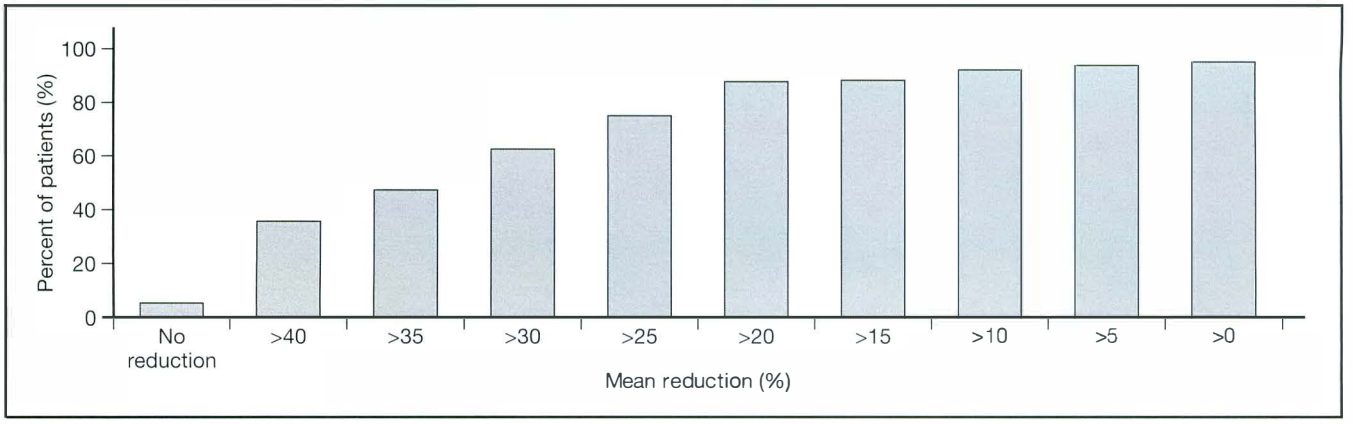
Discussion

The primary goal of glaucoma therapy is to prevent or minimise damage to the optic nerve brought about by the glaucomatous disease process. Lowering IOP has been found to reduce the risk of optic nerve damage and subsequent visual field loss. In patients with glaucoma, the most frequent approach to medical therapy has been to significantly lower IOP and achieve a specific pressure range as a clinical goal.

The choice of therapeutic agent(s) to bring about this goal is influenced by several factors. Effectiveness of IOP reduction, ocular and systemic safety, and tolerability are the most important factors. In this open-label trial, the clinical efficacy and safety of latanoprost in 721 patients with open angle glaucoma and ocular hypertension were evaluated in a 'real-life' clinical setting. Efficacy was judged on the basis of IOP reduction from baseline value, while assessment of safety and tolerability relied on observed and reported adverse events associated with therapy.

This trial has shown that once-daily latanoprost is effective in providing IOP control. This was shown by treatment-associated changes in mean IOP measurements, mean change in IOP from baseline, and in the percentage of patients reaching specific low target pressures. The results of this study compare favourably with those of previous clinical trials performed under more rigorous study conditions, such as trials conducted in the USA,[4] Scandinavia,[5] UK,[6] and Japan.[7]

Figure 2. Frequency distribution of patients with specific percentage reductions in intraocular pressure at the end of the study (n = 721).



The proven side effects of latanoprost include conjunctival hyperaemia and iris colour and eyelash changes. None of these side effects have been shown to be harmful. In this study, the most common side effect was mild conjunctival redness/hyperaemia, reported in about 10% of patients, 2 of whom discontinued treatment because of this. Ocular burning or stinging was reported by less than 1% of patients. No iris colour or eyelash changes were reported. The dark coloured irises of the study participants and the relatively short observation period probably explained this factor. No systemic or serious adverse events were reported. This safety profile was also consistent with previous studies conducted abroad. The favourable assessments given by both physicians and patients were a reflection of the excellent safety and efficacy of latanoprost in this clinical trial.

All studies have limitations that might affect the interpretation of the results. In this study of clinical efficacy and safety of latanoprost in a 'real life' clinical setting, physicians were given the freedom and flexibility to monitor their patients in a normal situation rather than being constrained by a strict study protocol. As this was a non-interventional study, all patients who were eligible to receive latanoprost were included in the study, irrespective of whether they had been newly prescribed latanoprost or had been switched to latanoprost, or whether there had been a wash-out of previously used prostaglandins. The protocol did not allow identification of such differences between cases.

In summary, this study has shown that latanoprost given once daily has significant and sustained ocular hypotensive efficacy and is relatively safe for use in patients with open angle glaucoma and ocular hypertension.

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Intraobserver and Interobserver Reliability of Measurements of Ultrasound Biomicroscopy Images in Primary Angle Closure Suspects

Krishna K Ramani, Mani Baskaran, Ronnie George, Joseph Roy, Lingam Vijaya
Sankara Nethralaya, Medical and Vision Research Foundation, Chennai, India

Aim: *To evaluate inter- and intraobserver reliability of measurements of ultrasound biomicroscopy images of primary angle closure suspects.*
Methods: *Ultrasound biomicroscopy images from all quadrants were obtained from 57 primary angle closure suspects between March 2003 and July 2003 at the glaucoma clinic of a tertiary eye care centre. One high-quality ultrasound biomicroscopy image, in which critical anatomical features were clearly visible, was selected for each patient. For interobserver reliability assessments, 2 experienced examiners independently measured 5 parameters of 20 randomly selected images using the calipers in the ultrasound biomicroscopy software. Randomisation was achieved by random clicking of the mouse pointer on the file names in the directory containing the 57 images. The parameters measured were angle opening distance, trabecular meshwork-ciliary process distance, iris thickness, anterior chamber angle, and iridociliary process distance. For intraobserver reliability assessments, these 5 parameters were measured twice in a different set of 25 randomly selected images by one of the examiners. Coefficients of variation were calculated for these observations as a measure of reliability.*
Results: *Interobserver reliability was rated good (coefficient of variation <10%) for angle opening distance, trabecular meshwork-ciliary process distance, and iris thickness only. Intraobserver reliability was good for all parameters.*
Conclusions: *Reliable measurements of ultrasound biomicroscopy parameters are possible in patients with narrow angle configuration and reliability is good when a single observer makes repeated measurements of a given ultrasound biomicroscopy image.*

Key words: *Angle-closure glaucoma, Early diagnosis, Observer variation, Ophthalmologic diagnostic techniques, Ultrasound biomicroscopy*

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Introduction

Ultrasound biomicroscopy (UBM) has provided an opportunity for clinicians and researchers to visualise, at near microscopic resolution, regions of the eye not easily examined otherwise. This paves the way for diagnoses and novel therapeutic interventions for patients with anterior segment disorders.[1] Using the calipers provided in the UBM software, anatomical variations in anterior segment parameters can be quantified in saved UBM images.[2] However, for a parameter to be useful quantitatively, it must be possible to measure it reproducibly. The configuration and relative proportions of structures in images obtained by scanning depend on the plane of section, degree of tilt from the perpendicular in the scanning probe, and the distance from the centre of the anterior chamber.[3] Thus, there is the potential for artifacts to confound the interpretation of results, especially the interpretation of sequential UBM mages obtained during follow-up of individual patients.

In this study, interobserver and intraobserver reliability of measurements of various parameters in UBM images obtained from primary angle closure (PAC) suspects (Figure 1) have been evaluated. Previous studies of normal angle eyes (Figure 2) showed good intraobserver reliability of angle measurement.[3-6] However, the effects on inter- and intraobserver reliability of measurements of UBM images of anterior crowding in PAC suspects have not previously been reported.

Correspondence: Dr Lingam Vijaya, Sankara Nethralaya, Medical and Vision Research Foundation, 18 College Road, Chennai 600 006, India. Tel: (91 044) 2823 3556/2827; Fax: (91 044) 2825 4180; E-mail: drlv@snmail.org

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Figure 1. Ultrasound biomicroscopy image of a primary angle closure suspect with narrow angle.

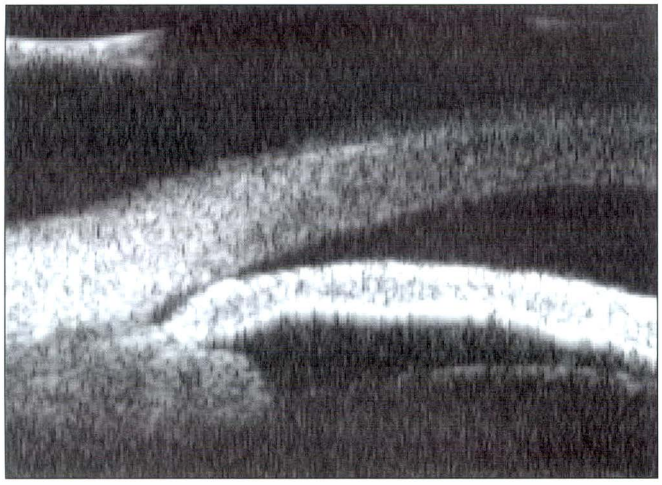
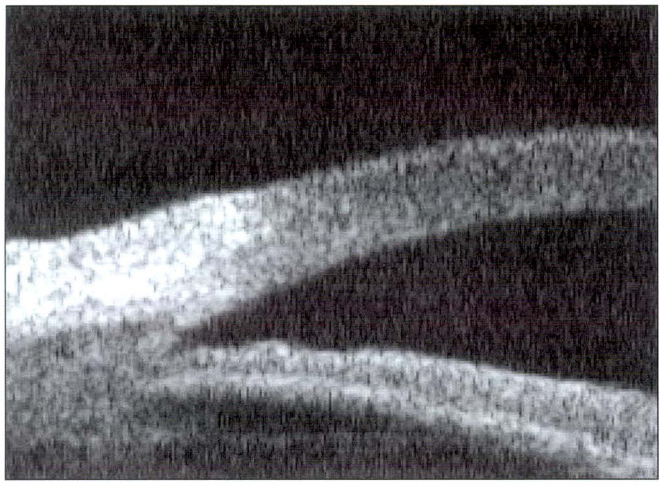


Figure 2. Ultrasound biomicroscopy image of a normal angle.



Methods

UBM (UBMP40, Paradigm, USA) images of all quadrants, scanned under dim-room illumination, were obtained from 57 PAC suspects by 2 of the authors between March 2003 and July 2003 at the glaucoma clinic of a tertiary eye care centre. These images were stored in a computer in the internal data format of the accompanying software. The criteria for inclusion of patients were posterior trabecular meshwork not visible gonioscopically for at least 180° (equivalent to modified Shaffer grade 1 or less), no synechial changes, normal intraocular pressure, and normal disc features. Patients who were asymptomatic PAC suspects were included. The exclusion criteria were peripheral anterior synechiae, plateau iris, and peripheral iridotomy. For each patient, a good quality UBM image showing clear demarcation of the scleral spur and the limbal architecture was selected.[3] From these 57 images, one set of 20 UBM images and a different set of 25 UBM images were randomly selected for inter- and intraobserver analysis, respectively. Randomisation was achieved by random clicking of the mouse pointer on the file names in the directory containing the 57 images. Two independent observers measured the parameters using the calipers available in the UBM software.[3]

Measurements of Ultrasound Biomicroscopy Images

UBM parameters commonly used in this clinical practice were measured, 4 measurements of distance and 2 angle measurements, as follows:

- trabecular meshwork-ciliary process distance (TCPD) — measured as a line extending from a point 500 mm anterior to the scleral spur along the corneal endothelium dropping perpendicularly through the iris to the most anterior ciliary process seen during scanning in that meridian
- iridociliary process distance (ICPD) — measured from the iris pigment epithelium to the ciliary process along the same line as TCPD
- iris thickness (IT) — measured along the same line as TCPD
- angle opening distance (AOD) — measured on a line perpendicular to the trabecular meshwork, 500 mm from the scleral spur to the iris stromal surface
- anterior chamber angle (ACA) — measured with the apex in the iris recess and the arms of the angle passing through a point on the trabecular meshwork 500 mm from the scleral spur and a point on the iris perpendicularly opposite.

Interobserver Reliability

Two of the authors, both experienced examiners, measured the parameters listed above in 20 images, processing each image in a fixed order. Each observer was unaware of the other's measurements. For each parameter, the coefficient of variation (CV) between the 2 observers was calculated.

Intraobserver Reliability

One of the examiners was shown 25 images on screen and was asked to measure the 5 parameters twice. The interval between the first and the second measurements of the same image was more than 2 days. The order of presentation of the images for the second measurement was varied randomly using computer-generated random numbers. For each parameter, the CV between the 2 measurements was obtained. A coefficient of variation of <10% was considered indicative of good reliability.[3]

Results

Interobserver reliability was good (CV <10%) for measurements of AOD, TCPD, and IT (Table 1). However, ICPD and ACA showed

Table 1. Interobserver reliability of the measurement of ultrasound biomicroscopy parameters.

Parameter*	Coefficient of variation (%)
Angle opening distance	1.58
Trabecular meshwork-ciliary process distance	3.73
Iridociliary process distance	13.21
Iris thickness	3.92
Anterior chamber angle	13.02

* Each parameter measured in 20 images by 2 observers.

Figure 3. Analysis of agreement between measurements of observers 1 and 2: angle opening distance (AOD).

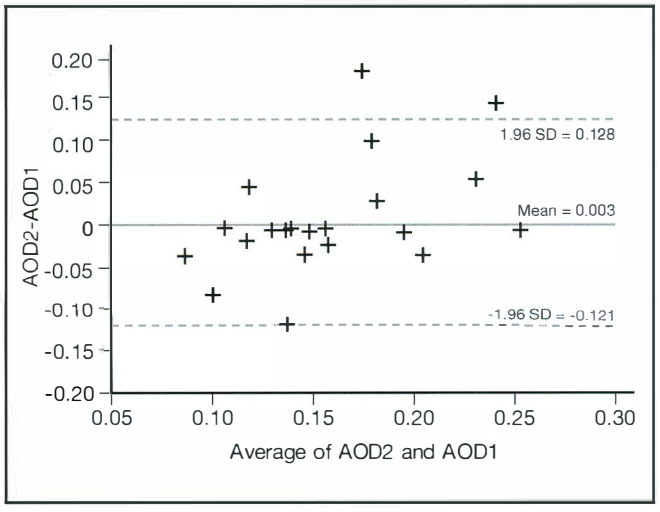
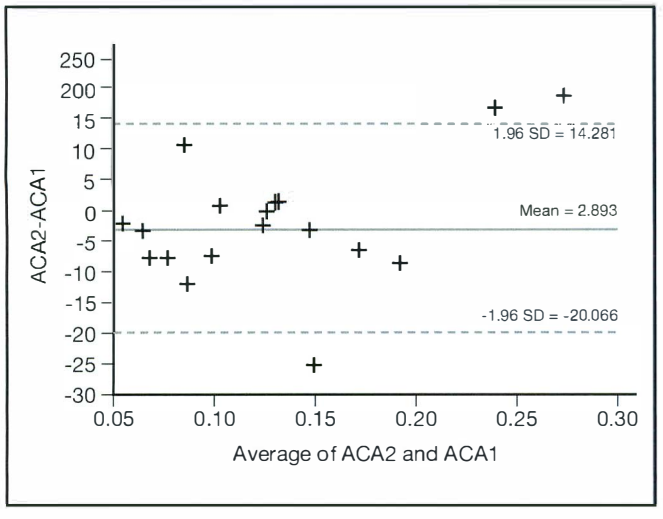


Figure 4. Analysis of agreement between observers 1 and 2: anterior chamber angle (ACA).



higher CV values suggestive of poor agreement between the examiners. Interobserver differences in the measurements of AOD and ACA analysed by the method of Bland and Altman[7] are shown in Figures 3 and 4. The mean difference was 0.003 (95% confidence interval [CI], 0.128 to -0.121) for AOD and -2.893 (95% CI, 14.28 to -20.66) for ACA. Intraobserver reliability was good for all 5 parameters measured (Table 2).

Table 2. Intraobserver reliability of the measurement of ultrasound biomicroscopy parameters.

Parameter*	Coefficient of variation (%)
Angle opening distance	0.36
Trabecular meshwork-ciliary process distance	0.24
Iridociliary process distance	0.30
Iris thickness	3.42
Anterior chamber angle	4.78

* Each parameter measured twice in 25 images by a single observer.

Discussion

Quantitative measurements of UBM images are useful for evaluating the pathophysiology of angle closure mechanisms for research purposes. This technique may also be used for follow-up of patients with narrow angle or angle closure glaucoma. Research studies involving UBM of angle closure glaucoma have included anterior segment imaging and quantitative measurements.[8-11] However, the reproducibility of parameters assessed by UBM needs to be evaluated before this procedure can be used routinely in clinical practice.

Inadequate reproducibility or excessive between-measurement variability can arise from systematic differences between observers or the instruments used or from physiological changes in the parameters measured.[3] Several studies have reported that intraobserver reliability of measurement (repeated measurements by the same individual) was good for most of the parameters assessed in UBM images.[3-6] However, interobserver reliability was poor for some parameters and varied between studies. The quality of images was suggested as the major reason for this variability; but even when good quality images were chosen the variability remained. All previous studies used UBM images of normal eyes for evaluating inter- and intraobserver reliability of quantitative assessment of UBM parameters.

This study reports the inter- and intraobserver reliability of measuring 5 parameters in good quality UBM images of PAC suspects for the first time. Some of the parameters included (AOD500, IT, and TCPD) have well-defined landmarks for measurement, while the landmarks are more ambiguous for others (ICPD and ACA). Intraobserver reliability was good for all parameters assessed. Interobserver reliability was poor for 2 parameters, ICPD and ACA. However, Bland and Altman's analysis[7] showed good agreement between 2 observers for AOD and ACA measurements. Tello et al reported similar results for normal eyes.[3]

The variability in measurements between individual observers may be due to variations in identifying the anatomical location of the scleral spur, a defined reference point for some measurements. When the same examiner measures an image repeatedly, the location of this reference point may show little variation, perhaps explaining the good intraobserver reproducibility achieved. In this

study, errors in measurement tended to occur when measuring ICPD, which involves locating a starting and end point, both of which are ill defined, and ACA, which requires locating more than 2 points. In contrast, parameters such as AOD500, TCPD and IT, which rely on well-defined landmarks, showed good reliability.

