Journal of the South East Asia Glaucoma Interest Group

Volume 10 Number 2 April 2008

Asian Journal of OPHTHALMOLOGY

Peripapillary Atrophy

Latanoprost Monotherapy in Asia

Phototherapeutic Keratectomy

Low Vision in Elderly People

Scientific Communications

Endurance

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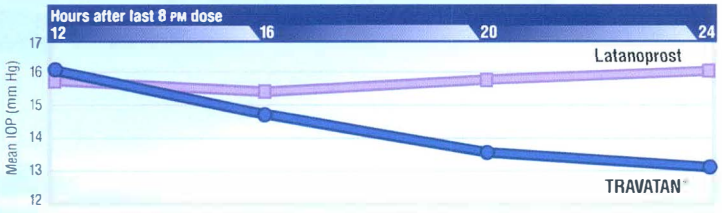

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TRAVATAN® (travoprost 0.004%) Ophthalmic Solution Sterile **DESCRIPTION** Travoprost is a highly selective, potent agonist for the FP prostanoid receptor. Its chemical name is isopropyl (Z)-7-[(1*R*,2*R*,3*R*,5*S*)-3,5-dihydroxy-2-[(1*E*,3*R*)-3-hydroxy-4-[[$\alpha\alpha$,$\alpha\alpha$,$\alpha\alpha$-trifluoro-*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: polyoxyl 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, blephanitis, 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 (20 hours), and 3.1 mm Hg (24 hours). The difference between the two groups at 24 hours post dose was statistically significant (p=0.0117).

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Asian Journal of
OPHTHALMOLOGY

Volume 10 Number 2 April 2008

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South East Asia Glaucoma Interest Group

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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
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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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Scientific Communications

ISSN 1560-2133

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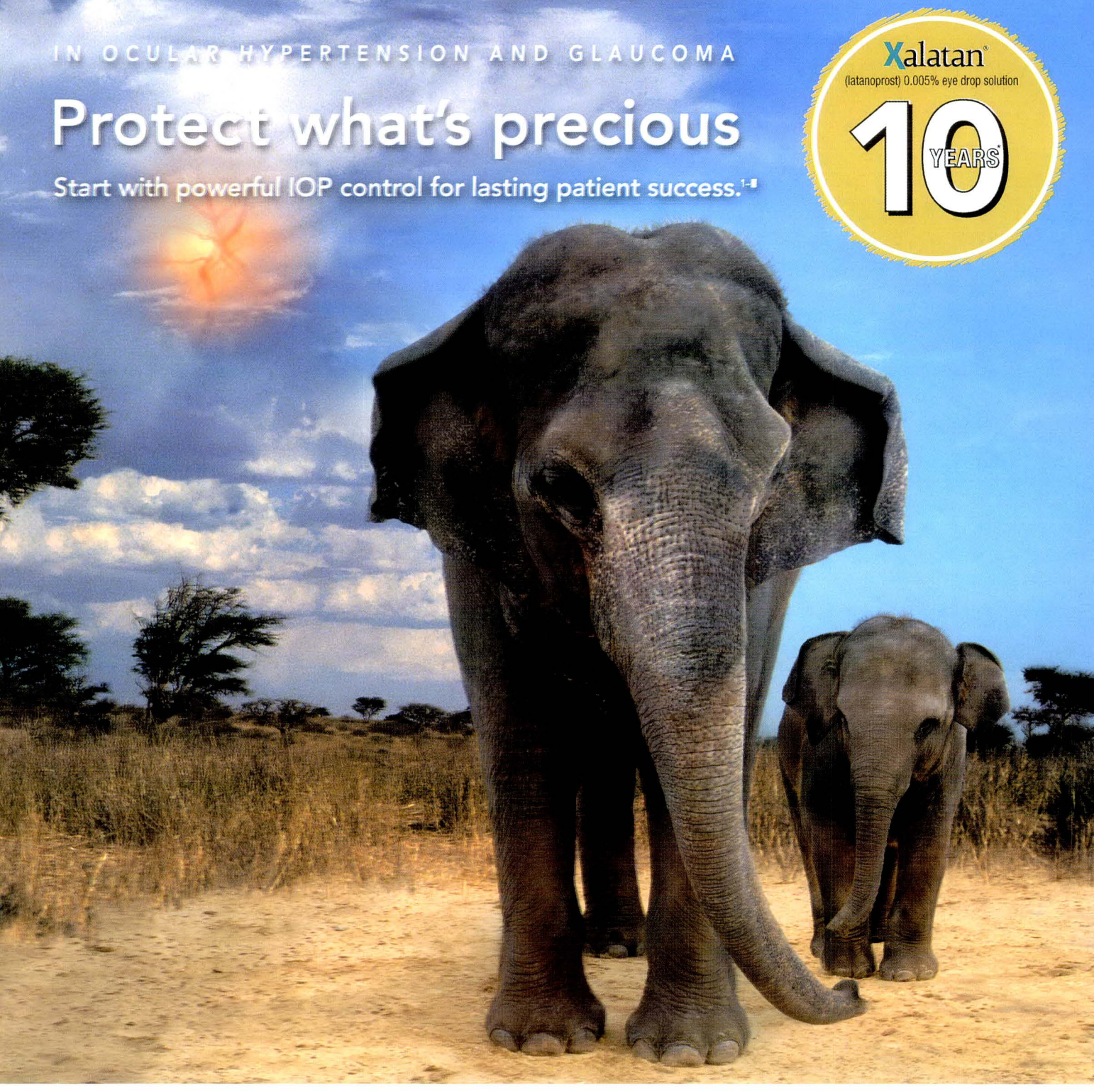