Some of the limitations of this study were as follows: only 5 of all the UBM parameters reported in the literature were assessed, only the software available with the UBM instrument was used, and variability using the UBM Pro 2000 software available for measuring other parameters such as angle recess area was not assessed. Measurement of the latter parameter with UBM Pro 2000 is semi-automated and is reported to be a useful parameter for assessing angle configuration.[12] Semi-automation of imaging tools may offer a solution to interobserver variability.

In summary, this study of PAC suspects indicates that caution should be exercised when interpreting quantitative differences in parameters measured in UBM images by different individuals and highlights the subjective nature of measuring some of these parameters. It is therefore suggested that interpretations of repeated measurements of the same image or follow-up images based on assessments by more than one observer should be avoided until acceptable and reliable objective alternatives are found. Alternatively, the parameters chosen when follow-up measurements are required should have well-defined starting and end points, as for AOD500, TCPD, and IT. The results of this study of eyes of PAC suspects, which are similar to those obtained for normal eyes,[3-6] show that reliable measurements of UBM parameters are possible with narrow angle configuration and that reliability is good when a single observer makes repeated measurements of a given UBM image.

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The Effects of Topical Antiglaucoma Drugs on the Conjunctival Cell Profile of Asian Patients

Ahmad Tajudin Liza-Sharmini,[1] Mutalib O Abdul,[1] Manoharan Madhavan[2]
[1]Department of Ophthalmology, and [2]Department of Pathology, School of Medical Sciences, Universiti Sains Malaysia, Kota Bharu, Malaysia

Aim: To determine the effects of topical antiglaucoma drugs on the conjunctival cell profile of glaucomatous Malaysian patients.
Methods: Quantitative histological analysis of goblet cells, inflammatory cells, mast cells, and fibroblasts of 22 conjunctival biopsies was performed using a light microscope. These biopsies were obtained from consenting patients during trabeculectomy, triple procedure, or cataract surgery. Eleven biopsies were obtained from glaucomatous eyes that had been exposed to topical antiglaucoma drugs over a minimum period of 3 months. This group was further subdivided into single- and multiple-treatment groups according to the number of drugs received. Age-matched conjunctival biopsies obtained from 11 non-glaucomatous eyes during cataract surgery served as controls.
Results: Mean duration of topical antiglaucoma drug treatment was 22.8 months (SD, 16.1 months). There were significant increases in the numbers of lymphocytes ($p = 0.01$) and plasma cells ($p = 0.013$) in conjunctiva exposed to topical antiglaucoma drugs compared with those from the control group. Macrophages were absent from both groups of conjunctival biopsies. There also appeared to be fewer polymorphs, mast cells, and goblet cells in the study group compared with controls. There were no statistically significant differences between the conjunctival cell profiles of the single- and multiple-treatment groups.
Conclusion: Although limited by small sample size, this study has provided minimal evidence of subclinical chronic inflammation in conjunctiva exposed to topical antiglaucoma drugs.

Key words: Adverse effects, Conjunctiva, Cytology, Eyedrops, Filtering surgery, Glaucoma

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Introduction

The management of glaucoma presents a great challenge to the ophthalmologist. The main aim is to improve the quality of life and to retard the progression of optic nerve damage. The relative merits of surgical intervention, mainly trabeculectomy, versus medical treatment have been debated for decades. Trabeculectomy is reported to reduce intraocular pressure (IOP) fluctuations more effectively than medical treatment[1] and the Cochrane database[2] offers some evidence that trabeculectomy is more effective in retarding visual field deterioration in severe cases of open angle glaucoma. The Cochrane database was compiled during the era when pilocarpine was used as the first-line drug. Since then, the availability of more potent drugs and reports of a higher incidence of cataract post-trabeculectomy[3,4] have resulted in a sharp decline in the rate of trabeculectomy surgery. However, long-term treatment with topical antiglaucoma drugs has been postulated to induce excessive healing, which is associated with failure of trabeculectomy surgery.[5-7]

The conjunctiva acts as a passive, semipermeable barrier that allows entry of topical antiglaucoma drugs and is therefore exposed to the effects of these drugs. The conjunctiva is also the most delicate and crucial tissue encountered during trabeculectomy surgery. The success of trabeculectomy surgery depends on the state of the conjunctiva, which influences the healing process at the conjunctival-scleral interface and the maintenance of bleb function. Thus, the conjunctiva plays an important role in both the medical and surgical treatment of glaucoma.

Subclinical inflammation of the conjunctiva is believed to be either a direct effect of topical drugs such as miotics or sympathomimetics or an indirect effect of the preservatives used, especially benzalkonium chloride.[8,9] The duration of treatment (time of exposure) and the number of topical drugs prescribed has also

Correspondence: Dr Ahmad Tajudin Liza-Sharmini, Department of Ophthalmology, School of Medical Sciences, Health Campus, 16150 Kota Bharu, Kelantan, Malaysia.
Tel: (60 9) 766 4563; Fax: (60 9) 765 3370;
E-mail: liza@kb.usm.my

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been identified as an important risk factor for trabeculectomy failure, as well as the type of glaucoma, age, previous failed trabeculectomy, and previous ocular surgery.[10,11]

Ethnicity is believed to be another factor that determines the success of trabeculectomy.[12] The success rate of primary trabeculectomy among Asian patients appears to be lower than among Caucasian and black patients.[12-16] There have been several studies of the effect of topical antiglaucoma drugs on the conjunctival cell profile of Caucasian and black patients[5-7,14] but no comparable study of Asian patients has been reported. The aim of this study was to evaluate the effect of topical antiglaucoma drugs and the impact of the number of drugs used for treatment on the conjunctival cell profile of Asian patients to gain insight into factors contributing to the low success rate of trabeculectomy among Asian patients compared with other ethnic groups.

Methods

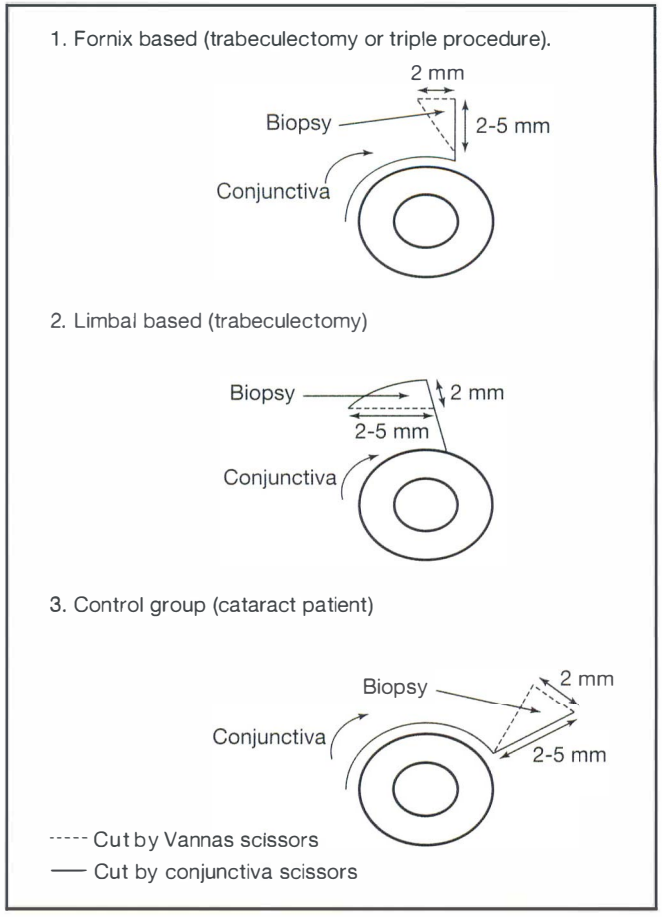
The participants in this cross-sectional, comparative study were glaucoma patients, with or without the presence of visually significant cataract, for whom either primary trabeculectomy or a triple procedure was indicated after failure of treatment with topical antiglaucoma drugs (group 1) and an age-matched control group (group 2). Conjunctival biopsies were obtained from the patients during surgery at the Hospital Universiti Sains Malaysia, Kelantan, Malaysia, from 1999 to 2000. This study was conducted with the approval of the Ethical Committee, School of Medical Sciences, Universiti Sains Malaysia, and written consents were obtained from all patients.

Additional selection criteria for patients in group 1 were previous treatment with topical antiglaucoma drugs for a minimum period of 3 months and age between 40 and 80 years. Patients with a history of acute glaucoma, neovascular glaucoma, uveitic glaucoma, aphakic glaucoma, secondary glaucoma associated with systemic disease, any ocular manifestation involving the conjunctiva, or previous ocular surgery were excluded. Group 1 was further subdivided into groups 1A and 1B depending on previous treatment with topical antiglaucoma drugs. Patients in group 1A had been treated with a single drug while those in group 1B had been treated with more than one drug.

The control group (group 2) consisted of patients, age-matched to group 1, from whom conjunctival biopsies were obtained during cataract surgery. Exclusion criteria included any ocular problem other than cataract, any ocular manifestation involving the conjunctiva, previous ocular surgery, or chronic use of any topical eye drops for more than 6 months prior to surgery.

Wedge-shaped conjunctival biopsies were obtained while forming the fornix-based conjunctival flap in the superotemporal bulbar area during the first step of surgery (Figure 1). Biopsies were 2 mm wide and 2 to 5 mm long, depending on the amount of tissue available without compromising the surgery. Conjunctival forceps were used to lift the conjunctiva and a Weck's cell was passed below the dissected Tenon's capsule to minimise damage and crumpling of the conjunctiva. However, the Tenon's capsule was not included in the histological analysis. The conjunctiva was then cut using Vannas scissors.

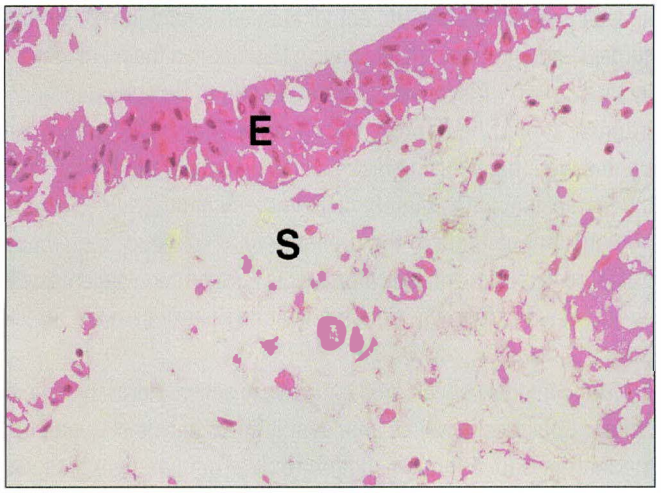
Figure 1. Diagram of the technique for obtaining a conjunctival biopsy during trabeculectomy, triple procedure, and cataract surgery.



The specimen was fixed immediately in 10% formalin and sent to the Histopathology Laboratory, Hospital Universiti Sains Malaysia, for routine tissue processing, blocking, sectioning, and staining. Three slides of each specimen (3 to 4 sections per slide) were stained with either haematoxylin and eosin (H&E), alcian blue, or toluidine blue. Alcian blue stains goblet cells, toluidine blue specifically stains mast cells, and H&E staining allows assessment of inflammatory cells.

Histological analysis was performed with a Leica DMR light microscope and a 40x objective. The microscope was connected to a Leica Q500IW computer and images were analysed using Leica Q Win software. Both the epithelial layer and substantia propria

Figure 2. Photomicrograph showing the epithelium (E) and the substantia propria (S) of a conjunctival biopsy. Note the presence of goblet cells in the epithelial layer and inflammatory cells in the substantia propria (haematoxylin and eosin stain; original magnification, x 400).



were assessed. The area of each field of view was 0.1 μm² and 1 section provided 20 fields of view per tissue layer. Two sections were selected on each slide and cells were counted in a total area of 0.8 mm² in each layer.

Two investigators, who were unaware of patient identity, identified and counted the following cell types independently: goblet cells (alcian blue-stained) and non-epidermal cells in the epithelial layer, and lymphocytes, neutrophils or polymorphs, plasma cells, macrophages, mast cells (toluidine-blue stained), and fibroblasts in the substantia propria. All extravascular cells in the specified area were counted except those adjacent to blood vessels (Figure 2). To obtain an overall estimate of the numbers of each cell type present in each specimen, the counts of the 2 investigators were averaged. Statistical analysis was performed using the Statistical Package for the Social Sciences version 10 and the non-parametric Mann-Whitney *U* test.

Results

The demographic data of patients involved in the study are given in Table 1. The majority of conjunctival biopsies were from Malay patients (59.1%) followed by Chinese (36.4%) and Indian (4.5%) patients, which generally reflects local ethnicity. Diagnoses of glaucoma type in group 1 patients are indicated in Table 1. The mean duration of topical antiglaucoma drug treatment in group 1 was 22.8 months (SD, 16.1 months). The multiple-treatment group (group 1B) had been exposed to antiglaucoma drugs for a longer period than the single-treatment group (group 1B) at 24.2 months (SD, 19.0 months) compared with 21.2 months (SD,13.9 months), respectively, but this difference was not significant. The medications each patient received are indicated in Table 1.

Table 1. Demographic characteristics.

Characteristic	Study group (n = 11)	Control group (n = 11)
Mean age (SD) [years]	66.9 (9.7)	65.6 (8.8)
Sex		
Male	7	6
Female	4	5
Race		
Malay	5	8
Chinese	5	3
Indian	1	0
Diagnosis		
Primary open angle glaucoma	6	0
Chronic angle closure glaucoma	3	0
Pseudoexfoliation glaucoma	2	0
Cataract	0	11
Treatment		
Timolol only	5	0
Timolol/pilocarpine	4	0
Timolol/dorzolamide	1	0
Timolol/latanoprost	1	0

Table 2. Comparison of conjunctival cell counts in glaucoma patients (group 1) and controls (group 2).

Cell type	Number of cells per 0.8 mm²		p Value*
	Group 1 Mean (SD)	Group 2 Mean (SD)	
Epithelial layer			
Goblet cells	50.6 (65.3)	41.4 (30.6)	0.470
Substantia propria			
Lymphocytes	6.7 (9.6)	22.1 (19.2)	0.010†
Polymorphs	7.0 (16.4)	4.1 (4.3)	0.512
Plasma cells	3.3 (4.0)	17.4 (18.1)	0.013†
Mast cells	92.0 (32.0)	78.1 (31.1)	0.193
Fibroblasts	256.1 (68.1)	210.4 (86.1)	0.217

* Indicates significance of difference between values for 2 groups, Mann-Whitney *U* test.
† Values for this cell type are significantly different.

Table 2 illustrates the mean conjunctival cell counts for groups 1 and 2. There was a significant increase in the lymphocyte and plasma cell count in the study group compared with the control group. A total absence of macrophages was noted in both groups. Extensive presence of pigment was noted in all biopsies. There were apparent reductions in the numbers of goblet cells, mast cells, and fibroblasts in the study group compared with controls but these differences were not statistically significant. Table 3 shows that there were no statistically significant differences between the conjunctival cell profile of the single-treatment group (group 1A) and that of the multiple-treatment group (group 1B).

Discussion

Although the evidence is inconclusive, long-term treatment with multiple topical antiglaucoma drugs is regarded as an important risk factor for failure of filtering surgery. The conjunctival cell profile of patients exposed to topical antiglaucoma drugs has been shown

Table 3. Comparison of conjunctival cell counts in glaucoma patients treated with one drug (group 1A) or multiple drugs (group 1B).

Cell type	Number of cells per 0.8 mm²		p Value*
	Group 1A Mean (SD)	Group 1B Mean (SD)	
Epithelial layer			
Goblet cells	54.6 (38.6)	30.3 (18.8)	0.25
Substantia propria			
Lymphocytes	23.8 (20.3)	20.7 (20.0)	0.66
Polymorphs	2.0 (1.4)	5.8 (5.3)	0.25
Plasma cells	22.6 (20.3)	13.0 (10.1)	0.43
Mast cells	85.0 (34.8)	65.7 (23.7)	0.18
Fibroblasts	207.2 (77.3)	213.0 (100.1)	0.93

* Indicates significance of difference between values for the 2 groups, Mann-Whitney *U* test.

to be enriched in inflammatory markers and macrophages.[5-8] The greater number of macrophages in the conjunctival cell profile of black patients was thought to be responsible for inducing excessive healing post-trabeculectomy, leading to a poor success rate.[14]

Macrophages play a pivotal role throughout the sequence of events post-trabeculectomy surgery. Macrophages are thought to be the major source of fibrogenic and angiogenic cytokines, which are important in the normal healing process and are essential markers for chronic inflammation. In the present study, no macrophages were found in either the control or study groups, despite the fact that the area analysed histologically was larger than in previous studies.[5-7] This is not unexpected as few macrophages are found in the deeper layers of the substantia propria of the normal conjunctiva and the subtenon layer. Allansmith has reported a similar absence of macrophages in the normal palpebral and forniceal conjunctiva assessed by conjunctival impression cytology.[17] However, others have reported the absence of macrophages from some, but not all, conjunctival biopsies both from glaucoma patients and controls.[18] Thus, the apparent absence of macrophages in the present study may have been due to the small number of conjunctival biopsies assessed.

Previous studies of cell numbers in glaucoma patients have indicated a significant increase for all inflammatory cells and a reduction for goblet cells.[5-7] In the present study of Asian eyes, only lymphocytes and plasma cells showed a significant increase in eyes exposed to topical antiglaucoma drugs. Increased numbers of lymphocytes and plasma cells, which are the predominant immunocompetent cells in the normal conjunctiva, may be an early sign of inflammation. Plasma cells, which are activated B lymphocytes and the primary source of circulating antibodies, may be an indication that topical antiglaucoma drugs have the ability to activate the immune system. Pre-existing persistent activity of the conjunctival immune system may predispose to overproduction of pro-inflammatory and profibrogenic cytokines during the wound healing process post-trabeculectomy.[19]

Baun et al have claimed that observed increases in inflammatory cells may be due to surgical trauma.[18] However, the technique adopted in the present study minimises surgical trauma as well as representing the actual surgical technique of filtering surgery and may induce less surgical trauma than the method used by Baun et al.[18] Polymorphs, the first cells to be activated post-trauma, should have been significantly increased if surgical trauma were the inducing factor. Thus, it appears more likely that the increase in inflammatory cells in the conjunctival cell profile of glaucoma patients in the present study was due to previous exposure to topical antiglaucoma drugs. Furthermore, patients with uveitic glaucoma or any glaucoma with a history of acute attack were excluded.