Xalatan® is indicated for the reduction of elevated intraocular pressure (IOP) in patients with open angle glaucoma (OAG) and ocular hypertension (OH). Prescribing Information. Please refer to the SmPC before prescribing Xalatan® 0.005% eye drops solution (latanoprost) **Presentation:** Plastic bottle containing 2.5ml eye drops. Each 1ml contains latanoprost 50 micrograms (0.005%) and benzalkonium chloride 0.20mg. Indication Reduction of elevated intraocular pressure in patients with OAG and ocular hypertension. **Dosage and Administration:** *Adults including the Elderly:* One eye drop into the affected eye(s) once daily in the evening. Contact lenses should be removed before instillation of the eye drops and may be reinserted after 15 minutes (see Precautions). *Children:* Not recommended. **Contra-indications:** Known hypersensitivity to any component. **Precautions:** Xalatan may increase brown pigment within the iris leading to a gradual change in eye colour usually within the first 8 months. This has predominantly been seen in patients with mixed coloured irides and may be permanent. Patients should be examined regularly and treatment discontinued if appropriate. Unilateral treatment can result in permanent heterochromia. Exercise caution in patients with severe or brittle asthma, inflammatory ocular conditions and other types of glaucoma, including OAG of pseudophakic patients, aphakic patients, pseudophakic patients with torn posterior lens capsule or anterior chamber lenses or patients with known risk factors for cystoid macular oedema. Xalatan contains the preservative benzalkonium chloride which has been reported to cause punctate keratopathy and/or toxic ulcerative keratopathy, may cause eye irritation and is known to discolour soft contact lenses. Close monitoring required with frequent or prolonged use of Xalatan in dry eye patients/conditions where the cornea is compromised. Contact lenses may absorb benzalkonium chloride. These should be removed before applying Xalatan but may be reinserted after 15 minutes (see Dosage and Administration). **Pregnancy:** Do not use. **Lactation:** Do not use or stop breast feeding. **Interactions:** Definitive data are not available. However, any other eye drops should be administered five minutes apart. **Side Effects:** Ocular side effects – Very common (>1/10): Increased iris pigmentation, eye irritation (including slight foreign body sensation), eyelash changes (darkening, thickening, lengthening, increased number); Common (>1/100and <1/10): Mild to moderate conjunctival hyperaemia, transient punctate epithelial erosions (mostly without symptoms), blepharitis, eye pain. Please refer to SmPC for other ocular side-effects. Non-ocular side-effects – Uncommon (>1/1000 and <1/100): Skin rash; Rare (<1/1000): Asthma, asthma exacerbation and dyspnoea; Very rare (<1/10,000): Aggravation of angina in patients with pre-existing disease, chest pain. **Driving:** Vision may be blurred following eye drop instillation. **Overdosage:** Symptomatic treatment. **Pharmaceutical Precautions:** Store at +2°C – +8°C. Protect from light. Once opened, store at room temperature (≤25°C) and discard after 1 month. **Legal category:** POM. **Packaging Quantities and Basic NHS price:** 2.5 ml £13.14. **PL number:** PL 00032/0220. **PL Holder:** Pharmacia Limited, Ramsgate Road, Sandwich, Kent, CT13 9NJ, UK. **Date of preparation of PI:** September 2006. Further information is available on request from: Pfizer Limited, Walton Oaks, Dorking Road, Tadworth, Surrey, KT20 7NS, UK.

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Peripapillary Atrophy

Mani Baskaran
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Peripapillary atrophy (PPA) and its significance in glaucoma has been a subject of research interest since 1968. However, PPA remains an enigma due to the controversial literature on its correlation with the diagnosis and progression of glaucoma.

In this issue, Pan et al, in their research into PPA in primary open angle glaucoma and normal tension glaucoma (NTG), found PPA to be more weakly correlated with visual field defect than neuroretinal rim (NRR) parameters.[1] These researchers discuss the varied opinions that exist in the literature relating to the significance of PPA as a clinical feature in glaucoma.

A review article on PPA by Jonas emphasises that α and β zones of atrophy are second only to NRR parameters for detection of glaucomatous optic nerve damage.[2] However, PPA is associated with glaucoma, especially NTG, and eventual development of disc haemorrhages, independent of a small NRR area, and progression of the disease.

The presence of PPA, especially β-zone atrophy, at areas of NRR changes is well documented,[2] which is in favour of the association with glaucoma, although such eyes are present in small numbers in most studies. More studies are needed to identify specific risk factors for PPA in such eyes.

There is controversial evidence on the negative or weak association of PPA with glaucoma detection and progression in the literature,[1] suggesting that studies of large series of patients with proper documentation and sound statistical methods, especially as part of epidemiological studies, may be welcome in this interesting area. The fact that unilateral glaucoma does not have an association with PPA when compared with normal contralateral eyes[1] is intriguing, since the reasons for this are unclear. It is also unclear whether PPA precedes glaucomatous damage and progression or follows the disease process.

Investigation into the vascular aetiology, as highlighted by the experimental study of Hayreh et al, shows a higher occurrence of PPA among glaucomatous, arterial hypertension–positive rhesus monkeys.[3] The presence of disc haemorrhages in the later stages of the disease process,[2] and the association of NTG with PPA suggest that PPA could possibly be related to intraocular pressure–independent mechanisms. Some indirect evidence is available in the literature on PPA and acute primary angle closure; Lee et al found a weak correlation of PPA at 4 months follow-up.[4] Contrary to this is the absence of enlargement of PPA in arteritic anterior ischaemic optic neuropathy.[2]

Recent evidence from genetic studies of twins by Healey et al suggests that β-zone PPA can be genetically influenced, with a small amount of this genetic effect shared with the genes involved in myopia.[5] Follow-up of these studies may provide guidance on whether PPA is an independent factor in glaucoma.

While Europeans and South Indians have no differences in the occurrence of PPA,[2] the prevalence of α- and β-zone atrophy in a Chinese population older than 40 years is 70% and 20%, respectively.[6] This may indicate a higher prevalence of PPA in the general population and a racial difference, which might influence the possible association with glaucoma in future studies.

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The Relationship between Peripapillary Atrophy and Primary Open Angle Glaucoma

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Aim: To evaluate the relationship between peripapillary atrophy, cup-disc ratio, and visual field defect in Chinese patients with primary open angle glaucoma.
Methods: The study included 45 eyes of 45 patients with primary open angle glaucoma with high intraocular pressure and 40 eyes of 40 patients with normal tension glaucoma. Forty patients had unilateral visual field defects. Stereoscopic colour optic disc photographs were morphometrically evaluated.
Results: Both the α-zone area and the β-zone area weakly correlated with glaucomatous visual field defects, while cup-disc ratio showed a relatively strong correlation with visual field defects. Only cup-disc ratio and age were found to be risk factors for the occurrence of visual field defects by logistic regression analysis. Among the 40 patients with unilateral visual field defects, the cup area, cup-disc ratio, and α-zone area of the eyes with visual field defects were significantly greater than in the eyes without visual field defects (cup area, $p < 0.001$; cup-disc ratio, $p < 0.0001$; α-zone area, $p = 0.0045$). There was no significant difference in β-zone area between the 2 eyes ($p = 0.426$). The frequency of occurrence of peripapillary atrophy was also similar between the 2 eyes.
Conclusions: The relationship between peripapillary atrophy and the severity of visual field defects might not be as strong as that between cup-disc ratio and visual field defects. The occurrence and the areas of peripapillary atrophy may not be as clinically useful as the classical optic disc parameters of cup-disc ratio, either for diagnosing or for predicting the status of visual field defects in patients with glaucoma.

Key words: *Atrophy, Glaucoma, open-angle, Visual fields*

Asian J Ophthalmol. 2008;10:114-7

Introduction

The relationship between peripapillary chorioretinal atrophy (also called parapapillary chorioretinal atrophy; PPA) and glaucoma was first described in the 1920s, when PPA was thought to be an early sign of glaucoma.[1] In the past 20 years, a number of investigators in various countries have reported that the area of PPA is larger and the prevalence rate is higher in patients with glaucoma than in people without glaucoma.[2-5] However, there are no data on the relationship between PPA and glaucoma among Chinese people with glaucoma and minor refraction errors. Therefore, a retrospective clinical study of the presence of PPA among 85 Chinese patients with primary open angle glaucoma (POAG) and normal tension glaucoma (NTG) with refraction <3 D was conducted. A comparison of PPA and optic disc parameters between the 2 eyes of 40 patients with unilateral visual field defects due to POAG or NTG was performed.

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Methods

Patients

The study sequentially enrolled 45 patients (45 eyes) with POAG and 40 patients (40 eyes) with NTG attending the Department of Ophthalmology, Peking University First Hospital, Beijing, China, between 2001 and 2003. All patients had documented high-quality stereoscopic colour optic disc photographs. Among the 85 patients, 40 had unilateral visual field defects (20 eyes with POAG and 20 eyes with NTG). All patients gave informed consent for the study.

All patients underwent complete ophthalmological examination, including visual acuity and refraction, slit-lamp biomicroscopy, direct opthalmoscopic fundus examination, Goldmann dynamic visual field examinations, gonioscopy, diurnal intraocular pressure

(IOP) curve assessment with Goldmann applanation tonometry, and stereoscopic colour optic disc photographs (Retinal Camera, TRC-SS; Topcon Corp, Tokyo, Japan).

POAG was defined as the presence of typical glaucomatous optic nerve damage and reproducible glaucomatous visual field defects, open angles on gonioscopy, IOP >21 mm Hg at the time of diagnosis or at any time during the course of disease, and absence of other ocular or intracranial disease that might affect the optic disc or visual field. The diagnostic criteria for NTG were the same as for POAG, except that the patients had never experienced an increase of IOP to ≥21 mm Hg.

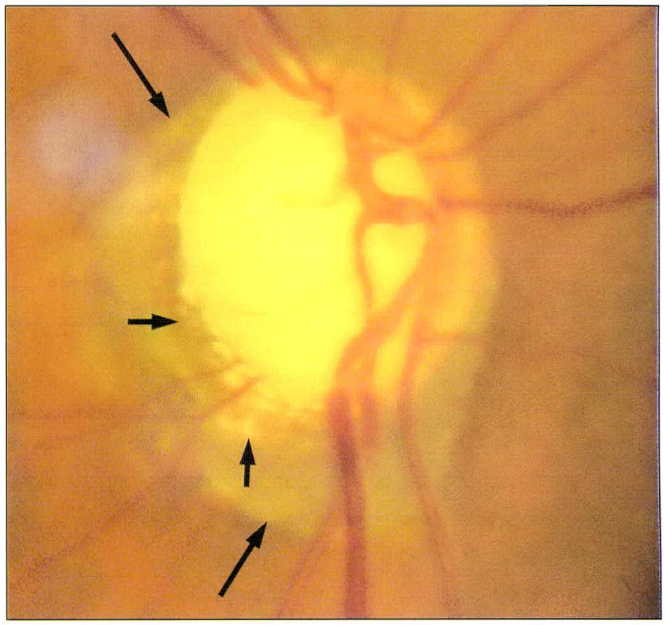
Semiquantitative grading was performed according to the Goldmann visual field examination results, using the I4e test object, as follows: 1, mild visual field defect (paracentral scotoma or nasal steps); 2, moderate visual field defect (arcuate scotoma in the upper or lower area); and 3, serious visual field defect (ring scotoma or a small island of central vision with or without an accompanying temporal island).

Inclusion criteria included a clear stereoscopic colour optic disc photograph (colour reversal film) obtained within 3 months of a reproducible visual field examination. Patients were excluded if they had a spherical equivalent refractive error >+3.00 D or <-3.00 D, best-corrected visual acuity of <0.8, or a history of other eye diseases, surgery to the eye, optic disc anomalies, or other related fundus lesions likely to affect the optic disc or peripapillary region measurements such as lens opacity. Only one eye was selected for each patient; the selection was random for patients with 2 eyes meeting the inclusion criteria.

Design

Video camera was used to transform the stereoscopic colour photographs of the optic disc and peripapillary region into electrical signals (the patients' names were blinded). An image collection plate was used to convert the signals into digital images composed of 640 x 480 points, which were displayed on the computer screen. The MPIAS-500 multimedia colour graph text analysis system (Qianping Image Engineering Corp, Wuhan, China) was used to delimit the boundaries of these regions manually, via man-machine conversation using the stereoscopic colour optic disc photograph as a reference, and the computer system automatically measured the delimited area. The disc margin was defined as the inner border of the scleral ring of Elschnig. The β-zone was an area with large scleral and choroidal vessels exposed next to optic disc, and the α-zone was the peripheral area with irregular high or low pigments (Figure 1). Calibration was conducted before each measurement. The intraobserver reproducibility of this method of measuring PPA has been described in a previous publication.[6]

Figure 1. α-Zone (long arrow) and β-zone (short arrow) in a glaucomatous eye.



Data Collection and Statistical Analysis

Data collection included the following:

- age, sex, and strength of the refraction error
- structural parameters of the optic disc and PPA, including disc area, cup area, cup-disc ratio, α-zone area (αA), β-zone area (βA), and occurrence rates of the α- and β-zones
- degree of visual field defects.

The Stata version 8.0 statistical package (Statacorp, Texas, USA) was used for statistical analysis. Spearman correlation analysis was used to check the correlativity between the 2 variables. Multiple factor logistic regression analysis was performed on the correlative factors of glaucomatous visual field defects. Paired comparison was performed on the distribution of the dioptric strength of 2 eyes, with 1 D as a demarcation. For the paired data of 2 eyes, *t* test and paired symbol rank test were used for measurement data and McNemar test was used for enumeration data. A p value of <0.05 was considered to be statistically significant.

Results

The rank correlation analysis showed that there was low correlation between αA, βA and the degree of visual field damage (αA, $r = 0.246$, $p = 0.005$; βA, $r = 0.2302$, $p = 0.0092$), but there was a relatively strong correlation between cup-disc ratio and degree of visual field damage ($r = 0.5624$, $p \leq 0.0001$).

In the regression analysis of the occurrence of glaucomatous visual field damage and possible correlation factors, presence of visual field damage of glaucoma was used as a dependent variable, and age, sex, dioptric strength, graded cup-disc ratio,

Table 1. Regression analysis of factors correlating with the occurrence of glaucoma.

Variable	Coefficient of regression	Standard error	Wald χ^2	df	p Value	Odds ratio	95% Confidence interval
Age	0.050	0.021	5.566	1	0.018*	1.051	1.008-1.095
Graded cup-disc ratio†	2.351	0.445	27.916	1	0.000*	10.491	4.387-25.089
Constant	6.206	1.579	15.446	1	0.000	0.002	

* Statistically significant factors.
† Cup-disc ratio was graded as: <0.4, ≥0.4, <0.6, and ≥0.6.

Table 2. Comparison of disc area, cup area, and cup-disc ratio between the affected and fellow eyes of patients with unilateral visual field defects (n = 40).