The conjunctival cell profile may vary according to the site of biopsy. Goblet cells will be abundant if the biopsy is derived from the inferior site. Although superior bulbar conjunctival biopsies are not from the area most exposed to topical drugs,[20] they are representative of histological changes that may take place post-trabeculectomy.

The duration of exposure to topical antiglaucoma drugs may play an important role in the induction of changes in the conjunctival cell profile. Significant changes in the conjunctival cell profile have been observed after exposure of at least 3 years[6] or 7.7 years.[5] Broadway et al found an inverse correlation for the goblet cell count and a significant increase in inflammatory cells with cumulative duration of exposure to topical treatment.[6] They also observed less significant changes in the conjunctival cell profile in eyes exposed to the topical antiglaucoma drugs for less than 3 years. It is possible that the shorter mean duration of exposure to topical antiglaucoma drugs in the present study (1.9 years) may account for the minimal changes in the conjunctival cell profile observed.

The number of antiglaucoma drugs was found to have no significant effect on the conjunctival cell profile, although there was an apparent increase in inflammatory cell numbers in patients receiving multiple treatments. In previous studies, the extensive use of sympathomimetics, especially the combined use of a β-blocker and miotics, was associated with significant conjunctival cell profile changes and poorer trabeculectomy outcome.[6,21] Discontinuation of sympathomimetics preoperatively and treatment with topical steroids has resulted in reversal of such changes.[21] This suggests that not only the number of medications used but also the type of medication, especially sympathomimetics, influence the induction of subclinical inflammation. However, the results of another larger study do not support this suggestion.[6] Recent advances in pharmacological treatment of glaucoma have led to decreased use of sympathomimetics. The minimal conjunctival cell profile changes observed in the present study may also be a

reflection of the absence of sympathomimetics from the treatment regimens. A majority of the patients were exposed to a β-blocker as monotherapy or in combination with miotics, dorzolamide, or latanoprost. It is possible that the presence of pigment in the conjunctiva of Asian patients may have protected against any adverse effect of topical timolol. Timolol must be used at a higher concentration (0.5%) to achieve its maximum IOP-lowering effect in individuals with dark iris colour.[22,23] Despite this, changes in the conjunctival cell profile were minimal in the present study.

It is not clear whether the active ingredient or the preservative in topical antiglaucoma drugs is more responsible for inducing conjunctival cell profile changes. Preservatives, especially benzalkonium chloride, have been shown to cause elevation of inflammatory markers in tissue culture and animal models.[9,24-26] Using impression cytology to detect expression of interleukins and inflammatory markers, Baudouin et al found that preservative-free timolol induced less expression of immunoinflammatory markers and mediators than timolol with preservative.[27] Ideally, to resolve this issue, a comparison should be made with a group of patients exposed to preservative only but due mainly to ethical considerations, this group was not included.

A greater number of goblet cells and absence of abnormal cells in the epithelial layer has been postulated to be a protective effect in reducing the exaggerated scarring process of the bleb. Moreover, the relative absence of macrophages may also play a protective role in reducing formation of an encapsulated bleb and poor trabeculectomy outcome. Based on previous observations of excessive fibrosis of the conjunctival space in darker skinned people, the success rate of trabeculectomy among Asian patients might be expected to lie between that of Caucasian and black patients.[28] However, the overall success rate of trabeculectomy for Asian patients is lower than for Caucasian patients,[12,13,15,16] suggesting that other factors are involved.

The present study provided only minimal evidence of sub-clinical inflammation in Asian eyes exposed to topical antiglaucoma drugs, an outcome that may have been influenced by the type of topical antiglaucoma drugs used and the relatively short duration of treatment. This limited study did not provide any histological explanation for the known poor trabeculectomy success rate among Asian patients. However, a study of a larger number of patients with variable duration of drug treatment may provide useful information.

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Cavernous Haemangioma of the Orbit: Clinical Presentation and Surgical Outcome

Rajat Maheshwari
Shri Ganapati Netralaya, Jalna, India

Aim: To analyse the clinical presentation, surgical outcome, and visual prognosis in patients with orbital cavernous haemangioma after removal by the orbital approach.
Methods: This study was a retrospective analysis of 9 patients (5 men and 4 women, aged 4 to 65 years) who underwent surgical removal of orbital cavernous haemangiomas between January 1999 and December 2004. The same surgeon performed the procedure in each patient. Orbital echography and computed tomography were performed preoperatively to establish the extent and location of the tumour. All tumours were removed by lateral, anterior, or medial orbitotomy depending upon their location in the orbit. The excised tumours were subjected to histopathological analysis.
Results: The follow-up period ranged from 6 months to 4 years. Complete removal of the tumour was possible in all 9 patients. Postoperative visual acuity improved, proptosis resolved completely, and overall patient satisfaction was good for all patients.
Conclusion: Clinical examination in combination with radiological investigation is highly recommended for the diagnosis of cavernous haemangiomas. Location of the tumour determines the surgical approach and early surgery results in improvement of visual function. The orbital approach is highly successful for the removal of large extraconal and intraconal haemangiomas within the orbit.

Key words: Cavernous hemangioma, Orbit, Proptosis

Asian J Ophthalmol. 2007;9:23-6

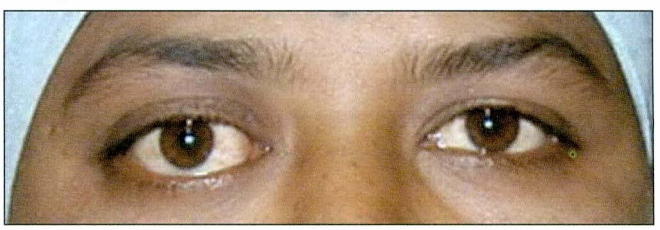
Introduction

Cavernous haemangioma is a common orbital tumour.[1-3] It is a benign, well-encapsulated, slowly progressive, and generally well-tolerated orbital neoplasm. However, because cavernous haemangiomas are frequently located intraconally, they may compromise optic nerve function and produce visual loss in otherwise healthy individuals if treatment is delayed. This study reviews the natural history, clinical features, and treatment outcomes of 9 patients with orbital cavernous haemangioma.

Methods

Complete medical records of 9 patients with cavernous haemangiomas of the orbit, treated over a 6-year period between January 1999 and December 2004, were reviewed retrospectively. Surgical removal and histological confirmation of the diagnosis was performed for all patients. Clinically, patients presented with a history of cavernous haemangioma persisting for 4 weeks to 4 years (average, 13.4 months). Presenting symptoms included protrusion of the eyeball (Figure 1), swelling, visual impairment, discomfort in the eye, and headache. None of the patients had any cutaneous vascular malformation or family history of vascular malformations. Clinical examination included assessment of visual acuity, motility, pupillary reflex, intraocular pressure, slit-lamp examination, and indirect ophthalmoscopy. This examination was carried out preoperatively and repeated at 1 and 6 weeks after surgery and 6 monthly thereafter.

Figure 1. Female patient aged 25 years with history of axial proptosis of the right eyeball of 3 months' duration.



All patients underwent orbital echography, utilising both A and B mode ultrasound (10 MHz), and orbital computed tomography (CT) to corroborate the clinical diagnosis of cavernous haemangioma and locate the lesion. The need for surgical intervention was

Correspondence: Dr Rajat Maheshwari, Shri Ganapati Netralaya, Jalna 431 203, Maharashtra, India.
Tel: (91 248) 223 7202; Fax: (91 248) 223 9001;
E-mail: rajatm@netralaya.org

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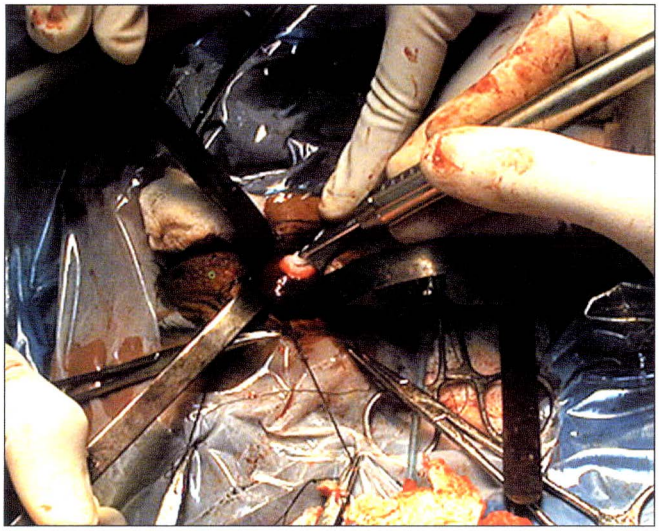
Figure 2. Large intraconal haemangioma being removed with help of a cryoprobe.



discussed with the patients or their guardians. In all patients, total excision of the tumour was considered necessary to preserve complete neurological and muscular function.

All surgeries were performed under general anaesthesia by the same orbital surgeon. Lateral orbitotomy was performed for 5 patients with large intraconal tumours located lateral to the optic nerve and medial orbitotomy was performed for 1 patient whose tumour was located medial to the optic nerve in the extraconal space. For 1 patient with tumours located intraconally between the optic nerve and medial rectus muscle, anterior lid splitting orbitomy was performed, involving a vertical lid split incision at the junction of the medial and central third of the upper lid to gain access to the medial intraconal space. In 2 patients with extraconal mass the tumor was removed via the anterior orbital approach. A cryoprobe was used to facilitate complete removal of the tumour (Figure 2). Patients' characteristics are summarised in Table 1.

All tumours were fixed in 10% formalin and subjected to histopathological examination after processing in a routine manner. The pathologist who made the diagnosis of cavernous haemangioma in all patients reviewed haematoxylin and eosin–stained slides.

Results

The average age of the 9 patients with histologically confirmed orbital cavernous haemangioma reviewed in this study was 32.4 years (range, 4 to 55 years). Six patients had right-sided involvement and 3 had left-sided involvement; 6 of the tumours were located within the muscle cone. One tumour was in the lacrimal gland fossa and 2 were in the extraconal space in the retrobulbar area. Patients' symptoms included proptosis, diminished visual acuity, palpable mass, or swelling of the lid (Table 1). Pain was not a major complaint of any of the patients, although 4 patients complained of heaviness and discomfort in the involved eye.

Objective signs of impaired visual function present in 7 patients were decreased visual acuity, afferent defect, choroidal folds, and disc oedema and/or pallor. All these patients had tumours located within the muscle cone (Table 1). Five patients had acquired anisometropia with an average value of +3.95 D (range, +1.75 to +8.00 D), which was reduced postoperatively to +1.40 D (range, 0.50 to 2.50 D). Two patients had afferent pupillary defect with partial optic atrophy.

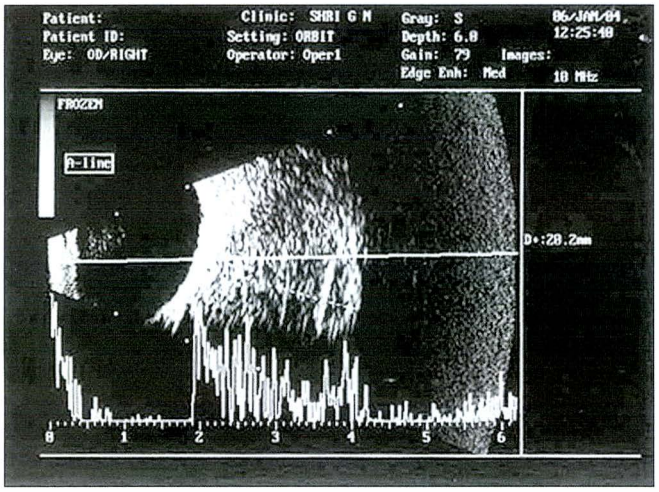
A-mode orbital echography demonstrated a pattern of uniform high reflectivity with regular internal structure, while B-mode echography revealed that the tumour had a well-demarcated border and the body of the tumour was sonoluscent with good sound transmission (Figure 3). CT, which visualised the location, shape and size of the cavernous haemangiomas, showed them as round or oval, smooth, well-defined masses with mild to moderate contrast enhancement (Figure 4).

Table 1. Characteristics of patients, haemangiomas, and surgery.

Patient number	Age (years)	Sex	Eye	Symptoms	Duration	Location	Visual acuity		Refraction (D)		Fundus present	Surgery	Comment
							Pre-operative	Post-operative	Pre-operative	Post-operative			
1	35	F	Right	P, V, Pu, E	2 years	Intraconal	CF 0.5 m	6/90	+8.00	+2.50	Present	LO	Optic atrophy
2	42	M	Right	P, S, E	6 months	Intraconal	6/6	6/6	+2.50	+1.50	Present	AO	
3	25	F	Right	P, V	3 months	Intraconal	6/6	6/6	+3.00	+0.50	Present	LO	
4	4	F	Left	P	1 month	Extraconal	6/6	6/6	—	—	—	MO	
5	11	M	Right	S	6 months	Extraconal	6/6	6/6	—	—	—	AO	
6	45	M	Left	P, S	3 months	Intraconal	6/6	6/6	—	—	Present	LO	
7	55	F	Left	P, V, E	4 years	Intraconal	CF 2 m	6/9	+4.00	+2.00	Present	LO	Partial optic atrophy
8	40	M	Right	P, V	2 years	Intraconal	6/12	6/6	+3.00	+1.00	Present	LO	
9	35	M	Right	S	6 months	Extraconal	6/6	6/6	—	—	—	AO	Haemangioma in lacrimal gland fossa

Abbreviations: P = protrusion; V = diminution of vision; Pu = afferent pupillary defect; E = restriction of extraocular movements; S = swelling; CF = counting fingers; LO = lateral orbitotomy; MO = medial orbitotomy; AO = anterior orbitotomy.

Figure 3. Echography of haemangioma. The A-mode scan shows moderate to high internal reflectivity. The B-mode scan shows well-defined borders with good sound transmission.



Complete removal of the tumour was achieved in all patients and there were no surgery-related complications. On gross examination, the tumours were well encapsulated and varied in colour from reddish blue to purple (Figure 5). Histological examination revealed that the tumours were composed of widely dilated vascular channels lined by endothelial cells, which often contained red blood cells (Figure 6).

Discussion

Cavernous haemangiomas or cavernomas are common benign neoplasms of the orbit in adults.[1-3] They are low-flow malformations that consist of ectatic, largely thrombosed and septated venous convulsions embedded in a compact capsule. Cavernomas grow as slow, painless, progressive, non-pulsatile lesions and commonly manifest in the fourth and fifth decade with a 60% to 70% female preponderance.[2,4,5] The expression of progesterone receptors in the epithelial cells of orbital cavernomas has been suggested as the cause of the high incidence in female patients.[6] All patients in this series had slow, painless, progressive proptosis. Reduced

Figure 4. Coronal computed tomography of the patient in Figure 1, in which the lesion appears as a well-defined mass in the muscle cone.

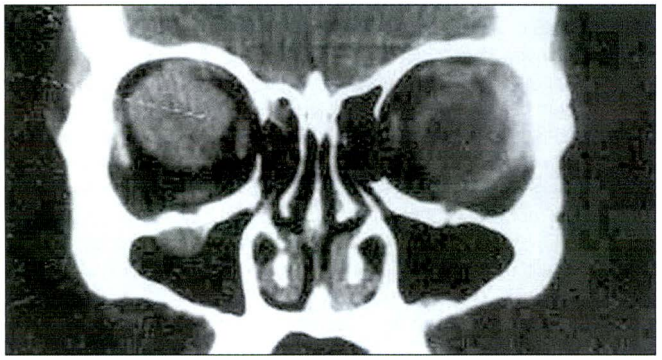
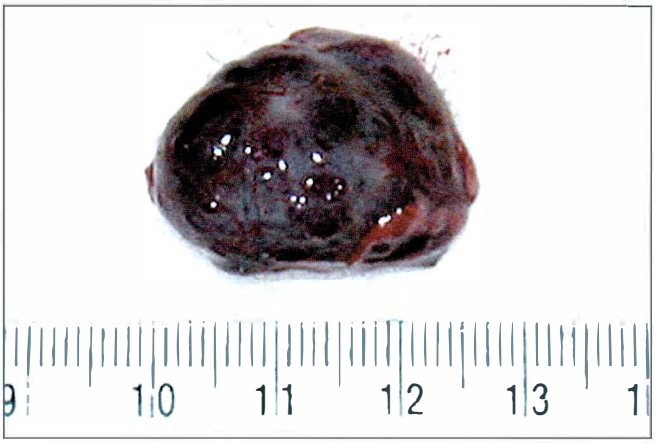


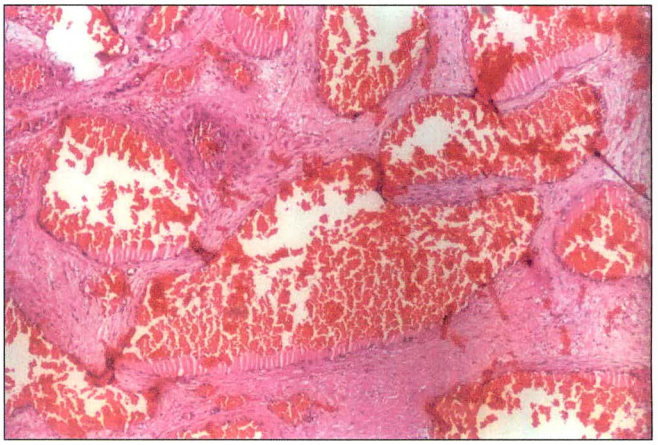
Figure 5. Well-encapsulated, reddish blue tumour with bosselated surface, removed via lateral orbitotomy from the right orbit of the patient in Figure 1.



visual acuity was due to tumour-induced hyperopia or retinopathy, which was reversible in all except 1 patient who had optic atrophy secondary to a long-standing tumour. The most common finding on ophthalmoscopy was choroidal folds followed by disc oedema and either disc pallor or atrophy.