Eye	Disc area (SD) [mm]	Cup area (SD) [mm]	Cup-disc ratio (SD) [mm]
Affected eye	2.23 (0.37)	1.11 (0.37)*	0.49 (0.10)†
Fellow eye	2.17 (0.38)	0.87 (0.36)	0.39 (0.12)
Difference	0.06 (0.21)	0.24 (0.28)	0.10 (0.12)

* Significance: $t = 5.332$, $p < 0.001$.
† Significance: $t = 5.126$, $p < 0.0001$.

area of α-zone, and presence of β-zone were used as independent variables. The results showed that only age and graded cup-disc ratio were possible influencing factors (Table 1).

The disc area, cup area, cup-disc ratio, αA, and βA were compared between the affected and fellow eyes of patients with POAG and NTG with unilateral visual field defects. Cup area, cup-disc ratio, and αA of eyes with visual field defects were significantly greater than those of eyes without visual field defects. However, there was no significant difference in βA between the 2 eyes (Tables 2 and 3). The frequency of PPA occurrence was also similar between the 2 eyes (Tables 4 and 5). There was no statistically significant difference in the distribution of refraction error between the 2 eyes ($Z = -0.577$, $p = 0.564$).

Discussion

So far, there is no definitive conclusion on the role of PPA in the diagnosis of glaucoma. Many authors have reported that there is a significant association between PPA and glaucomatous optic neuropathy and visual field defects.[3,7,8] Some researchers have found that the large area of the β-zone or PPA-disc ratio to be predictive factors for the progression of glaucomatous optic neuropathy and visual field defects,[3,7] and noted that the rate of occurrence of β-zone increased with glaucoma progression.[8] Conversely, other researchers did not find this relationship between PPA and glaucomatous optic neuropathy, especially in patients with unilateral glaucoma.[9-11] Nevarez et al reported that when IOP increases, resulting in manifestations of glaucomatous impairment, there is no significant change in PPA, and only some patients with late-stage glaucoma have enlarged PPA due to atrophy of the retinal pigment epithelium.[9] Puska and Raitta suggested that PPA is an inborn feature of the eye; optic nerve impairment is not necessarily accompanied by PPA, and nerve fibre damage might occur in people with PPA when the IOP increases.[10] Quigley et al also found that there was no statistically significant difference between the prevalence of PPA in eyes with progression of glaucoma and non-progressive ocular hypertension.[11]

As there were no significant differences in either the morphometric or visual field analysis between patients with POAG and NTG in this study, they were analysed together; the average and standard deviation for the α- and β-PPA areas in each type of glaucoma was reported in a previous study.[12] The correlation analysis for this study showed that there was a strong correlation between cup-disc ratio and the degree of visual field defect, but

Table 3. Comparison of α-zone area (αA) and β-zone area (βA) between the affected and fellow eyes of patients with unilateral visual field defects (n = 40).

Eye	αA (SD) [mm]	βA (SD) [mm]
Affected eye	0.78 (0.64)*	0.16 (0.35)†
Fellow eye	0.53 (0.34)	0.13 (0.37)
Difference	0.25 (0.52)	0.02 (0.15)

* Significance: $t = 3.02$, $p = 0.0045$.
† Not significant: $S = 13.5$, $p = 0.426$ (paired symbol rank test).

Table 4. Comparison of the occurrence rates of α-zone between the affected and fellow eyes of patients with unilateral visual field defects (n = 40).

	Affected eyes		Total
Fellow eyes	Without α-zone	With α-zone	
Without α-zone	0	2	2
With α-zone	2	36*	38
Total	2	38	40

* $S = 0.0000$; $p = 1.000$, >0.05.

Table 5. Comparison of the occurrence rates of β-zone between the affected and fellow eyes of patients with unilateral visual field defects (n = 40).

	Affected eyes		Total
Fellow eyes	Without β-zone	With β-zone	
Without β-zone	26*	5	31
With β-zone	2	7	9
Total	28	12	40

* $S = 1.2857$; $p = 0.2568$, >0.05.

there was only a low correlation between the area of α-zone and β-zone and the degree of visual field defect in these patients. These findings agree with previous reports.[4,13,14]

For the multiple factor regression analysis, the presence of visual field defect was used as a dependent variable, and age, sex, refraction error, graded cup-disc ratio, αA, and presence of β-zone were used as independent variables. Only age and cup-disc ratio were possible influencing factors for glaucomatous visual field defects — the area of α-zone and presence of β-zone had no significant influence on the occurrence of glaucomatous visual field defects. These results agree with those of Budde and Jonas, who found that the proportion of enlarged β-zones was higher in patients with progressive glaucoma than in those with non-progressive glaucoma.[15] However, the enlarged β-zone was only present in a few patients with progressive glaucoma (5 of 81 patients). Since the prevalence rate was low, these authors believed that the increase of β-zone was of little significance for estimation of glaucoma progression. These findings suggest that the relationship between β-zone and glaucoma might not be as strong as that between the cup-disc ratio and visual field defects.

This study also compared the area and prevalence rate of PPA between the affected and fellow eyes of patients with unilateral visual field defects, and found that the cup area, cup-disc ratio, and αA in the eyes with visual field defects were significantly greater in the affected eyes than in the fellow eyes. However, the occurrence rates of α-zone and β-zone and the area of β-zone were similar in the 2 eyes. This result agrees with the results of other studies of PPA in patients with unilateral visual field defects due to glaucoma.[9,10] This suggests that although people with β-zones might have a high susceptibility to glaucoma, the disease may have a minimal influence on the structure of the β-zone. This would explain why a number of studies have shown that the relationship between PPA and visual field defects was not as strong as the relationship between traditional optic disc parameters, such as cup-disc ratio, and visual field defects. Glaucoma might lead to secondary PPA changes in some individuals, but these might be smaller than the visual field changes. This suggests that PPA might be a secondary structural lesion of the choroid and retina in the peripheral area of the optic disc caused by glaucoma in some specific populations.

Patients with myopia >-3.00 D were excluded from this study because PPA is different in eyes with moderate and high myopia than in healthy eyes. This could be a confounding factor in the research.

This study found a low correlation between PPA and the degree of visual field defects in patients with glaucoma, and multiple factor analysis could not confirm the influence of the area of α-zone and presence of β-zone on the occurrence of glaucomatous visual field defects. The cup-disc ratio was not only related to the severity of visual field impairment, but also to the risk for glaucomatous visual field defects. In this study, the relationship between α-zone, β-zone, and visual field defects was not as close as the relationship between cup-disc ratio and the degree of visual field defects. Therefore, PPA might not be effective as a sensitive specific independent diagnostic index for glaucoma. Further study into the susceptibility of individual patients to the secondary changes of PPA, the factors leading to these secondary changes, and the relationship between PPA (α-zone and β-zone) and glaucoma is needed.

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Response to Latanoprost Monotherapy among Malay Patients with Glaucoma

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Aim: *To determine the prevalence of Malay patients with glaucoma who failed to respond to once-daily latanoprost monotherapy with a clinically meaningful reduction of intraocular pressure.*

Methods: *This was a retrospective, non-comparative study of 67 Malay patients with newly diagnosed, previously untreated primary open angle glaucoma, ocular hypertension, or pseudoexfoliative glaucoma. Baseline intraocular pressure was documented from the clinical records of the selected patients. Evaluation of the intraocular pressure–lowering effect was documented after 3 months of treatment with once-daily latanoprost 0.005% monotherapy. Patients who achieved <20% intraocular pressure reduction after 3 months of treatment were considered non-responders.*

Results: *Topical latanoprost monotherapy provided significant intraocular pressure–lowering after 3 months of treatment (30.2%; 17.5 mm Hg [SD, 4.2 mm Hg]) compared with baseline ($p < 0.001$). Fourteen patients (20.9%) were non-responders according to the response criteria. These patients had a significantly higher intraocular pressure following treatment than responders (22.7 mm Hg [SD, 4.5 mm Hg] vs 16.1 mm Hg [SD, 2.8 mm Hg; $p < 0.001$). There were no significant differences in baseline intraocular pressure, age, and sex between responders and non-responders.*

Conclusions: *Topical latanoprost was proven to be an effective intraocular pressure–lowering antiglaucoma drug among Malay patients, with a small group of patients (20.9%) who were not responsive. It is important to identify this group of patients to maximise the intraocular pressure–lowering effect, minimise side effects, and promote compliance, thus delaying the progression of glaucoma.*

Key words: *Asian continental ancestry group, Glaucoma, open-angle, Latanoprost*

Asian J Ophthalmol. 2008;10:118-22

Introduction

The current definition of glaucoma identifies intraocular pressure (IOP) only as a risk factor — although it is the only modifiable risk factor[1] — which differs significantly from the previous theory that IOP was a causative factor for glaucoma. The Early Manifest Glaucoma Trial Group demonstrated a strong association between IOP reduction and progression of glaucoma.[2] A similar association was observed among patients with advanced glaucoma.[3] Medical treatment with topical antiglaucoma drugs has become the mainstay of management, due to the development of more potent topical antiglaucoma medications. The popularity of medical treatment escalated with the recent report of a high incidence of cataract formation following filtration surgery.[4]

The prostaglandin analogues, class 1 antiglaucoma drugs, are the most recent medications to be introduced for glaucoma treatment, and provide IOP reduction of 30%. Prostaglandin analogues such as latanoprost 0.005% are believed to reduce IOP by increasing the uveoscleral outflow,[5,6] unlike the action of topical β-blockers that inhibit aqueous production. Various studies have demonstrated the higher IOP-lowering effect of latanoprost over timolol for patients with primary open angle glaucoma (POAG),[7] ocular hypertension (OHT),[8] and pseudoexfoliation glaucoma,[9] as well as for chronic angle closure glaucoma.[10] Latanoprost is slowly replacing the inexpensive timolol as the first-line medication for glaucoma management. However, studies have demonstrated the

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presence of a subgroup of patients who failed to achieve clinically meaningful IOP reduction with topical latanoprost.[11-14] Scherer reported that 25% of Caucasian patients with glaucoma who were receiving latanoprost demonstrated IOP reduction of <20%,[11] which is equivalent to a class 3 antiglaucoma medication. However, no similar study has investigated non-responders among a Southeast Asian population. The aim of this study was to determine the percent of non-responders among a Malay population receiving topical latanoprost as monotherapy. Identifying this group of non-responders is essential for customising the treatment of glaucoma, maximizing the IOP-lowering effect, and minimising side effects.

Methods

Patients

The medical records of patients with newly diagnosed, previously untreated POAG, OHT, or pseudoexfoliative glaucoma who were given once-daily latanoprost 0.005% as initial monotherapy were reviewed. Eligible patients were recruited retrospectively from the glaucoma database of newly diagnosed patients with glaucoma who attended the Hospital Universiti Sains Malaysia, Kota Bharu, Malaysia, from January 2001 to January 2003. The inclusion criteria were newly diagnosed POAG, OHT, or pseudoexfoliative glaucoma in either 1 or both eyes, based on an IOP >21 mm Hg, glaucomatous characteristics of the optic disc, and visual field changes, supported by gonioscopic findings and slit-lamp examination. Only 1 eye was included in the study; the eye with the higher pretreatment IOP was selected for patients with bilateral glaucoma, and, if the pretreatment IOP was equal in both eyes, the right eye was chosen. Patients enrolled in the study were treatment-naïve Malays, older than 40 years, who subsequently started latanoprost 0.005% monotherapy.

Exclusion criteria were angle closure glaucoma; secondary glaucomas such as neovascular or inflammatory glaucoma; and history of intraocular surgery, laser surgery, or ocular inflammation such as uveitis prior to initiation of latanoprost treatment. Patients whose records included inadequate data on the criteria for diagnosis and who were documented as non-compliant by the treating ophthalmologist were also excluded.

Design

The pretreatment IOP measurement was obtained using Goldmann applanation tonometry between 8.00 am and 1.00 pm in the clinic setting. Patients were prescribed topical latanoprost 0.005% at night, and were advised about the correct administration technique and the importance of compliance. The IOP measurement after 3 months of treatment was obtained from the medical records and compared with the pretreatment IOP. The percent of IOP reduction was calculated based on the difference in IOP between baseline and after 3 months of treatment. Patients with IOP reduction <20% from baseline were considered non-responders.

Results

159 medical records of newly diagnosed Malay patients with glaucoma who attended the Hospital Universiti Sains Malaysia from 2001 to 2003 were reviewed. Sixty seven patients with previously untreated POAG, OHT, or pseudoexfoliative glaucoma who met the study inclusion criteria were enrolled. There were 37 women (55.2%) and 30 men (44.8%). The mean age was 69.1 years (SD, 10.6 years; range, 44 to 89 years). The mean pretreatment IOP was 25.4 mm Hg (SD, 5.2 mm Hg). The mean cup-disc ratio was 0.61 (SD, 0.07; range, 0.50 to 0.70), mean deviation (MD) was -8.84 (SD, 3.12; range, -0.36 to -19.78), and pattern standard deviation (PSD) was 3.00 (SD, 2.06; range, 1.03 to 11.82). The overall mean IOP after 3 months of treatment with latanoprost monotherapy was 17.5 mm Hg (SD, 4.2 mm Hg), representing a statistically significant decrease from baseline of 30.2% ($p < 0.001$, paired *t* test) [Figure 1].

Fourteen patients (20.9%) did not respond to treatment (Table 1). Five patients demonstrated <10% reduction in IOP, with the lowest IOP reduction being 5.9% (Table 2). The IOP of non-responders (22.7 mm Hg; SD, 4.5 mm Hg) was significantly higher than that of responders (16.1 mm Hg; SD, 2.8 mm Hg) [$p < 0.001$, non-paired *t* test] after 3 months of treatment (Figure 2). However, there was no statistically significant difference in pretreatment IOP between the 2 groups (Table 1). In addition, there were no significant differences in age, sex, type of glaucoma, MD, or PSD between the responders and non-responders (Table 1).

Figure 1. Pre- and post-treatment intraocular pressures for newly diagnosed Malay patients with glaucoma.
* $p < 0.001$.