On ultrasonography, cavernous haemangiomas are well circumscribed with clear borders, good sound transmission, and moderate to high internal reflectivity showing the internal architecture of the lesion. A-scans show multiple high reflectivities of the echo signals due to the multiple blood-filled vascular channels. CT and magnetic resonance imaging (MRI) are particularly important in the diagnostic investigation of patients with vascular disorders of the orbit. Yan and Wu reported that 93% of patients with cavernous haemangioma could be accurately diagnosed preoperatively based on the results of imaging.[5] CT generally reveals a discrete lesion with a smooth surface and defines the shape, size, extent, and relationship of the tumour to adjoining structures. In addition to conventional MRI, dynamic contrast MRI (fast

Figure 6. Histopathology showing widely dilated, blood-filled vascular channels lined with endothelial cells (haematoxylin and eosin stain; original magnification, x 100).



spin-echo sequence, 20-second interval) after bolus administration of contrast material differentiates cavernous haemangioma by differences in the contrast-enhancement spread pattern. This is particularly helpful in differentiating haemangioma from schwannoma of the orbit.[7]

All tumours were removed by the orbital approach in this study. The size of the lesion, its relationship to the bone, periosteum and soft tissue, and the purpose of the surgery largely govern the choice of the incision site. The orbit can be approached from 5 routes: superior, lateral, inferior, medial, or anterior. Each route presents characteristic advantages and disadvantages. Surgeons must use their skill and experience to choose a route that minimises the disadvantages and maximises the advantages. More orbital lesions are located in the superior anterior region of the orbit than in any other location.[8] Lesions in this area can be reached via a transcutaneous or transconjunctival route. However, care must be taken to avoid damaging the levator and superior oblique muscles, trochlea, lacrimal gland, and sensory nerves and vessels leaving or entering the orbit along the superior orbital rim. The trans-septal route (transcutaneous) provides entry into the peripheral surgical space. The lid crease is an excellent location for skin incision for this route, because it provides good surgical exposure and the scar is hidden. The transconjunctival route can be used to reach the episcleral, central, or peripheral surgical spaces via incision in the superior conjunctiva. Vertical splitting of the upper lid at the junction of the medial and central thirds allows extended transconjunctival exposure for removal of superior medial intraconal tumours.

Lateral orbitotomy is widely accepted as the technique of choice for lesions confined to the lateral aspect of the orbit. First described by Kronlein in 1889,[9] technical advances and modifications have made the lateral orbitotomy an effective and safe procedure.[10] The procedure can provide access to the deep lateral portion of the muscle cone, providing an alternative to the transcranial approach in some patients. When operating on the posterior third of the muscle cone, branches of the oculomotor nerve may be encountered. Traumatic retraction of the lateral rectus muscle can cause abduction deficit, an injury of the nerve root of the ciliary ganglion, which may result in a tonic pupil. Nevertheless, the lateral approach offers a high degree of safety and considerably less morbidity than the transcranial procedure.[9] Patients in this study underwent lateral, medial, or anterior orbitotomy depending on the location of the tumour.

Cryoextraction, as used in the present study, greatly helps in excision of well-defined, solid, encapsulated lesions thus minimising trauma to the adjacent tissues. More importantly, the tumour can be removed without risk of capsular rupture.[11] Complete excision was achieved in all 9 patients in this study. The course of incompletely excised orbital cavernoma has seldom been discussed but there is no evidence of recurrence in such patients.[12,13] It has been hypothesised that patients with orbital cavernomas may benefit more from a partial but uncomplicated excision than complete removal associated with functional deficit.[14] Histological examination, particularly after partial excision, should be carried out to rule out lymphangioma[15] and haemangiopericytoma.[16]

In conclusion, the majority of patients with orbital cavernous haemangiomas can be managed by ophthalmologists with experience in orbital surgery. The combination of clinical signs and the results of appropriate radiologic examination is helpful when planning surgery and the management of these lesions. In the present study, in which all operations were performed by the orbital approach, complete excision was possible with subsequent improvement of visual function, relief of local discomfort, and a high degree of patient satisfaction.

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Needling Bleb Revision with Mitomycin C for Failed Molteno Tube Shunt Implant

Reza Zarei, Saeid Shahhosseini
Farabi Eye Research Center, Department of Ophthalmology, Tehran University of Medical Sciences, Tehran, Iran

Aim: *Needling bleb revision with mitomycin C is an accepted method of management of failed trabeculectomy with encapsulated bleb. We report the outcome of the needling bleb revision with mitomycin C in poorly functioning filtering blebs associated with the Molteno drainage device.*
Methods: *Sixteen eyes of 16 patients with encapsulated bleb around the Molteno plate and elevated intraocular pressure not controlled by medical management, underwent bleb revision with mitomycin C.*
Results: *There were 16 eyes of 16 patients aged 5 to 65 years (mean, 28.8 ± 22.7 years). Six patients were female and 10 patients were male. Aphakia and congenital glaucoma were the most common aetiologies. The mean period of follow-up was 24 months and the duration between surgery and needling was 18.25 ± 12.10 months. Mean intraocular pressure was reduced from 28.25 ± 3.70 mm Hg preoperatively to 16.69 ± 3.14 mm Hg at 3 months and 21.13 ± 4.11 mm Hg at 6 months of follow-up. The success rate was 87.5% at 3 months, 37.5% at 6 months, and 12.5% after 2 years of follow-up.*
Conclusions: *Needling bleb revision with mitomycin C is a relatively safe and effective method in the management of failed encapsulated Molteno tube implant. Although its effectiveness may be limited, it is a repeatable procedure.*

Key words: *Glaucoma, Mitomycin, Molteno implants, Prosthesis failure, Trabulectomy*

Asian J Ophthalmol. 2007;9:27-9

Introduction

The aqueous shunting procedure was introduced by Molteno in 1968 to treat refractory glaucoma. Molteno found that this device was successful in controlling intraocular pressure (IOP) in many patients who were otherwise poor surgical candidates.[1]

The principal candidates for tube shunt surgery are patients who have failed 1 or 2 conventional filtering procedures, patients with recurrent uveitis or neovascular glaucoma, patients with functional vision (better than 20/200) and failed filtering surgery, and before cyclodestructive procedure.[2] Other indications of tube shunt procedure are aphakic and pseudophakic glaucoma, traumatic glaucoma, and congenital and juvenile glaucoma.

Following glaucoma implant surgery, the IOP follows a typical course:

1. Hypotony (1 to 2 weeks postoperatively).
2. Hypertensive phase, which may last from 2 to 7 weeks, corresponding to the development of fibrous capsule around the plate, resulting in increased resistance to passive diffusion of aqueous. The IOP rarely reaches 30 mm Hg. Following this phase, the IOP gradually decreases over the ensuing weeks to months, providing longer-lasting IOP reduction.[3]
3. Delayed postoperative IOP elevation that occurs in the intermediate to late postoperative period (more than 3 to 6 months postoperatively). In the presence of a functioning tube shunt, it is most often caused by excessive thickening of the fibrous capsule surrounding the scleral plate of the implant.

The present treatments of encapsulated blebs include: medications, revision of original shunt with or without antifibrotic agents, additional shunt, or cyclodestructive procedures.[4] The purpose of this study was to assess the efficacy of needling bleb revision with mitomycin C (MMC) in patients with Molteno tube shunt and delayed IOP elevation postoperatively.

Correspondence: Dr Reza Zarei, Farabi Eye Research Center, Department of Ophthalmology, Tehran University of Medical Sciences, No 8 Golsang Ave, Niavaran Street, Tehran 19798, Iran.
Tel: (98 21) 2273 1328; Fax: (98 21) 2273 1328;
E-mail: rzareia@yahoo.com

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Methods

This before-after (paired) observational study was conducted from September 2000 to September 2002 at the Farabi Eye Hospital, Tehran University of Medical Sciences, Tehran, Iran. Sixteen of 64 glaucomatous patients who had undergone monoplate Molteno implant surgery had IOPs greater than 21 mm Hg in delayed postoperative phase (with medical treatment). These 16 patients underwent needling bleb revision with MMC.

Needling was performed in the operating room (because of better management of complications and uncooperative patients) as follows: after preparation and drape and under topical anaesthesia, a 27-gauge needle was introduced into the subconjunctival space about 6 mm from the plate. Balanced Salt Solution was injected around the bleb. Then the needle was pushed forward to pass through the cyst wall and enter its space. Thereafter, with a gentle sweeping motion of the needle tip, the cyst wall was torn. After seeing the aqueous flow under the conjunctiva, the needle was withdrawn and a cotton applicator was compressed lightly at the entrance site to cease probable leakage. Finally, 0.01 mL MMC (0.04%) was injected subconjunctivally 180° away from the needling site and the eye was patched after instillation of chloramphenicol eye drops. Betamethasone and chloramphenicol eye drops were administered to all patients for 1 week and antiglaucoma medications were titrated according to the measured IOPs at follow-up visits.

For the purpose of this study, the procedure was considered a success if the IOP was ≤21 mm Hg with or without use of antiglaucoma medications and a failure was defined as IOP >21 mm Hg after 1 month with the use of medications.

The procedure was performed on all patients by a single individual and was repeated in failed cases within 1 month, if possible. The routine programme of follow-up was 1 day, 1 week, 2 weeks, 1 month, 3 months, 6 months, 9 months, 12 months, and 2 years after the procedure, but additional visits were performed if needed for complicated cases. Statistical analysis of the data included the paired 2-tailed Student's *t* test for preoperative and postoperative IOPs.

Results

Sixteen needling procedures were performed on 16 eyes of 16 patients. Patients were aged between 5 and 65 years (mean, 28.8 ± 22.7 years). Six patients (37.5%) were female and 10 patients (62.5%) were male. The most common types of glaucoma were aphakic and congenital (Table 1). The mean interval between surgery and needling was 18.25 ± 12.10 months (range, 6 to 48 months) and the mean follow-up of needling procedures was 24 months. Mean IOP decreased from 28.25 ± 3.70 mm Hg at baseline to 16.69 ± 3.14 mm Hg at 3 months of follow-up (2-tailed Student's *t* test; p = 0.000) and 21.13 ± 4.11 mm Hg at 6 months of follow-up (2-tailed Student's *t* test; p = 0.001). However, 24 months after the needling procedures, there was no significant difference between preoperative and postoperative IOPs (Figure 1). The only complication was subconjunctival haemorrhage that appeared after the use of MMC and was absorbed without any further problem (3 patients). The success rate was 87.5% after 3 months, 37.5% after 6 months, and 12.5% after 2 years. In 3 patients, needling was repeated within 1 month of the first procedure.

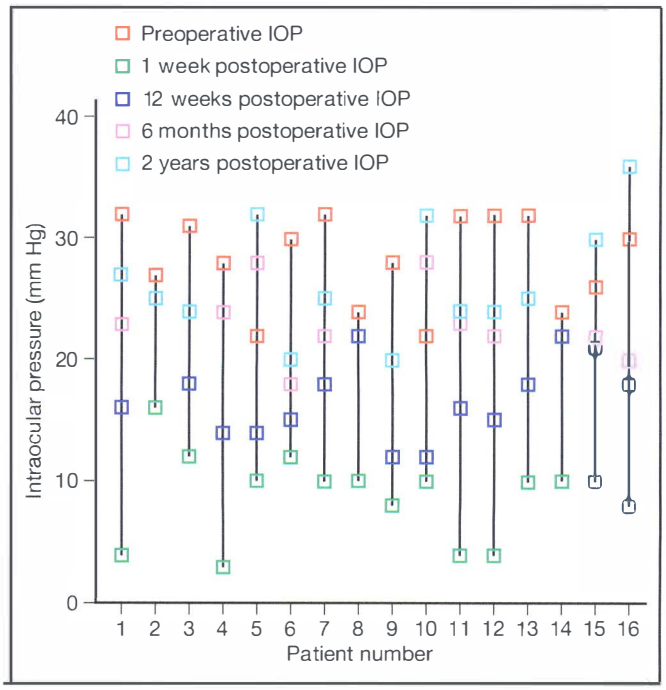
Table 1. Types of glaucoma among study patients.

Type of glaucoma	Frequency	Percent
Aphakic	5	31.3
Congenital	5	31.3
Pseudophakic	2	12.5
Sturge-Weber	2	12.5
Traumatic	2	12.5
Total	16	100

Discussion

Molteno tube shunt has been shown to be valuable in refractory glaucoma, but the most important problem in achieving successful control of IOP after placement of a drainage implant is the development of a fibrous capsule around the Molteno plate that may severely restrict the drainage of aqueous humor.[5-7] Excessive fibrosis limits the IOP-lowering effect of Molteno tube shunt.[8,9]

Figure 1. Follow-up intraocular pressure (IOP) after bleb revision with mitomycin C in 16 patients with failed Molteno tube shunt implant.



Many authors believe in conservative management (topical steroid, antiglaucoma medications, and digital massage) as the first step for encapsulated blebs.[10,11] Surgery will be required when conservative management fails.

MMC, an antitumour antibiotic isolated from *Streptomyces caespitosus*, inhibits the proliferation of fibroblasts and alters conjunctival vascular endothelium. It is 100 times more potent than 5-fluorouracil.[12,13] Needling bleb revision decreases resistance to outflow by creating a new outflow pathway and the use of MMC helps the stability of the new artificial pathway for aqueous drainage.[14] In previous studies, the method of antifibrotic agent injection varies; some authors injected MMC before needling and others after this procedure. Also, the site of injection is different between studies: over the bleb, a few millimeters peripheral to the bleb, or 180° away from the bleb (to avoid possible anterior chamber entrance of MMC and potential endothelial toxicity).[15-18]

In this study, we injected MMC after needling and 180° away from the plate for increased safety and confidence. Nevertheless, the amount of MMC used in this study is insufficient to cause endothelial toxicity in a competent cornea, even if the entire amount was inadvertently washed into the anterior chamber. If this unlikely event were to occur, the anterior chamber concentration of 16 μg/mL (based on an anterior chamber volume of 0.25 mL) would be well below the level known to cause corneal endothelial toxicity (approximately 200 μg/mL).[19] In this study, none of the patients presented with significant corneal oedema at slit lamp examination. The only complication was subconjuctival haemorrhage that occurred in 3 cases (18.75%) after injection of MMC and was absorbed without any further problem.

There are few studies in the literature of needling bleb revision of encapsulated drainage implants with MMC. Chen and Palmberg reported the success rate of a needling bleb revision of glaucoma device, without MMC application, at approximately 43% with a mean follow-up of 14.6 months.[20] Lam noted the benefit of MMC injection in bleb revision of the glaucoma device.[21]

In this study, the success rate diminished with time and after about 2 years there was no significant difference between pre- and post-needling IOPs. As needling bleb revision with MMC is technically easy and has minimal complications in comparison with other alternatives (such as surgical revision, implant exchange, and cyclodestructive procedures), it can be repeated several times until the IOP is successfully lowered by creating a passage through the fibrous tenon cyst into the subconjunctival space.[22,23]

The results of this study suggest that needling bleb revision with MMC may be a useful method for the management of encapsulated Molteno tube implants. Implanting another drainage device is very difficult (if not impossible) because of scarified conjunctiva after multiple surgeries in such patients. Although its effectiveness may be limited and relatively short, it is a repeatable, inexpensive and relatively safe procedure. A large study with more patients, in which the safety of this procedure can be evaluated by pachymetry and specular microscopy measurements, is recommended.

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Brucellosis: a Forgotten Cause of Uveitis?

Tanya N Moutray, Michael A Williams, Richard M Best, Gerald F McGinnity
Department of Ophthalmology, Royal Victoria Hospital, Belfast, UK

There are many occupational hazards associated with working in an agricultural environment. This report highlights a particular cause of visual problems, brucellosis, a condition historically associated with working with animals that still occurs today.

Key words: *Agriculture, Brucellosis, Eye diseases, Uveitis*

Asian J Ophthalmol. 2007;9:30-1

Introduction

Whilst most cases of acute anterior uveitis tend to be idiopathic, patients with chronic, bilateral, or posterior uveitis or presenting with systemic symptoms must be investigated for an underlying cause. This report is of a patient with bilateral uveitis associated with brucellosis who presented initially with constitutional symptoms.

Case Report

A 45-year-old man presented with a history of lethargy, diarrhoea, and chronic cough over a period of several months. He worked on a farm and had never travelled outside the UK. He was admitted to hospital for investigation of his symptoms but no cause for his illness was found. One year later, he presented with bilateral blurred vision for 1 month and loss of weight. Signs of inflammation were present bilaterally, in the form of anterior uveitis and pars planitis. Blood test results were unremarkable apart from positive serology results for *Brucella* species. He was prescribed a course of oral rifampicin and doxycycline together with topical dexamethasone. His systemic symptoms improved but he had intermittent episodes of iritis and vitritis, which were treated with oral prednisolone. The patient was eventually diagnosed with brucellosis. His most recent unaided Snellen visual acuities were 6/6 in the right eye and 6/7.5 in the left. Informed consent was obtained from the patient for potential publication of this information in publicly available media.

Discussion

Brucellosis can infect humans directly, through skin abrasions or inhalation of airborne particles from animal manure, or indirectly, through consumption of infected animal products such as unpasteurised milk products, raw liver, or spleen. Infection has also been reported from beauty products prepared from bovine placental extracts.[1]

Brucellosis remains a health problem in developing areas of the world[2] and may be increasing in the present era of international tourism and imported food products.[3] However, the diagnosis of brucellosis should still be considered in the developed world, particularly in those who have a history of working with animals, e.g., farmers, veterinarians, abattoir staff, and shepherds, as well as dairy industry workers and those working in microbiology laboratories.

Diagnosis is made by measuring the blood titre of antibodies to the bacterial antigens using a serum agglutination test but there are problems with this approach. Seroconversion may not occur early in the course of disease, cross-reactivity with other infective agents can occur, and agglutination cannot be used for follow-up. Culturing the bacterium would be useful but the sensitivity of culture of blood or tissue samples varies widely.[2] Enzyme-linked immunosorbent assays and polymerase chain reaction are alternative tests.

Brucellosis in humans has a broad spectrum of clinical presentations. Non-specific symptoms occur, such as fever, malaise, anorexia, headache, arthralgia, backache, and malodorous perspiration. Osteoarticular infection is the most common organ-specific manifestation; epididymo-orchitis and hepatitis can also occur. Neurobrucellosis is a rare but serious complication. Endocarditis is the most common fatal complication of brucellosis.[4] After the acute presentation, the subsequent clinical course can be chronic and relapsing. Given the non-specific nature of its systemic manifestations, tuberculosis may be suspected and the diagnosis of brucellosis may be missed initially.

Brucellosis has several ocular manifestations: conjunctivitis, nummular keratitis, chronic anterior uveitis, multifocal or geographic choroiditis, exudative retinal detachment, optic neuritis,

Correspondence: Dr Tanya Moutray, Eye and Ear Clinic, Royal Victoria Hospital, Belfast, BT12 6BA, UK.
Tel: (44 28) 9045 8457; Fax: (44 28) 3083 3311;
E-mail: tanya.moutray@btopenworld.com

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dacryoadenitis, or episcleritis. Uveitis due to brucellosis is typically chronic and granulomatous, similar to uveitis due to tuberculosis. Unlike ocular aspergillosis, for example, ocular brucellosis is thought to be a non-infectious immune response, although *Brucella* species have been cultured from vitreous aspirate.[5] Treatment of brucellosis uveitis therefore consists of administering non-specific anti-inflammatory agents, such as topical and occasionally systemic steroids, together with systemic antibiotics. The recurrences of iritis and vitritis in the patient described here were presumed to be due to non-infectious immune reactions to *Brucella*-related antigens and were controlled with oral steroid.

Potentially a multitude of investigations could be justified for uveitis, ranging from serum angiotensin-converting enzyme and computed tomography of the chest to vitreous tap and cytological analysis. However, tests should be based on directed questioning about systemic symptoms, past medical problems and risk factors (including the risk of exposure to *Brucella* species), systemic signs, and the course and nature of the ocular inflammation. A good visual prognosis is possible with the appropriate systemic treatment.

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Primary Localised High-grade Lymphoma of the Lacrimal Gland

BS Yadav,[1] Sastri G Jayant,[1] G Nalini,[2] K Gunaseelan,[1] Suresh C Sharma[1]
[1]Department of Radiotherapy and Oncology, and [2]Department of Pathology, Post Graduate Institute of Medical Education and Research, Chandigarh, India

Non-Hodgkin's lymphoma of the lacrimal gland is rare and generally secondary to primary central nervous system lymphoma. This report describes a patient with primary high-grade non-Hodgkin's lymphoma localised to the lacrimal gland.

Key words: *Lymphoma, non-Hodgkin, Lacrimal apparatus*

Asian J Ophthalmol. 2007;9:32-5

Introduction

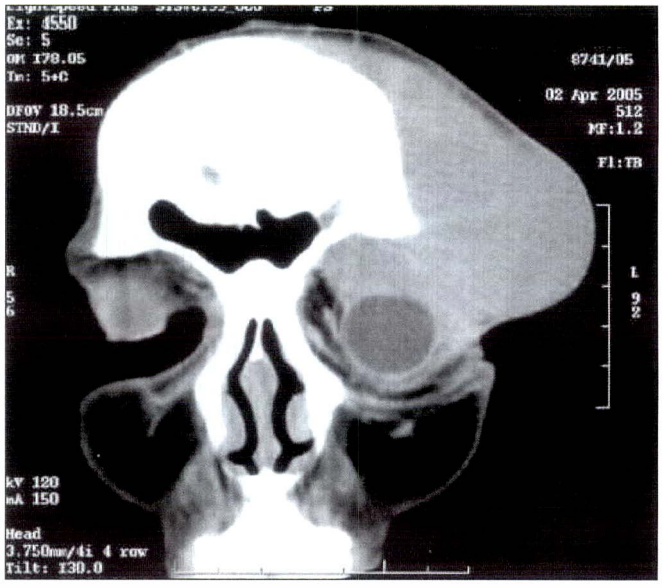
Ocular adnexal lymphomas represent the malignant end of the spectrum of lymphoproliferative tumours that occur in the orbital adnexa, including the lacrimal gland with its resident lymphocytes. The incidence of ocular adnexal lymphomas is reported to be less than 10% of all extranodal lymphomas.[1] The majority of patients with lacrimal gland or orbital adnexal lymphomas have low-grade mucosa-associated lymphoid tissue (MALT) lymphomas, which are marginal zone B-cell lymphomas according to the Revised European American Lymphoma (REAL) Classification system.[2] High-grade non-Hodgkin's lymphoma (NHL) of the lacrimal gland occurs more rarely. Although rare, these tumours are important because of the potential for significant morbidity and mortality. This report describes a patient with high-grade NHL of the lacrimal gland who, despite aggressive chemotherapy, had a probable central nervous system (CNS) relapse.

Case Report

The clinical records of a 40-year-old woman with localised high grade NHL of the lacrimal gland were reviewed. The patient presented to the outpatient department of a tertiary care academic hospital with complaints of progressive swelling in the lateral aspect of the left orbit and diminution of vision for the previous 4 months. She also had a history of loss of appetite preceding these symptoms. There were no other systemic complaints. Examination of the peripheral lymph nodes revealed no gross abnormality. At local examination there was a 4 x 4-cm cystic swelling in the lateral aspect of the supra-orbital region. She was unable to open the left eyelid and had restriction of eyeball movements. Systemic examination revealed no abnormality.

Correspondence: Dr Suresh C Sharma, Department of Radiotherapy and Oncology, Post Graduate Institute of Medical Education and Research, Chandigarh 160 012, India.
Tel: (91 172) 274 7585; Fax: (91 172) 274 4401;
E-mail: sureshfiruza@rediffmail.com

Figure 1. Contrast-enhanced computed tomography (coronal section) of the orbit and head of a patient with non-Hodgkin's lymphoma of the lacrimal gland.



Contrast-enhanced computed tomography of the orbit and head revealed a large homogenously enhancing soft tissue lesion in relation to the superolateral aspect of the orbit involving the lacrimal fossa and left orbit (Figure 1). The bulk of the mass was present in the superolateral aspect of the orbit and extraconally pushing the extraocular muscles medially and causing proptosis of the left eyeball with extra calvarial extension cranially up to the external temporal fossa and caudally up to the level of the ramus (Figure 2). No intracranial extension was present. There were no intracranial, space-occupying lesions or periventricular enhancement. Fine-needle aspiration cytology was performed on the supra-orbital swelling (Figures 3 and 4). The smears were stained using May-Grünwald-Geimsa stain or haematoxylin and eosin. The

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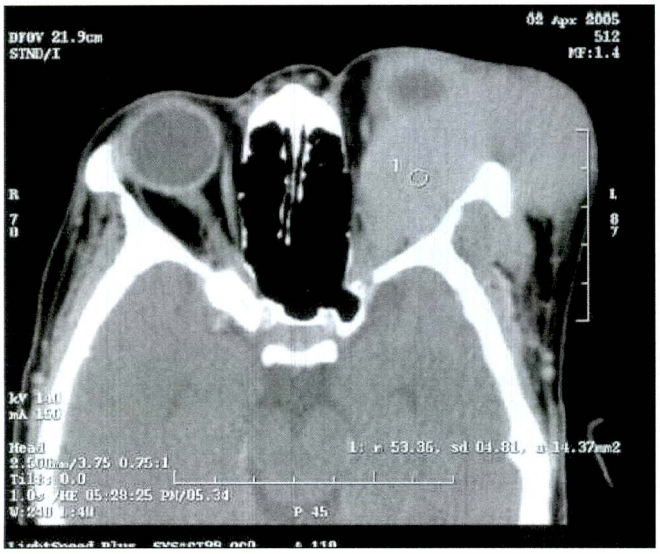
Figure 2. Contrast-enhanced computed tomography (axial section) of the orbit and head of the patient shown in Figure 1.



smears were cellular and showed a monomorphic population of atypical lymphoid cells with a high nuclear/cytoplasmic ratio, scanty cytoplasm, non-condensed chromatin, and prominent nucleoli. Mature lymphocytes and many lymph glandular bodies were visible in the background. Immunocytochemistry revealed that the tumour cells were positive for CD20 and negative for CD3. Ultrasonography of the abdomen and pelvis revealed no infradigpragmatic disease. Bone marrow biopsy was also performed and did not show any infiltration by NHL cells. Lumbar puncture was attempted twice but produced a dry tap on both occasions. Thus, cerebrospinal fluid cytology could not be assessed to exclude leptomeningeal involvement.

A diagnosis of high grade NHL stage IE was made and the patient commenced combination chemotherapy with cyclophosphamide

Figure 3. Low-power photomicrograph showing a monomorphic population of lymphoid cells in a patient with non-Hodgkin's lymphoma (haematoxylin and eosin stain; original magnification, x 256).

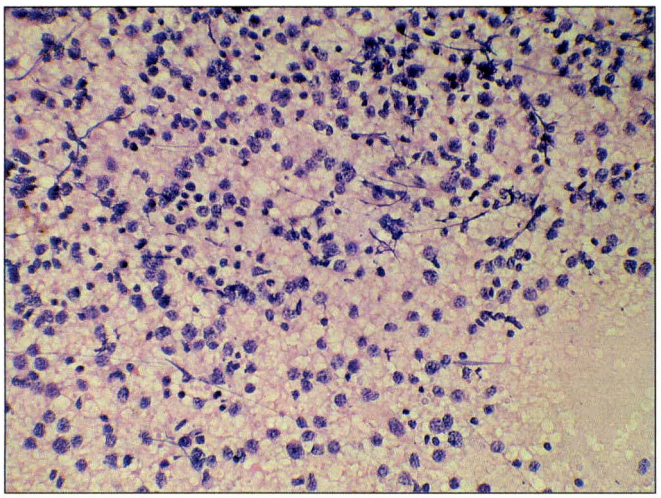
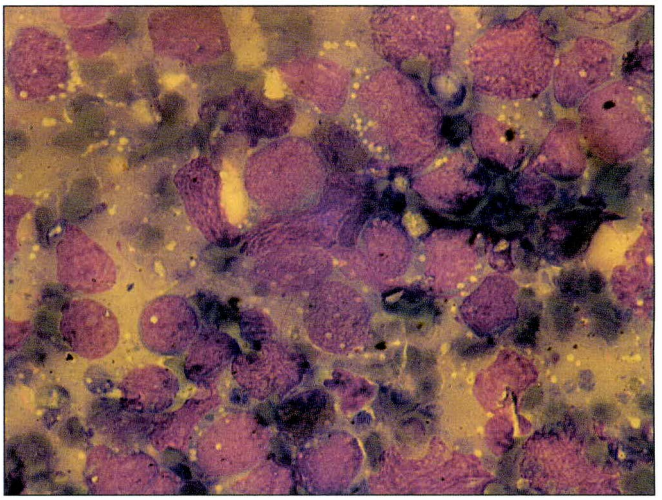


Figure 4. High-power photomicrograph showing lymphoid cells with scanty cytoplasm, non-condensed chromatin, and prominent nucleoli in a patient with non-Hodgkin's lymphoma (haematoxylin and eosin stain; original magnification, x 1150).



650 mg/m², adriamycin 40 mg/m², vincristine 1.5 mg/m², and prednisolone 40 mg/m² for 5 days because the lesion was of such a high grade. The patient completed 6 courses of chemotherapy in May 2005. During the course of the treatment, swelling completely subsided and vision gradually began to improve. However, 4 months post-chemotherapy, the patient presented with aphasia and increasing somnolence, which progressed to loss of consciousness and death. CNS relapse was strongly suspected on the basis of the clinical presentation.

Discussion

In the past, orbital adnexal lymphomas were graded according to the National Cancer Institute's Working Formulation. Based on this classification, most orbital lymphomas were diagnosed as either low- or intermediate-grade tumours. With advances in immunohistochemical methods, the REAL classification has taken precedence over the Working Formulation. The REAL classification and the new World Health Organization (WHO) classification of lymphoid and haematopoetic tissue are the most suitable for subdividing the ocular adnexal lymphomas.[3]

The patient described here had high-grade lymphoma based on the Working Formulation. In most cases,[4-6] the most common histological subtype is MALT lymphoma, which accounts for more than half the cases classified as extranodal marginal zone B-cell lymphoma according to the REAL classification[6] and marginal zone B-cell lymphoma according to the WHO classification.[7] Standard teaching is that the majority of patients with orbital adnexal MALT lymphoma tend to present with stage IE disease. However, recent studies suggest that approximately 20% to 30% of such patients may have distant metastasis.[8-10]

Table 1. Management outcomes of patients with non-Hodgkin's lymphoma of the lacrimal gland: a literature review.

Year	Authors	Number of patients	Mean age (years)	Lymphoma grade/type	Treatment	Response (%)		DFS (months)
						CR	LR	
1996	Esik et al[15]	26	44	Low	Surg + RT + CCT	98	2	40
1997	Galieni et al[12]	8	55	Low	CCT + RT	93	7	—
1999	Bolek at al[4]	1	68	Low	RT	100	—	28
2001	Stafford et al[5]	5	68	Low	RT	98	3	64
2001	Mohammad and Kroosh[14]	13	—	Low and intermediate	Surg	100	0	—
2003	Fung et al[6]	23	63	Mantle zone and follicular	CCT + RT	98	2	40
2005	Cassidy et al[13]	3	41	Low	Surg + RT	100	0	—
2006	Ejima et al[16]	10	—	MALT (low)	RT ± CCT	84	—	—
2005	Farmer et al[11]	15	60	Low and high	RT ± CCT	—	—	48
2007	Yadav et al	1	40	High	CCT	—	—	4

Abbreviations: CR = complete remission; LR = local recurrence; DFS = disease-free survival; Surg = surgery; RT = radiation therapy; CCT = combination chemotherapy; MALT = mucosa-associated lymphoid tissue.

To obtain additional information relevant to this report, a thorough search of the MEDLINE database for reports of cases of primary NHL of the lacrimal gland was carried out. Only English language documents were reviewed, including abstracts when full articles were not available. A total of 110 patients with primary lacrimal gland involvement were identified, most of whom had low-grade histology (Table 1). There were few reports of either de novo high-grade lymphomas[3] or low-grade lymphomas undergoing transformation into high-grade pathology.[11] Thus, primary localised lymphoma of the lacrimal gland is a rare event[12] and high-grade non-Hodgkin's lymphoma occurs even more rarely. Management of patients with orbital adnexal lymphomas should include a thorough systemic medical examination, appropriate radiological investigations, and invasive procedures (for example, cerebrospinal fluid cytology) to establish the clinical stage of the disease.

Several controversial issues exist relating to the optimal management of these tumours. A variety of therapeutic approaches have been used by the authors of relevant studies published to date.[4-6,12-16] However, no definite management guidelines have been established for these patients. Reported complete remission rates vary from 93% to 100%, local recurrence rates from 0% to 7%, and disease-free survival periods from 28 to 64 months for either single or combined modality treatment for low- to intermediate-grade lymphomas (Table 1). Patients with high-grade disease may have early relapse, as in the patient reported here, due to subclinical systemic disease and therefore warrant a combined modality approach. In a study by Martinet et al, 2 of 6 patients with high-grade lymphoma of the orbital adnexal region (33%) progressed to systemic disease despite chemotherapy.[17] Similarly, Bessel et al found that for patients with stage I disease, the 5-year actuarial risk of disseminated disease was 63% for those with high-grade disease compared with 20% for those with low-grade disease.[18]

Currently oncologists advocate radiotherapy for stage IE (localised) low-grade lymphomas.[4,5] When the lacrimal gland is the only subsite of the orbital structures involved, it is unclear whether radiotherapy should include the entire orbit. Conventionally, the entire orbit is included because of the risk of local recurrences within the orbit itself. A dose of >30 Gy in conventional fractionation is sufficient to achieve a complete response.[4,5] If permanent local control is not achieved within a reasonable time, recurrence and dissemination of the disease may occur, particularly in high-grade NHL. Thus, overall survival may be poorer after primary chemotherapy (even with salvage radiotherapy) than when radiotherapy is the initial treatment and a combined approach is preferable. Surgical excision of the tumour has also been suggested as one of the curative modalities for low-grade lymphoma localised to the lacrimal gland without any other orbital or systemic involvement.[14] This approach circumvents the potential ocular complications of radiotherapy. However, a single study is not sufficient to establish this conclusively.[14]

Despite demonstrating an indolent course, extranodal marginal zone B-cell lymphomas are known to recur in extranodal sites, including other ocular adnexal sites. Long-term follow-up with 6-monthly examinations is therefore recommended. However, if histology indicates a high grade tumour, it may be useful to examine the patients at closer intervals once they have achieved complete remission after the treatment.

Major prognostic criteria for orbital adnexal lymphomas include anatomic location of the tumour, stage of disease at first presentation, lymphoma subtype as determined using the REAL classification, presence of immunohistochemical markers related to factors such as tumour growth rate, and the serum lactate dehydrogenase level.[13]

The patient described here presented within 4 months of completion of chemotherapy with features of CNS relapse, although

this could not be confirmed radiologically. There are 4 possible explanations for this outcome:

- the tumour may have been highly aggressive given its high-grade histology
- the patient may have received suboptimal treatment, e.g., local radiation therapy to the orbit may have been required
- there may have been subclinical disease in the CNS, which could not be treated effectively by chemotherapy alone due to lack of CNS penetration
- the disease may have spread along the optic nerve as evidenced by the progressive dimunition of the patient's vision.

In conclusion, primary lymphoma of the lacrimal gland is usually low to intermediate grade, as illustrated by the collated data presented here. However, high-grade lymphomas are a rare occurrence and need to be recognised and differentiated from primary high-grade non-Hodgkin's lymphoma with secondary involvement. Literature providing treatment guidelines is scarce due to the rarity of the condition. Management decisions should be based on the stage and grade of the disease, most importantly, after excluding CNS involvement. High-grade lymphomas of the lacrimal gland may have a fulminant course with a bad prognosis if not treated aggressively.