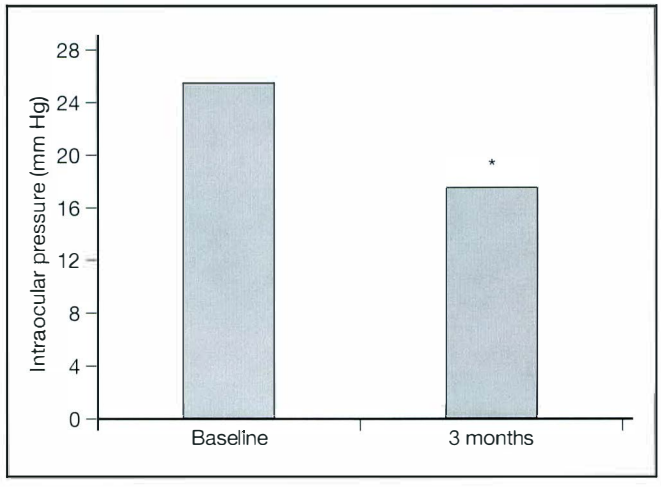


Table 1. Characteristics of responders and non-responders to latanoprost monotherapy in a Malay population with glaucoma (n = 67).

	Responders (n = 53; 79.1%)	Non-responders (n = 14; 20.9%)	p Value*
Sex			
Male	26	4	0.39
Female	27	10	
Mean age (SD) [years]	68.5 (10.7)	71.1 (11.1)	0.42
Type of glaucoma			
Primary open angle	45	11	
Ocular hypertension	2	0	0.49
Pseudoexfoliation	6	3	
Mean deviation (SD)	-9.0 (3.3)	-8.2 (2.2)	1.00
Pattern standard deviation (SD)	3.2 (2.3)	2.4 (0.9)	1.00

* Pearson chi-squared test.

Discussion

Topical latanoprost 0.005% monotherapy was effective for lowering IOP in this study of Malay patients with open angle glaucoma, which is in agreement with studies conducted in various populations.[11-14] This retrospective review was conducted during the first few years of topical latanoprost use in Malaysia. During this period, 42.1% of all newly diagnosed Malay patients with glaucoma (67 patients) were treated with latanoprost monotherapy. The majority of the patients had mild to moderate glaucoma. Other newly diagnosed patients with glaucoma were treated with other medications such as timolol or given latanoprost as adjunctive therapy. Based on the definition of a poor responder as <20% IOP reduction from baseline, 14 patients (20.9%) in this study were poor responders. The definition of a non-responder varies widely; if <30% IOP reduction had been selected as a cut-off point, the number of poor responders would be greater.

In a small retrospective study involving 20 patients with glaucoma, Scherer also reported a subgroup of Caucasian patients who did not respond with the expected IOP reduction.[11] This researcher found that 5 patients (25%) failed to achieve ≥20% IOP reduction or a reduction of >5 mm Hg from baseline, which is similar to the outcome of this study. In a larger scale study, a similar non-responder rate was found 3 months after treatment, with a lower IOP reduction (<15%) as the definition of non-responder.[15] This invalidated the initial hypothesis of this study of a possible higher non-responder rate among a pigmented population. Although latanoprost is known to induce iris pigmentation by increasing melanocyte synthesis,[16] unlike timolol,[17] the concentration or effectiveness is not affected by the amount of pigmentation in an individual. A study to compare the effectiveness of latanoprost and timolol in 8 different populations, half of whom were Asian, found that mean diurnal IOP reduction was significantly better in Asian patients treated with latanoprost.[14] Several studies have reported a lower percentage of non-responders among various Asian populations, indicating that latanoprost is more effective in pigmented individuals.[12,14] A similar finding was observed in a study comparing latanoprost and timolol among black and Caucasian populations.[18] This study was similar to a USA study[15] in terms of baseline IOP, but the mean IOP reduction was higher in this Malaysian population (Table 3[12,15,19,20]). However, other studies failed to significantly correlate racial difference with response rate to latanoprost due to the inclusion of a smaller number of different races.[8,21]

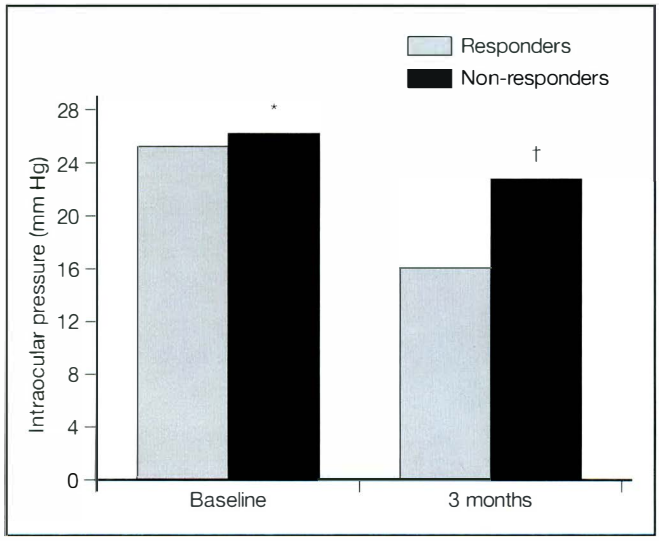
Bayer et al investigated the possible clinical parameters for predicting the response to latanoprost among patients with glaucoma.[21] Although a moderate direct correlation with pretreatment IOP and weak inverse correlation with age were found by Bayer et al,[21] there was no significant association with clinical parameters in this study. A non-responder group with a lower mean IOP before treatment could have a bearing on the interpretation of the results, as a lower initial IOP might be

Table 2. Demographic characteristics and intraocular pressure of non-responders.

Patient number	Sex	Age (years)	Type of glaucoma	Baseline IOP (mm Hg)	Post-treatment IOP (mm Hg)	IOP reduction (mm Hg)	Percent IOP reduction
1	Female	45	POAG	23	19	4	17.4
2	Female	61	POAG	24	20	4	16.7
3	Female	79	POAG	26	22	4	15.4
4	Female	82	POAG	34	28	6	17.6
5	Female	60	POAG	34	32	2	5.9
6	Male	83	POAG	23	19	4	17.4
7	Female	60	POAG	22	20	2	9.1
8	Male	82	POAG	22	20	2	9.1
9	Female	72	POAG	22	18	4	18.2
10	Female	74	POAG	32	26	6	18.8
11	Female	69	POAG	28	24	4	14.3
12	Male	71	PXG	32	30	2	6.3
13	Female	79	PXG	22	20	2	9.1
14	Male	79	PXG	23	20	3	13.0

Abbreviations: IOP = intraocular pressure; POAG = primary open angle glaucoma; PXG = pseudoexfoliation glaucoma.

Figure 2. Comparison of intraocular pressure at baseline versus 3 months after treatment between responders and non-responders to latanoprost monotherapy.
* $p < 0.52$.
† $p < 0.001$.



expected to exhibit a reduced response to therapy. However, as latanoprost acts on uveoscleral outflow, which is considered to be pressure independent, the pretreatment IOP might not influence the action of latanoprost, although some investigators have found otherwise.[21,22] A pretreatment IOP of <15 mm Hg has been found to be significantly associated with non-response to latanoprost in Japanese patients, most of whom had normal tension glaucoma.[23]

The response rate is not affected by age, which contradicts an earlier hypothesis that the ageing ciliary muscle in older patients modifies uveoscleral outflow, and results in a better effect for elderly patients.[24] In this study, the effect of latanoprost for younger patients (younger than 40 years) was not investigated, although latanoprost has been found to be more effective for younger patients.[21] This study was conducted among patients with POAG, OHT, or pseudoexfoliation glaucoma; there was no significant association for type of glaucoma with the response rate due to the small number of patients with OHT or pseudoexfoliation glaucoma. Although there was no association between poor response and OHT in this study, this may not be a true reflection for this type of glaucoma. There was also no significant association between sex and response to latanoprost in this study, similar to the results from previous studies.[8,15]

Table 3. Comparison of intraocular pressure (IOP) for different study populations.

	Mean baseline IOP (mm Hg)	Mean IOP reduction (SD) [mm Hg]	Mean IOP reduction (95% confidence interval)
USA[15]	25.5	6.7 (3.4)	6.2-7.2
Scandinavia[19]	25.1	7.7 (2.9)	7.3-8.1
UK[20]	25.2	8.6 (2.6)	8.2-9.0
India[12]	24.9	8.8 (3.3)	8.2-9.2
Malaysia (current study)	25.4	7.8 (5.3)	6.7-9.2

There are limitations to this study, primarily due to the retrospective nature of the study design. It was not possible to standardise the exact time of day that IOP measurements were taken and to ascertain the diurnal variation, although the IOP measurements were conducted between 8.00 am and 1.00 pm. The morning IOP measurement obtained in this study may have resulted in an inaccurate IOP reduction due to the time of administration of the drug. Topical latanoprost provides its maximum effect 12 to 18 hours after instillation.[25] Twenty four–hour IOP monitoring would better show the IOP-lowering effect of topical latanoprost and the IOP fluctuation between responders and non-responders.[26] Further, compliance was not monitored among the participants and compliance was assumed based on regular follow-up visits. The response rate was limited to 3 months of treatment. Camras et al found that the non-responders tend to improve over a longer duration of follow-up, as 26% of the non-responders had a response after 6 months of follow-up.[15] A longer treatment duration of up to 12 months might reduce the percentage of non-responders.

In conclusion, this retrospective review indicated that 20.9% of previously untreated Malay patients diagnosed with POAG, OHT, or pseudoexfoliative glaucoma did not achieve a clinically meaningful reduction in IOP when treated with once-daily latanoprost monotherapy.

Acknowledgement

The authors thank Dr Wan Hazabbah Wan Hitam, Head of Department, Department of Ophthalmology, Universiti Sains Malaysia Hospital, Kota Bharu, Malaysia, for his support and encouragement.

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Phototherapeutic Keratectomy for Granular Dystrophy

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Aim: *To determine the effect of phototherapeutic keratectomy for patients with granular dystrophy.*
Methods: *Eight eyes of 5 patients who underwent phototherapeutic keratectomy for granular dystrophy were enrolled; 3 patients underwent phototherapeutic keratectomy in both eyes. The outcome measures were pre- and postprocedure uncorrected visual acuity, best spectacle-corrected visual acuity, and postoperative refraction.*
Results: *The mean age of the patients was 20.6 years (SD, 6.7 years). All patients presented with decreased vision. The mean preoperative uncorrected visual acuity was 6/24, which improved to 6/15 postoperatively. The pre–phototherapeutic keratectomy best spectacle-corrected visual acuity was 6/12, which improved to 6/6 postoperatively ($p = 0.0088$). Refraction was available for 5 eyes; the mean postoperative refraction was +2.15 D (SD, +0.45 D). All patients had a clear visual axis postoperatively and no complications were encountered. None of the patients had recurrence by the last follow-up (mean, 8.8 months; SD, 8.2 months).*
Conclusions: *This small series of patients found phototherapeutic keratectomy to be a safe and effective technique for the management for granular dystrophy. Larger case-control studies comparing phototherapeutic keratectomy with other techniques are required to validate these results.*

Key words: *Corneal surgery, laser, Granular dystrophy, corneal, Lasers, excimer, Hyperopia, Recurrence*

Asian J Ophthalmol. 2008;10:123-5

Introduction

Granular dystrophy is an autosomal dominant corneal stromal dystrophy, characterised by the presence of sharply demarcated anterior and midstromal opacities in the centre of the cornea.[1] The stroma between the opacities remains clear and the limbus is spared.[1] In advanced disease, the opacities may increase in size and coalesce, resulting in decreased vision.[1] Visual rehabilitation is done by either penetrating or lamellar keratoplasty, each of which has limitations. Phototherapeutic keratectomy (PTK) is an alternative management approach for stromal disease.[2-4] Excimer laser is used to excise diseased tissue with precision without damaging the adjacent corneal tissues. The safety and efficacy of PTK has been established for the management of anterior corneal diseases such as spheroidal degeneration, corneal dystrophies, band-shaped keratopathy, and scars.[2-4] This study was performed to determine the effect of PTK for patients with granular dystrophy.

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Presented as a poster at the European Society of Cataract and Refractive Surgery Congress, Munich, Germany, 6-10 September 2003, and at the All India Ophthalmological Society Meeting, Varanasi, India, 8-11 January 2004. Presented as a free paper at the Maharashtra Ophthalmological Society Meeting, Mumbai, India, 5-6 November 2005.

Methods

Patients

The data of 5 patients diagnosed with granular dystrophy who underwent PTK were collected from the medical records. The criteria for diagnosis were the presence of grey-white opacities in the anterior and mid-stroma, with clear areas in between, sparing the limbus in both eyes (Figure 1). All patients underwent complete ophthalmological examination, including uncorrected visual acuity (UCVA), best spectacle-corrected visual acuity (BSCVA), slit-lamp biomicroscopy, and ultrasound pachymetry using Tomey's pachymeter; some patients also underwent manifest refraction and fundoscopy. All patients gave informed consent.

Procedure

The Apex Plus excimer laser (Summit Technology Inc, Waltham, USA) with a repetition rate of 10 Hz and fluence of 180 mJ/cm^2 was used to perform PTK. The eye was anaesthetised with topical lidocaine 4%. The lids were separated with a wire speculum. Patients were asked to fixate on a green target light within the delivery system. The epithelium was debrided manually with

Figure 1. Preoperative photograph of granular dystrophy showing anterior and midstromal corneal opacities with clear areas in between and sparing the limbus.