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Recurrent Endophthalmitis Due to *Acanthamoeba*

Avinash Pathengay,[1] Geeta K Vemuganti,[2] Gaurav Y Shah,[1] Taraprasad Das,[1] Savitri Sharma[3]
[1]*Smt Kanuri Santhamma Retina Vitreous Centre,* [2]*Ophthalmic Pathology Service, and* [3]*Jhaveri Microbiology Centre, LV Prasad Eye Institute, Hyderabad, India*

Although extremely rare, Acanthamoeba *infection may present as recurrent endophthalmitis following penetrating injury. This report describes a 5-year-old boy who developed* Acanthamoeba *endophthalmitis following penetrating trauma.*

Key words: *Acanthamoeba, Differential diagnosis, Endophthalmitis, Penetrating eye injury*

Asian J Ophthalmol. 2007;9:36-8

Introduction

Endophthalmitis is an important complication of open globe injuries. Posterior segment involvement due to *Acanthamoeba* is rare.[1-5] This report describes a patient with recurrent endophthalmitis due to *Acanthamoeba* following penetrating trauma.

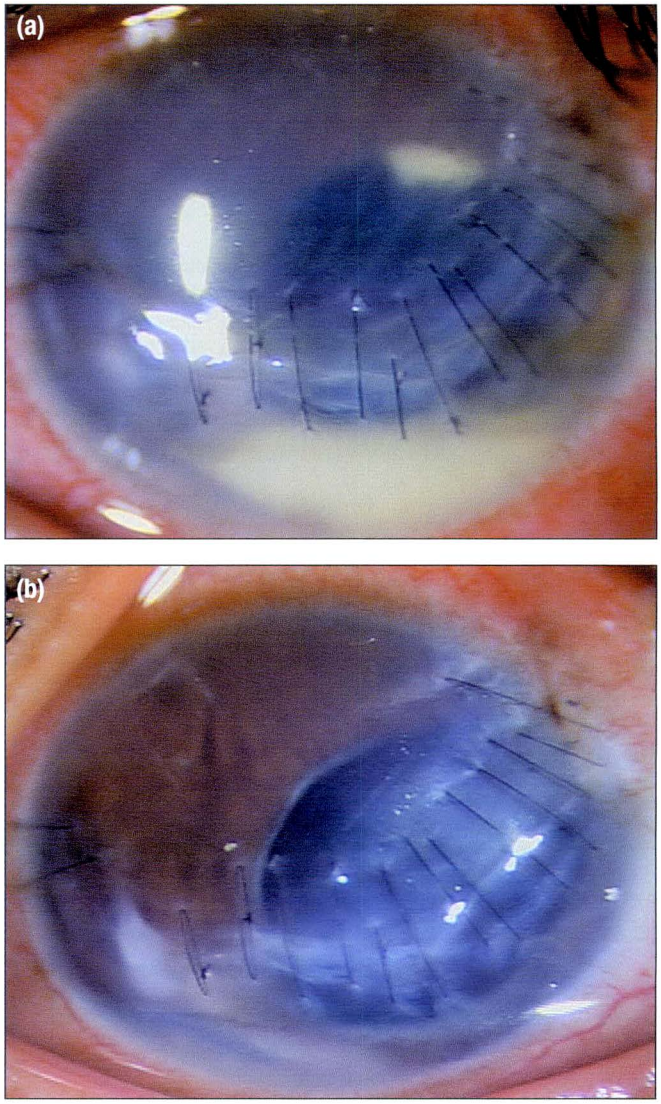
Case Report

A 5-year-old boy was referred with a diagnosis of right eye traumatic endophthalmitis following accidental injury with a wooden stick sustained the previous day. Best-corrected visual acuity in the right eye was perception of light with accurate projection of rays and 20/20 in the left eye. Examination of the right eye revealed oedematous lids, congested conjunctiva, and corneal laceration with hypopyon (Figure 1a). Ultrasound B-scan performed gently through closed lids revealed multiple dot and membrane-like echoes in the vitreous cavity with an attached retina.

He underwent corneal tear repair, lensectomy, vitrectomy, intraocular foreign body removal (fragment of wood, noted intraoperatively), and intravitreal injection of vancomycin 1 mg/0.1 mL, amikacin 400 µg/0.1 mL, and amphotericin B 5 µg/0.1 mL. Vitreous microscopy with Gram staining showed gram-negative diplobacilli. He was treated with topical 0.3% ciprofloxacin and 1% betamethasone every hour, topical 2% homatropine 3 times a day, and intravenous cefazolin 125 mg 4 times a day and gentamicin 20 mg twice a day.

Vitreous culture grew *Sphingomonas paucimobilis* and *Pseudomonas aeruginosa,* identified using the API 20 NE system

Figure 1. Slit-lamp photographs. (a) Seven days after the initial surgical intervention, hypopyon is present; and (b) after 4 weeks' treatment, hypopyon has resolved.



Correspondence: Dr Avinash Pathengay, Smt Kanuri-Santhamma Retina Vitreous Centre, LV Prasad Eye Institute, LV Prasad Marg, Banjara Hills, Hyderabad 500 034, India.
Tel: (91 040) 2354 5305; Fax: (91 040) 2354 8271;
E-mail: avinash@vizag-lvpei.org

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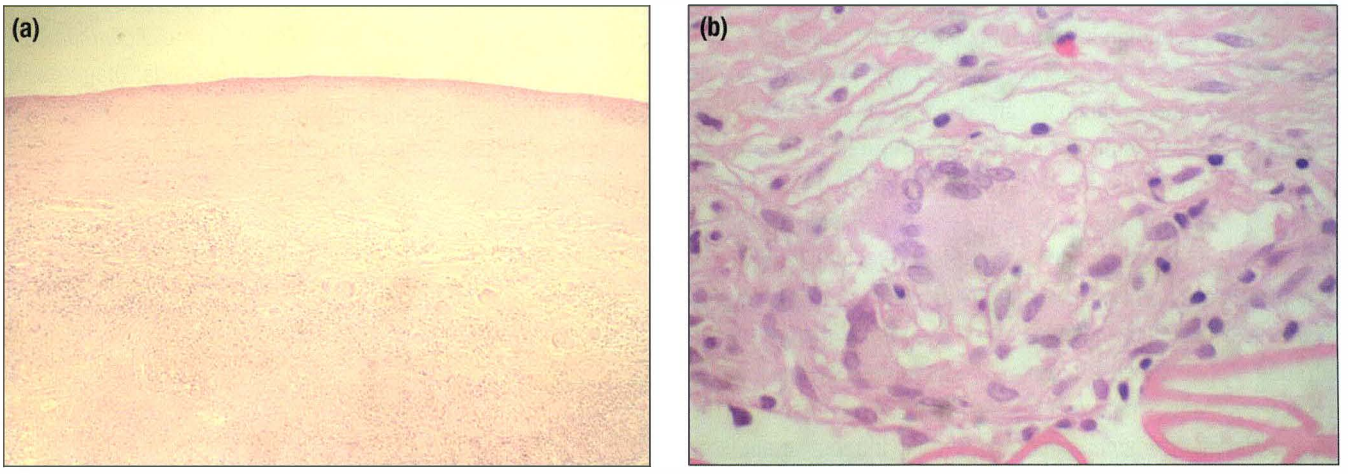
Figure 2. Histopathological sections of the cornea. (a) Granulomatous inflammation with necrosis (haematoxylin and eosin stain; original magnification, x 20); and (b) giant cells around a fragmented Descemet's membrane (haematoxylin and eosin stain; original magnification, x 400).



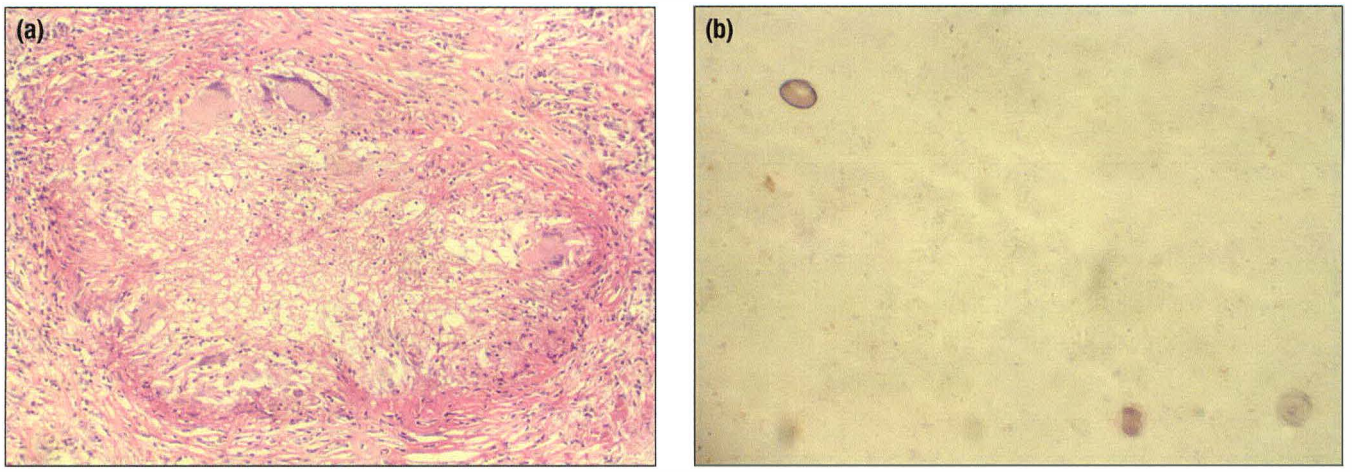
(bioMerieux, Marcy l'Etoile, France). Culture of the foreign body grew *Fusarium* species. *S paucimobilis* was sensitive to vancomycin, cefazolin, ciprofloxacin, ofloxacin, and chloramphenicol but resistant to amikacin, gentamicin, and ceftazidime. *P aeruginosa* was sensitive to amikacin, gentamicin, ciprofloxacin, ofloxacin, and chloramphenicol but resistant to vancomycin, cefazolin, and ceftazidime.

Antibiotic susceptibility was assessed using the Kirby Bauer disc diffusion method. Considering the growth of *Fusarium* species from the foreign body, topical 5% natamycin was instilled 10 times a day and 100 mg ketoconazole was administered orally twice a day after testing for normal liver function. Intravenous antibiotics were discontinued on the seventh day and ketoconazole was continued for 4 weeks. During this period, vision improved to counting fingers close to the face, there was a marked decrease in vitritis, and the fundus examination showed attached retina (Figure 1b).

However, the patient returned 6 weeks later complaining of increased pain in the right eye. Vision was reduced to perception of light with recurrence of hypopyon and vitreous opacification had worsened. On the same day he underwent vitreous lavage and intravitreal injection of vancomycin 1 mg/0.1 mL, amikacin 400 µg/0.1 mL, and amphotericin B 5 µg/0.1 mL. Vitreous biopsy and culture were repeated but did not reveal any of the organisms noted previously. Over the next 5 days, perception of light was lost, pain worsened, and a central arcuate-shaped corneal stromal infiltrate developed. The painful blind eye was eviscerated.

Histopathological sections of the intraocular contents showed granulomatous inflammation in the corneal stroma (Figure 2) and in the vitreous cavity (Figure 3a) surrounding necrotic material and exudates. Within the exudates of the vitreous, there were many double-walled rounded cysts of *Acanthamoeba*, which stained black with Gomori's methenamine silver stain (Figure 3b) and were periodic acid-Schiff–positive.

Figure 3. Histopathology of the vitreous cavity. (a) Section showing central necrosis with palisading epithelioid cells (haematoxylin and eosin stain; original magnification, x 100); and (b) double-walled cyst, stained black (Gomori's methenamine silver stain; original magnification, x 400).



Discussion

The reported frequency of post-traumatic endophthalmitis is up to 13% and this condition is commonly associated with poor visual outcome.[6,7] Documented posterior segment manifestations include chorioretinitis, endophthalmitis, and panophthalmitis.[1-5]

Recurrence of endophthalmitis is attributed to the use of ineffective antibiotics, the presence of gram-negative bacilli, multidrug resistance, and inadequate exposure time.[8] In the patient described here, inflammation recurred following initial resolution. The initial resolution of the inflammation following administration of effective antibiotics and the absence of organisms in the second vitreous biopsy posed a diagnostic challenge, raising a doubt about the infectious nature of the recurrence of inflammation. The demonstration of *Acanthamoeba* cysts in the intraocular contents obtained by evisceration was an unexpected finding, which proved that the recurrence of inflammation was infectious.

In retrospect, it is likely that the presence of *Acanthamoeba* was overlooked in the initial microbiological examination. The trophozoites of *Acanthamoeba* may be mistaken for large macrophages, giant fibroblasts, and cellular debris.[5] The initial resolution of the inflammation may have been due to a partial response of the slow-growing amoeba to the antifungal agents used.[4]

The ubiquitous presence of *Acanthamoeba* in the environment explains the introduction of the parasite into the eye by the agent that caused the penetrating injury. Although rare, *Acanthamoeba* infection should be considered in the differential diagnosis of recurrent endophthalmitis following trauma and included in the microbiological assessment of such cases.

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Bimonthly Publication

Asian Journal of OPHTHALMOLOGY is pleased to announce that, from Volume 8 2006, publication has been increased from quarterly to bimonthly. The publication months will now be: February, April, June, August, October, and December.

This development is in response to the recent increase in manuscripts submitted to the Journal. Manuscripts may be submitted on-line via the SEAGIG website, at: **www.seagig.org**, or by e-mail, to: **manuscripts@seagig.org**.

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Neurotrophic Keratitis Secondary to Electrocution Injury

Mohamad Aziz Salowi, Yee Fong Choong
Department of Ophthalmology, Selayang Hospital, Selangor, Malaysia

Electrically induced injuries may present with a variety of ocular manifestations. This report describes a child who presented with neurotrophic keratitis following an electrocution injury.

Key words: *Electric burns, Keratitis, Neurologic manifestation*

Asian J Ophthalmol. 2007;9:39-40

Introduction

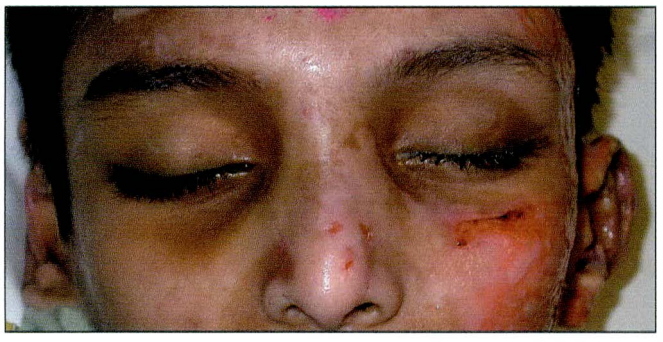
Electrical injury is a potentially devastating form of multisystem injury with high morbidity and mortality. Electrically induced injuries can present with a variety of ocular manifestations, which may occur either simultaneously or sequentially. This case report describes a child who presented with neurotrophic keratitis following an electrocution injury.

Case Report

An 11-year-old boy climbed onto the roof of a stationary train and inadvertently came in contact with the high voltage powerline when he touched the overhead cable. He sustained multiple second degree burns over the left side of the face and the upper chest. No ocular involvement was noted at the time.

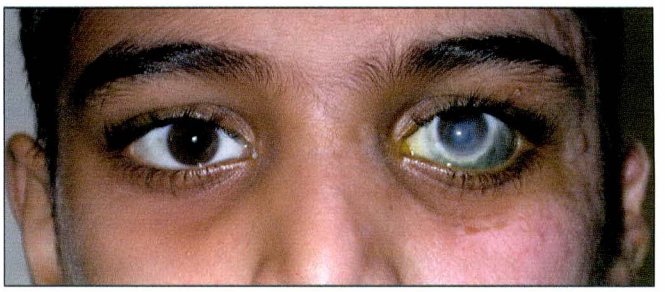
Three days later he developed left eye redness associated with discharge. Ocular examination revealed a left-sided facial burn sparing the upper and lower lid with full lid closure (Figure 1). Visual acuity was 6/9 in the right eye and hand movement in the left eye. Intraocular pressures were normal and pupils appeared equal and reactive. The left eye showed limbal ischaemia at the inferotemporal quadrant with corneal ulcer and hypopyon and the fundus view was hazy. Corneal sensation was absent. B-scan ultrasound of the eye did not reveal any abnormalities. Extraocular movements and the results of other ocular examinations were normal.

Figure 1. Left-sided facial burn sparing the lids with full lid closure.



Correspondence: Dr Mohamad Aziz Salowi, Department of Ophthalmology, Selayang Hospital, Lebuhraya Kepong-Selayang, Batu Caves, Selangor 68100, Malaysia.
Tel: (60 3) 6120 3233; Fax: (60 3) 6120 7564;
E-mail: tedmy@yahoo.com

Figure 2. Central corneal scar with corneoscleral thinning and left-sided facial scar.



Intensive ocular lubrication and topical antibiotics were commenced with a good response. After more than 3 months in hospital, the patient was discharged home. Outpatient follow-up revealed inferotemporal corneoscleral thinning with anterior staphyloma. Vision was 6/24 corrected to 6/18 with pinhole. Corneal sensation remained absent. The facial burn healed well and formed a keloid scar (Figure 2).

Discussion

Electrical injury occurs when a person comes into contact with a current produced by a variety of sources. This source may be man-made, such as a powerline, or natural, such as lightning.[1]

When electrocution occurs, the pathophysiology of ophthalmic manifestations may include one or more of the following:

- direct effect of the electrical current passing through the ocular structures, including nerves
- thermal energy absorbed by ocular tissues causing destruction and coagulative necrosis
- tissue ischaemia caused by either generalised vasoconstriction or cardiac arrhythmia
- mechanical injury due to falls or violent muscle contractions.[2-4]

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The severity of the injury depends on the intensity of the electrical current, the pathway it follows through the victim's body, and the duration of the contact with the source of the current.[2,3,5] The extent of damage also depends on the tissue's resistance to the current. Resistance varies between different body tissues and is known to be greatest in bone, with decreasing resistance in fat, tendon, skin, muscle, blood vessels, and nerves.[2]

A range of ocular disorders have been observed following electrical injury. Almost any part of the eye or orbit may be affected, including the eyelids, conjunctiva, extraocular muscles, cornea, iris and pupil, lens, retina, choroid, and optic nerve.[2,4] Involvement of the cornea may cause opacities, cell loss, thinning, necrosis, or even perforation.[2] The first report of electrical injury to the eye was published in 1722 by St Yves, who described crystalline lenticular changes in a field worker struck by lightning.[5] Grover and Goodwin have reviewed literature reports of cases of electrical injury with neuro-ophthalmological complications.[3] Documented eye manifestations included anisocoria, mydriasis, accommodation failure, nystagmus, ophthalmoplegia, papilloedema, and optic neuritis. Miller et al reported a patient who was accidentally electrocuted by a powerline and presented with anisocoria and sequential development of cataract, uveitis, macula cyst, and cystic macula oedema.[2]

The total and persistent corneal sensation loss in the patient reported here suggests that the most likely explanation for keratitis was a loss of the trophic effect of the first division of the trigeminal nerve.[6] However, other possible explanations include limbal ischaemia secondary to local vasoconstriction and compromised blood supply leading to loss of limbal stem cells and interrupted corneal wound repair[7] or direct thermal injury to limbal tissue and loss of corneal nerve function.

There is no specific therapy for electrical injury. The management is mainly symptomatic and depends on the organ involved.[1] However, prevention is still the best means of eliminating mortality and minimising the morbidity of electrical injuries.[1,8] Continuous public education should be provided by the media and schools. In addition, laws against building residential areas near railway tracks need to be strictly observed by the authorities.

Electrocution can present with late ocular complications.[2] Although the patient reported here presented with isolated corneal involvement, ongoing follow-up is essential to monitor for possible sequential complications, which may occur long after the inciting event.

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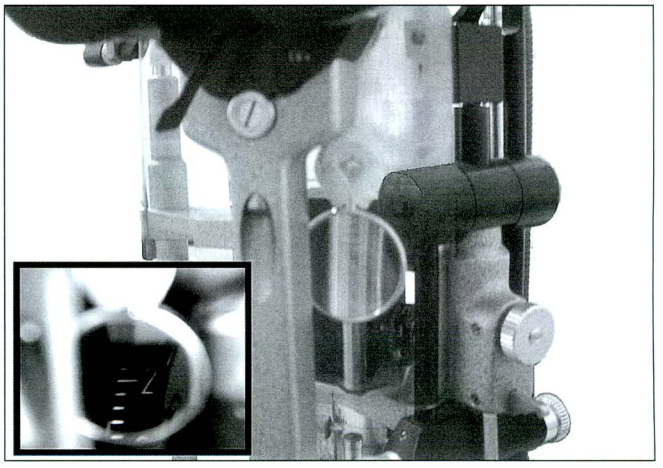
Reading Goldmann Tonometer Pressure Score: Help for the Presbyopic Ophthalmologist

Dear Editor,

The modern slit lamp is equipped with many accessories that extend its versatility for the examination of each part of the eye; this makes the slit lamp the basic instrument in the ophthalmologist's office.[1] We would like to present a simple handmade accessory, which we found useful for the ophthalmologist's daily use.

During most of his professional life, the ophthalmologist is presbyopic and frequently needs near correction. As most ophthalmologists are not using their reading glasses while looking through the slit lamp eyepiece, it is annoying to wear the near correction just for reading the pressure score. If hypermetropia is present, the need for near vision correction appears even earlier. When looking through the slit lamp eyepiece, the optical system of the slit lamp effectively compensates for the inability of the eye to accommodate. The Goldmann tonometer scale is situated about 25 cm in front of the examiner's eyes; hence, if he is presbyopic he may find it impossible to read the pressure score without near correction. This problem becomes even more difficult in darkened room conditions. A practical solution is the addition of a +8 diopters lens in front of the tonometer scale (Figure 1). The lens can be taken from the trial lens case found in each ophthalmologist's office, and is attached to the transparent plastic shield situated on the viewing arm of the slit lamp below the microscope. The +8 lens provides the near correction needed, and also supplies a significant magnification of the tonometer scale to make it easier even for the non-presbyopic ophthalmologist to read the scale in darkened room conditions.

Figure 1. The +8 lens attached to the plastic shield of a Haag-Streit slit lamp. Insert: Goldmann tonometer scale magnified as seen through the lens.



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Yehoshua Almog, Ari Nemet
Department of Ophthalmology, Meir Medical Center and Sackler Faculty of Medicine, Tel-Aviv University, Israel
E-mail: nemet.arik@gmail.com

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World Glaucoma Congress

Singapore, 18-21 July 2007

The Association of International Glaucoma Societies (AIGS) is an independent, impartial, ethical, global organisation for glaucoma science and care. Organised by AIGS, the objectives of the World Glaucoma Congress (WCG) are:

- to present new developments in diagnosis and therapy of glaucoma both to glaucoma experts and general ophthalmologists interested in glaucoma
- to enhance communication about glaucoma among ophthalmologists from all over the world
- to enhance exchange of knowledge between general ophthalmologists and glaucoma experts
- to maintain high scientific and ethical standards.

The AIGS Mission

To optimise the quality of glaucoma science and care through communication and cooperation among international glaucoma societies, with glaucoma industries, glaucoma patient organisations and all others in the glaucoma community.

The AIGS Vision

Curiosity, creativity, quality, integrity are essential ingredients for science and care. The AIGS is the first global subspecialty effort involving all stakeholders: ophthalmologists, other eye specialists, industrialists, and patients.

The AIGS Goals

- Unite
- Create personal contact
- Guide
- Aim for quality
- Communicate
- Support
- Educate
- Meet
- Inform
- Investigate

The AIGS aims at organising a top quality meeting for general ophthalmologists, members of the glaucoma societies and for all other health professionals with an interest in glaucoma. The WGC scientific interaction will be based on the AIGS Code of Practice, the AIGS Global Guidelines on Reporting and Publishing, and the AIGS Global Guidelines on Quality and Quantity of Glaucoma Meetings, which were conceived by committees involving both glaucomatologists and industry experts.

Scientific Programme

The Scientific Programme is based on the following principles:

- opening symposia and didactic sessions by invited top speakers
- consensus outcome updates, new consensus outcomes, and consensus implementation
- parallel research sessions
- original research posters and glaucoma society posters
- inter-glaucoma society discussion symposia
- glaucoma patient organisation symposium and course.

The Opening Ceremony and Symposium will present an overview of worldwide developments in glaucoma.

At the request of participants of the WGC 2005 in Vienna, the organisation committee has incorporated parallel clinical and basic science sessions, thus enabling general ophthalmologists and glaucoma experts to select sessions that fit their personal interest.

For further information, visit the website at: www.globalaigs.org

Association of International Glaucoma Societies

THE GLOBAL GLAUCOMA NETWORK

AIGS
WORLD GLAUCOMA CONGRESS

www.GlobalAIGS.org

Singapore, July 18-21 2007

7th International Symposium of Ophthalmology, Hong Kong

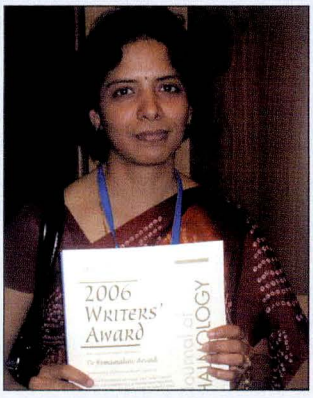
30 June-2 July 2007, Hong Kong

The 7th International Symposium of Ophthalmology, Hong Kong (ISOHK), will meet from 30 June to 2 July 2007. This year, the meeting will be co-sponsored by the Chinese University of Hong Kong and the European Society of Cataract and Refractive Surgeons (ESCRS). The meeting has the full support of the Chinese Ophthalmological Society. The conference will also host meetings of the Chinese Cataract Society, the Chinese Glaucoma Society, and the Chinese Refractive Surgery Society.

Global education is an important part of the mission of the ESCRS. The ISOHK meeting will feature well-known speakers from Asia, Europe, and the Americas. Hong Kong is well located, serving as a gateway for Chinese delegates and other people across the Asia Pacific region. With a population of more than one billion people, the demand for eye care in China is huge. The meeting offers delegates from mainland China the opportunity to learn the latest techniques.

The meeting provides a wonderful opportunity to make new friends, and to renew old friendships. The meeting takes place during a festive time in Hong Kong. The year 2007 marks the tenth anniversary of the assumption of sovereignty by the People's Republic of China. A highlight of the social programme will be an evening harbour cruise during a massive fireworks display. The conference will take place at the Hong Kong Convention and Exhibition Centre. Registration is now open, with a special discount for those who register by 1 May.

For further information, visit the website at: **www.isohk.org**



Winner of the 2006 Writer's Award

Congratulations to Dr Hemamalini Arvind, winner of the 2006 Writer's Award. Dr Arvind was selected by the Journal's independent advisory board panel for her paper: Arvind H, George R, Baskaran M, et al. Effect of extracapsular and manual small incision cataract surgery with intraocular lens on scanning polarimetry. Asian J Ophthalmol. 2006;8:86-90. The article was reprinted in the December 2006 issue of the Journal, which was distributed at the SEAGIG Chennai meeting.

Dr Arvind was presented with the award plus a financial contribution toward her research at the meeting.

March 2007

2-5 March
Asia ARVO
Singapore
Contact: Karen Chee, Singapore Eye Research Institute, 11 Third Hospital Avenue, #05-00, SNEC Building, Singapore 168751
Tel: (65) 6322 8311
Fax: (65) 6323 1903
E-mail: karen.chee.s.l@seri.com.sg
Website: www.seri.com.sg

28-31
6th International Glaucoma Symposium
Athens, Greece
Contact: Avital Rosen
Tel: (41 229) 080 488
Fax: (41 227) 322 850
E-mail: glaucoma@kenes.com

April 2007

19-20
International Ophthalmology 2007: Practical Solutions for the Developing World and Your World
Charlottesville, VA, USA
Contact: Ashley Schauer
Tel: (1 434) 295 3227
E-mail: aschauer@iris2020.org
Website: www.IRIS2020.org

28-2 May
2007 Annual Symposium and Congress of the American Society of Cataract and Refractive Surgery
San Diego, CA, USA
Contact: ASCRS-ASOA, 4000 Legato Road, Suite 850, Fairfax, Virginia 22033
Tel: (1 703) 591 2220
Fax: (1 703) 591 0614
E-mail: ascrs@ascrs.org/asoa@asoa.org

May 2007

6-11
Association for Research in Vision and Ophthalmology Annual Meeting
Fort Lauderdale, FL, USA
Contact: Congress Secretariat
Tel: (1 240) 221 2900
Fax: (1 240) 221 0370
Website: www.arvo.org

20-23
Annual Meeting Of The European Strabismological Association
Mykonos, Greece
Contact: Organizing Secretariat, Aktina-City Congress
Tel: (30 210) 323 2433
Fax: (30 210) 323 2338
E-mail: dch@citycongress.com
Website: www.esa-strabismology.com

June 2007

9-12
2007 Congress of the European Society of Ophthalmology
Vienna, Austria
Contact: Britta Sjöblom
Tel: (46 84) 596 650
Fax: (46 86) 619 125
E-mail: britta.sjoblom@congrex.se

16-18
Indonesian Ophthalmologist Association Annual Meeting
Jakarta, Indonesia
Contact: Johnny Zulkarnain, Department of Ophthalmology FKUI-RSCM, Jl Salemba No. 6, Jakarta Pusat, Indonesia
Tel: (62 21) 315 8926
Fax: (62 21) 391 9594
E-mail: pit33jakarta@perdami.or.id

20
Asia Pacific Society of Ophthalmic Plastic and Reconstructive Surgery Annual Meeting
Seoul, Korea
Contact: Dr Sang In Khwarg
E-mail: khwarg2000@yahoo.com

21-22
Korean Society of Ophthalmic Plastic and Reconstructive Surgery International Symposium
Seoul, Korea
Contact: Dr Sang In Khwarg
E-mail: khwarg2000@yahoo.com.

July 2007

18-21
World Glaucoma Congress
Singapore

Note to Readers
This section is intended to highlight activities of interest to glaucoma specialists and ophthalmologists in Asia. Please let us know of any forthcoming activities that you may be organising or wish to feature on this section.

Contact: Congress Organizer/Scientific Secretariat, AIGS Meeting Office, Jan van Goyenkade 11, 1075 HP Amsterdam, The Netherlands
Tel: (31 20) 679 3411
Fax: (31 20) 673 7306
E-mail: meetingoffice@globalaigs.org
Website: www.globalaigs.org

September 2007

8-12
XXV Congress of the ESCRS
Stockholm, Sweden
Contact: Congress Secretariat
Tel: (353) 1209 1100
Fax: (353) 1209 1112
E-mail: escrs@escrs.org
Website: www.escrs.org

November 2007

10-13
2007 Annual Meeting of the American Academy of Ophthalmology (AAO)
New Orleans, USA
Contact: American Academy of Ophthalmology
Tel: (1 415) 561 8500
Fax: (1 415) 561 8533
E-mail: aaoe@aao.org
Website: www.aao.org/annual_meeting/2006.cfm

December 2007

7-8
Retinal and Glaucoma Imaging 2008: Ocular Coherence Tomography (OCT) Applications and Future Technology
Palm Beach, FL, USA
Contact: Department of CME, Bascom Palmer Eye Institute Dept. of CME
Tel: (1 305) 326 6110
Fax: (1 305) 326 6518
E-mail: bpeicme@med.miami.edu
Website: www.bascompalmer.org

ALLERGAN

Progression in Glaucoma

Professor Anders Heijl
Department of Ophthalmology
Malmo University Hospital
Lund University
Lund, Sweden

Only 2 trials have prospectively studied the natural history of glaucoma: the Early Manifest Glaucoma Trial (EMGT)[1] and the Collaborative Normal-Tension Glaucoma Study (CNTGS).[2] The EMGT investigated patients with mild glaucoma and elevated intraocular pressure (IOP). The median time to progression (-2 dB) was 4 years.[1] In the CNTGS, the median time to progression was 5.5 years and the median rate of progression was -0.4 dB per year.[2]

In a subset of untreated patients in the EMGT observed for IOP changes, the IOP remained stable for patients with primary open angle glaucoma (POAG) and ocular hypertension, but increased by 1.5 mm Hg per year for those with exfoliation glaucoma.[1] The median visual field change was -2.4dB, with a mean of-1 dB per year. However, there were large differences between the groups, with exfoliation glaucoma showing greater visual field loss (Table 1). The natural history for exfoliation glaucoma is therefore different to that of POAG and normal-tension glaucoma (NTG) in that the IOP increases quickly and visual field progression is rapid; the mean time to progression was 1.5 years.

Table 1. Mean progression according to type of glaucoma.

Glaucoma type	Mean change (dB per year)
Primary open angle glaucoma	>1.0
Normal tension glaucoma	0.5
Exfoliation glaucoma	3.3

A retrospective clinical study of 600 patients showed a mean visual field loss of -0.86 dB per year over 5 years of follow-up. This group of patients were older than those in the EMGT study, with more baseline damage and higher IOPs, and a greater percentage of exfoliation glaucoma, thus the more rapid progression.

The natural history of glaucoma progression is now known for patients with IOP up to 30 mm Hg. IOP varies little if left untreated except for patients with exfoliation glaucoma. The average untreated visual field progression is relatively moderate, is lower in patients with NTG than in those with POAG, and is highest in those with exfoliation glaucoma. However, the variation seen in clinical practice may be large, so regular follow-up of all patients is required.

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Role of Combination Therapy

Dr Anton Hommer
Department of Ophthalmology
Hera Hospital
Vienna, Austria

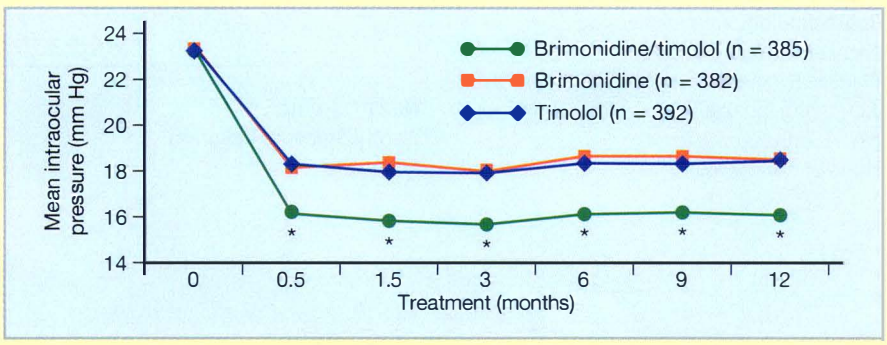
Before considering combination therapy, monotherapy options should be optimised. However, monotherapy is often limited by inadequate efficacy, loss of persistency, and side effects. For optimal monotherapy, the drugs should be effective, with minimal side effects.

When monotherapy does not sufficiently lower the intraocular pressure (IOP), the options are to switch therapy or add a new drug. Switch therapy is indicated for patients who do not respond to the initial medication or who find the side effects intolerable. Add-on or combination therapy is indicated when monotherapy is effective and tolerable, but does not lower the IOP to the desired level. However, the treatment should be simple, effective, tolerable, and affordable.

The available IOP-lowering drugs have different mechanisms of action — decrease aqueous humor production, increase trabecular outflow and increase uveoscleral outflow. The ideal combination therapy should decrease inflow and increase outflow.

Considerations for the type of combination therapy include compliance and the washout effect. For compliance, the more drugs a patient needs to instil, the less they are likely to adhere to the regimen. Patel and Spaeth found that only 50% of patients are compliant with one medication, with the rate decreasing to 32% for 2 medications.[1] The washout effect can be avoided by administering a fixed combination at one time instead of 2 medications sequentially. The advantages of a fixed combination are therefore reduced frequency of administration, increased convenience, better compliance, reduced exposure

Figure 1. Mean intraocular pressure at 10 am (peak effect).
* p < 0.001 vs brimonidine or timolol.



to preservatives and no wash-out effect. The only disadvantage is that it may not be possible to know which component is causing any potential side effects. There are several fixed combination therapies available. Combigan® is a fixed combination of brimonidine 0.2% and timolol 0.5% that enhances both the inflow and outflow effects. The fixed combination provides significantly better IOP-lowering than either drug administered alone ($p < 0.001$) [Figure 1].[2] Ganfort® is a fixed combination of bimatoprost 0.03% and timolol 0.5%. This combination has been demonstrated to be at least as effective as bimatoprost administered once daily and timolol administered twice daily. The use of fixed combination therapies is more effective than administration of the same drugs separately and the simplified dosing will aid compliance.

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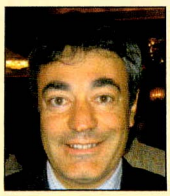
Managing the Progressing Patient



Dr Luca Rossetti
Department of Ophthalmology
University of Milan
Milan, Italy

A number of studies have shown that lowering intraocular pressure (IOP) is effective for reducing progression of glaucoma. However, research results need to be translated into clinical practice. Meta-analysis enables the results of clinical studies to be summarised and will indicate which treatments are most effective. A meta-analysis of clinical trials investigating the effectiveness of medical treatment in patients with chronic open angle glaucoma showed a protective effect of treatment of 50% against progression of the disease. However, approximately 15% of patients progressed despite treatment.

Trials have shown that the diurnal IOP is an important consideration. Newer drugs such as prostaglandin analogues provide stable IOP reduction throughout the day and night compared with timolol and dorzolamide. A comparison of the 24-hour effect of bimatoprost, latanoprost, and travoprost found that bimatoprost was the most effective drug.[1]

In a meta-analysis of 115 clinical trials comparing the effectiveness of the prostaglandin analogues, 8 compared bimatoprost with at least one other drug in this class. The baseline IOP was 24 mm Hg, and the average IOP reduction for all drugs was >30% (7.6 mm Hg). Bimatoprost resulted in more significant IOP-lowering than the other prostaglandin analogues, by approximately 1 mm Hg. While bimatoprost was associated with more side effects than the other drugs, the incidence of severe side effects was not significantly different. There are a number of variables that may influence the management of glaucoma. However, reduction of clinically significant IOP is the primary treatment goal.

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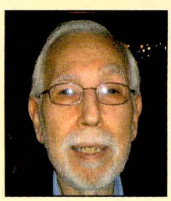
Update on Neuroprotection



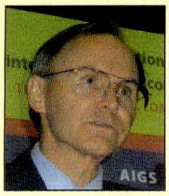
Dr Theodore Krupin
Feinberg School of Medicine
Northwestern University
Chicago, Illinois, USA

The definition of glaucoma has evolved to that of an optic neuropathy characterised to a specific pattern of optic nerve and visual field damage that results in a number of different conditions, most, but not all, of which are associated with elevated intraocular pressure (IOP). Glaucoma is a multifactorial optic neuropathy characterised by the death of retinal ganglion cells (RCGs) and their axons, resulting in optic nerve cupping and visual field functional loss. This concept highlights that structural damage occurs prior to functional loss. Clinical trials have provided evidence that IOP is an important risk factor for both the onset and progression of glaucoma. IOP is currently the only modifiable risk factor and the benefit of lowering IOP has been shown. However, this treatment is not always successful in halting disease progression, indicating the contribution of IOP-independent factors. The goal of treatment is to stop neurodegeneration of the RGCs and halt visual field damage.

Neuroprotection is a strategy directed at keeping RCGs alive and functioning independently of IOP level, ocular blood flow, and other mechanisms. Glaucoma has a number of characteristics that may be responsive to neuroprotective therapies. The early glaucomatous process involves only RGC axons with gradual death of cell bodies over hours to days, in contrast to central nervous system insults that result in immediate direct damage to multiple cell bodies with irreversible injury. The Low-pressure Glaucoma Treatment Study (LoGTS) is currently investigating the role of brimonidine versus timolol in neuroprotection. Visual field progression is the primary endpoint and optic nerve and central corneal thickness are being investigated. Memantine is also under investigation for neuro-protection. These trials will show whether neuroprotection is a viable clinical concept for the treatment of glaucoma.

From the Allergan Asia Pacific satellite symposium held at the SEAGIG International Glaucoma Convention, Chennai, India, 3 December 2006.

Controlling Intraocular Pressure



Professor Paul Palmberg
Bascom Palmer Eye Institute
University of Miami School of Medicine
Miami, Florida, USA

In the 1970s, the natural history of glaucoma was uncertain, making the effect of treatment difficult to assess. Epidemiological studies at the time suggested that only one-third of glaucomatous damage was associated with increased intraocular pressure (IOP). Information about progression of the disease and the role of IOP was therefore needed. Recently, several clinical trials have begun to answer these questions.[1-3]

Intraocular Pressure-dependent Glaucoma

A study investigating 4000 people with healthy eyes (mean IOP, 15 mm Hg), normal pressure glaucoma, and glaucoma (mean IOP, >21 mm Hg) found that the ratio of patients with high IOPs to those with glaucoma was 10:1. In a subset of elderly patients, only 30% of patients with high IOPs had glaucoma, suggesting that increased IOP alone is not sufficient to cause glaucoma. Moreover, one-third of eyes with glaucoma had statistically normal IOPs, indicating a weak relationship between IOP and glaucomatous damage. However, only one person in the lower half of the IOP distribution had glaucoma, suggesting that low IOP may compensate for another causative mechanism for glaucoma.

The Baltimore Eye Survey showed similar results: for every 3 mm Hg, the prevalence of glaucoma increased by 50%.[4] In eyes with low IOPs, at a level similar to that of episcleral venous pressure, the prevalence of glaucoma remained low. This may be due to a protective effect of low to normal IOP, in which case, a large proportion of glaucoma may be IOP-dependent even if IOP is not the direct cause.

Clinical experience supports the concept of maintaining low IOP for the treatment of glaucoma. In 1960, Chandler found that eyes with advanced glaucoma required IOPs below the average normal of 15 mm Hg.[5] Eyes with mild early disc damage could withstand IOPs within the mid-normal range (15 to 17 mm Hg) and eyes with ocular hypertension but no disc damage could tolerate higher IOPs (Table 1). Disc examination will therefore indicate the aggressiveness of the condition and guide the treatment.

In 1982, in a long-term follow-up study of patients with high IOPs (in the 30s and 40s), Grant and Burke found that patients with mild glaucoma (slight disc cupping with no visual field loss) who achieved IOPs ≤20 mm Hg did not progress over 10 to 20 years.[6] However, patients with moderate disc damage and mild visual field loss generally required a reduction in IOP to ≤17 mm Hg to halt progression, and those with advanced damage required a reduction in IOP to <15 mm Hg.

Overall, it was recognised that lowering IOP reduced the risk for glaucoma progression, but there was little consensus as to the optimal IOP required to prevent damage. Since then, a number of clinical trials investigating the association of IOP and glaucoma have been performed.

Setting a Target Intraocular Pressure

The Advanced Glaucoma Intervention Study (AGIS) randomised patients with -10 dB visual field loss and high IOPs (26 mm Hg) to receive laser trabeculoplasty or surgery.[1] Patients with IOPs consistently <18 mm Hg had no net visual field progression after 8 years of follow-up, while patients with IOPs >18 mm Hg had an average visual field progression of -2 to -3 dB. The risk for glaucoma progression increased with increasing IOP.

This result suggests that a target pressure is required for patients with glaucoma. The concept of target pressure is based on how low the IOP needs to be for an individual patient to avoid IOP-dependent further damage. It is advisable to continue increasing treatment until the target pressure is achieved when this can be accomplished by using low-risk therapies such as medication or laser. If surgery would be required to reach the target pressure, one must weigh the risks versus benefits of such intervention in each individual patient before proceeding.

Prof Palmberg's study in Miami investigated 212 eyes with a mean deviation of -14 dB that underwent filtering surgery to adjust the IOP to approximately 10 mm Hg. There was no net visual field loss over an average follow-up period of 7.6 years, suggesting that progression can be halted, even when the damage is advanced.

The Collaborative Initial Glaucoma Treatment Study (CIGTS) investigated patients with untreated glaucoma with IOPs of approximately 27 mm Hg and a mean deviation of -5 dB.[2] The approach to target pressure was aggressive, with a target reduction in IOP of 35% to 17.5 mm Hg for the medical-treatment group. A reduction of 38% was achieved in the group initially treated with medications and laser, resulting in no net visual field loss over 5 years. In a subset of patients with more advanced glaucoma (mean deviation, -10 dB), there was less visual field loss progression among patients who had undergone surgery, with a 52% IOP reduction.

In the Early Manifest Glaucoma Trial (EMGT), there was no target pressure utilized, although the average IOP-lowering was 29%.[3] However, 45% of patients progressed in 5 years in the treated group, versus 62% in those observed without treatment.

Interestingly, the CIGTS and EMGT were similar studies, except that CIGTS mandated

Table 1. Intraocular pressure requirements according to Chandler.[5]

Glaucoma type	Intraocular pressure
Advanced glaucoma	< 15 mm Hg
Mild glaucoma (one hemi-field)	15-18 mm Hg
Ocular hypertension	May observe up to 30 mm Hg

reaching a target pressure. The IOP reduction was only a third more in the CIGTS (38% and 29%, respectively). However, progression was substantially greater in the EMGT, suggesting that adopting target pressures is effective for stopping or slowing progression.

Achieving Target Pressure

Recent studies suggest that a goal for IOP reduction of 30% to 35% is reasonable, with up to 50% for advanced glaucoma. First-line therapy is usually a prostaglandin or β-blocker, and both drugs will achieve a flattened diurnal curve. However, IOPs <15 mm Hg are more achievable with a prostaglandin and prostaglandins have replaced β-blockers as the first choice of medical therapy in the USA. Approximately one-third of patients with advanced glaucoma will achieve the target pressure with latanoprost alone, while 50% to 60% of patients with mild initial disease can reach an appropriate level. By contrast, lower percentages will reach the goal with a β-blocker.

In the XLT study, there were no significant differences in effectiveness or endurance between latanoprost, travoprost, and bimatoprost, although the incidence of red eye was greater with bimatoprost.[7] Importantly, there was no difference between latanoprost and bimatoprost for achieving a 35% IOP reduction.

For AGIS-type patients with advanced disease and IOPs ≥27 mm Hg, the chance of reducing the IOP to 13 to 14 mm Hg with one drug is approximately 20%. However, once-daily combination therapy such as latanoprost and timolol (Xalacom™) could provide an additional 2.5 mm Hg IOP reduction and increase the rate to approximately 50%. For CIGTS-type patients, a once-daily prostaglandin will reduce the IOP to the target level for approximately one-half to two-thirds of patients.

Combination Therapy

Combination therapy such as latanoprost and timolol has the advantage of once-daily dosing without losing the effectiveness of either drug given separately. Initial studies of patients with stable glaucoma found that addition of timolol or latanoprost increased the IOP reduction by 2 to 3 mm Hg over either drug alone. Recent crossover studies have shown that latanoprost and timolol combination given in the evening is 2.5 mm Hg better than latanoprost alone; one study of Xalacom use demonstrated a 45% reduction in IOP from an initial pressure of 25 mm Hg.

While the registration trials in the US and in Europe that compared Xalacom to either latanoprost or timolol showed a disappointing 1 mm greater reduction with Xalacom over latanoprost, the studies were unfortunately conducted in patients who were often poor responders to timolol (entry criteria was IOP >25 mm Hg with timolol). This was required by the US Food and Drug Administration, which at that time saw latanoprost as a second-line drug. However, in a post-hoc analysis of those patients in whom the IOP fell at least 6 mm Hg during therapy with timolol, Xalacom outperformed latanoprost by 2 mm Hg in patients with ocular hypertension and by 3.3 mm Hg in patients with glaucoma.

Conclusions

Eyes with advanced glaucoma require IOPs below the average normal to halt progression. Eyes with limited disc cupping need an IOP reduction of 35% and eyes with ocular hypertension with a normal disc may not need treatment but only follow-up. Disc examination will determine the aggressiveness of the disease, which will guide the treatment according to the risks and benefits for each individual patient. If the target pressure is not achieved with one drug, adding another medication or laser therapy, or switching to combination therapy may help to attain stable visual fields.

Targeting Intraocular Pressure

- Eyes with advanced glaucoma require intraocular pressures below the average normal
- Eyes with limited disc cupping need an intraocular pressure reduction of 35%
- Eyes with ocular hypertension with a normal disc need frequent follow-up and medical therapy may be indicated for those at sufficient risk of damage
- Disc examination will determine the aggressiveness of the disease
- If the target pressure is not achieved with one drug, add another drug or switch to combination therapy

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From the Pfizer Ophthalmic satellite symposium Getting Control of IOP held at the SEAGIG International Glaucoma Convention, Chennai, India, 3 December 2006.

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Books and other monographs

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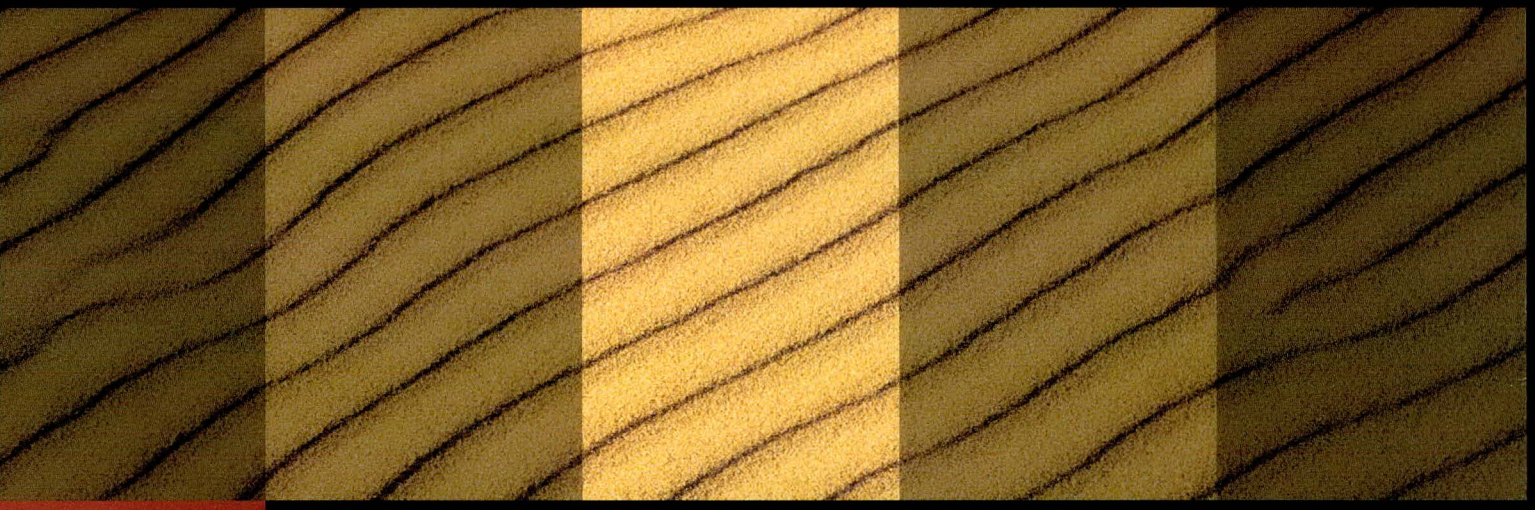

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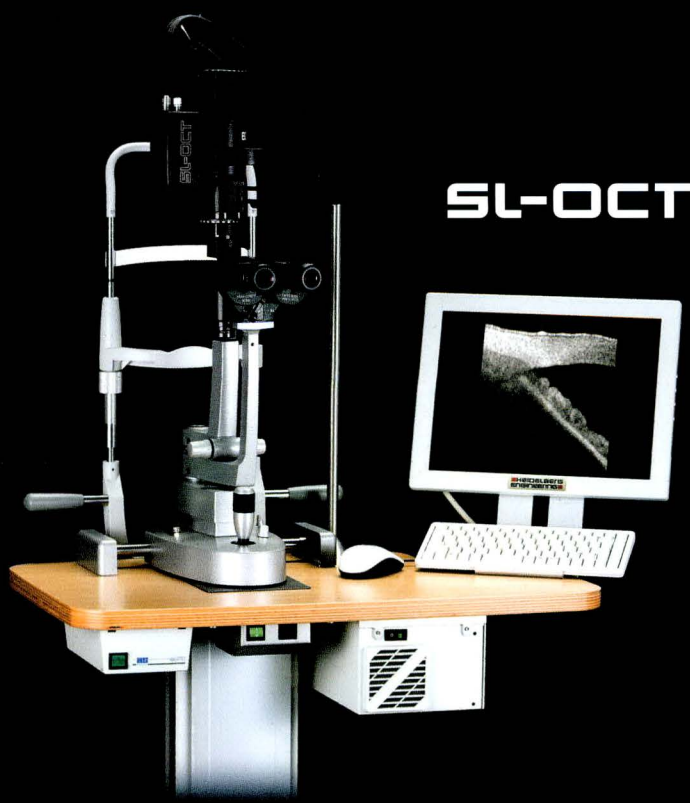

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XALACOM is contraindicated in patients with reactive airway disease, including bronchial asthma, a history of bronchial asthma, or severe chronic obstructive pulmonary disease; sinus bradycardia; second- or third-degree atrioventricular block; overt cardiac failure; cardiogenic shock; or hypersensitivity to any component of this product.

XALACOM has been reported to cause changes to pigmented tissues. The most frequently reported changes have been increased pigmentation and growth of eyelashes. The iris pigmentation changes may be permanent.

In the 6-month registration trials, the most frequent adverse events were eye irritation, including stinging, burning, and itching (12.0%); eye hyperaemia (7.4%); corneal disorders (3.0%); conjunctivitis (3.0%); blepharitis (2.5%); eye pain (2.3%); headache (2.3%); and skin rash (1.3%).

Please refer to product insert for full prescribing information.

References:
1. Higginbotham EJ, Feldman R, Stiles M, Dubiner H, for the Fixed Combination Investigative Group. Latanoprost and timolol combination therapy vs monotherapy: one-year randomized trial. *Arch Ophthalmol.* 2002;120:915-922. 2. Data on file. Pfizer Inc, New York, NY.

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Suite 701, Pacific Place,
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