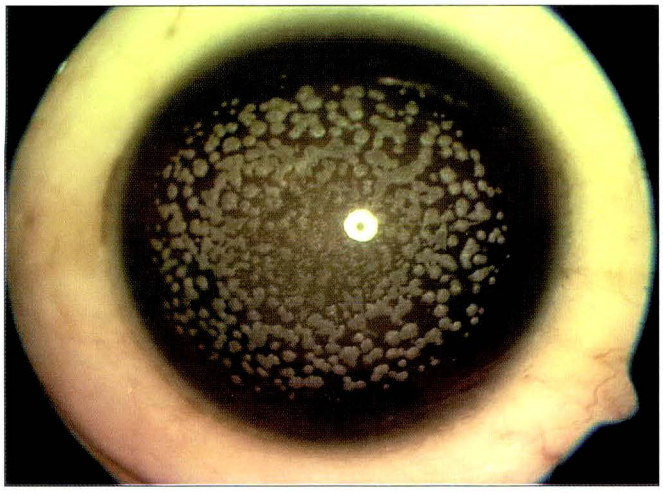
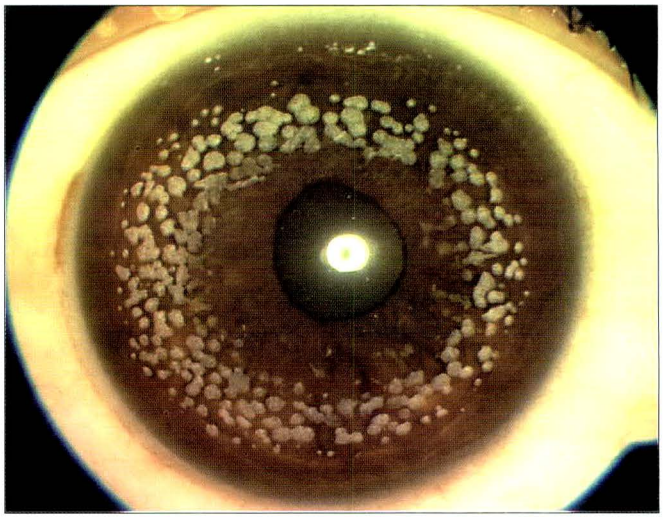


Figure 2. Postoperative photograph taken 3 months after phototherapeutic keratectomy showing a clear visual axis.



a hockey-stick knife. A 6-mm ablation zone was used and the pulses ranged from 152 to 250. After receiving 70% to 80% of the target pulses, the patients underwent slit-lamp biomicroscopy. Additional ablation was performed based on the central corneal clarity and preoperative pachymetry.

The surface was moistened with a cellulose sponge soaked in methylcellulose 0.7%, as a masking fluid, and was replenished as and when required. At completion, topical homatropine 2%, diclofenac 0.3%, and ciprofloxacin 0.3% were instilled and a pressure patch was applied to the eye. All eyes had a pressure patch applied daily until the epithelial defect healed. Fluorometholone 0.1% eye drops were administered every 4 hours for 1 week, with the dosing regimen tapered over 1 month, and topical methylcellulose 0.7% 4 times daily was given for 2 months.

Statistical analysis was done using ccstat software. Snellen visual acuity was converted to log MAR values for calculation of the mean and the results were reconverted into Snellen fractions. The p value was calculated using Student paired *t* test.

Results

There were 4 men and 1 woman. The mean age was 20.6 years (SD, 6.7 years; range, 14 to 30 years). The mean follow-up was 8.8 months (SD, 8.2 months; range, 1.5 to 22.0 months). Three patients underwent bilateral PTK. Complete re-epithelialisation occurred in all eyes within 3 days. All patients had a clear visual axis postoperatively (Figure 2). None of the patients had recurrence of granular dystrophy at the last follow-up. There were no laser-induced complications.

The mean UCVA was 6/24 preoperatively, which improved to 6/15 after PTK. The mean preoperative BSCVA was 6/12, which improved to 6/6 postoperatively; this difference was statistically significant ($p = 0.0088$). UCVA improved by 2 lines in 3 eyes and by 1 line in 2 eyes, decreased by 1 line in 2 eyes, and remained unchanged in 1 eye. BSCVA improved by ≥2 lines in 6 eyes and remained unchanged in 2 eyes. No eyes had loss of BSCVA.

Refraction data was available for 5 eyes (Table 1). All patients had hyperopia post-PTK (Table 2).

Discussion

Most stromal deposits are located in the anterior stroma.[5] Previously, either lamellar or penetrating keratoplasty was preferred for improving vision for these patients. However, with the advent of the Excimer laser, PTK has been shown to be safe and effective for the management of various corneal lesions, with improvement in BSCVA for anterior corneal disorders.[2-4] PTK smooths the corneal surface and improves vision, thereby avoiding or delaying corneal transplantation.

Maloney et al[2] and Campos et al[4] reported improvement in visual acuity by >2 Snellen lines in 45% to 50% of patients using PTK. In this study, BSCVA improved by ≥2 lines in 6 eyes (75%) at the last follow-up, and remained stable in the remaining 2 eyes. The clarity of the visual axis improved in all eyes (Figure 2).

While UCVA improved in 5 of 8 eyes, UCVA decreased or remained unchanged in 3 eyes. The reason for this was induced hyperopic shifts due to flattening of the cornea by ablation of the central tissue. However, the shift was small and was easily amenable to spectacle correction. Other authors have reported a greater degree of postoperative hyperopia in a higher percentage of patients.[2,4,6,7] In this study, use of a masking agent, smaller depth of ablation, and greater ablation zone may have limited the severity of postoperative hyperopia.

Table 1. Patients' characteristics before and after phototherapeutic keratectomy.

Patient number/ eye	Age (years)/ sex	Preoperative			Zone diameter (mm)	Number of pulses	Postoperative			Follow-up (months)
		UCVA	Refraction	BSCVA			UCVA	Refraction	BSCVA	
1/R	14/M	6/9	± /-0.50x30	6/6	6	152	6/12	+2.00/+1.00x5	6/6	10.0
1/L		6/9	± /-0.50x150	6/6	6	200	6/12	+1.00/+1.75x75	6/6	1.5
2/L	16/M	6/12	ND	6/12	6	250	6/12	+0.75-1.25x80	6/6	1.5
3/L	30/M	6/60	+1.50/-3.25x100	6/12	6	200	6/18	+0.75+1.50x90	6/6	13.0
4/R	25/F	6/60	± /-2.50x30	6/24	6	200	6/36	+1.50/-1.50x90	6/6	22.0
4/L		6/60	+0.50-3x180	6/36	6	200	6/12	+1.00	6/6	18.0
5/R	18/M	6/18	ND	6/18	6	198	6/12	± /-2.00x30	6/6	2.5
5/L		6/24	ND	6/24	6	200	6/12	+0.50+0.75x180	6/6	2.0

Abbreviations: BSCVA = best spectacle-corrected visual acuity; L = left; ND = not done; R = right; UCVA = uncorrected visual acuity.

Table 2. Mean refractive spherical equivalent before and after phototherapeutic keratectomy.

Patient number/eye	Pre–phototherapeutic keratectomy	Post–phototherapeutic keratectomy		
		1 week	5 weeks	Last follow-up (months)
1/R	-0.25	0.75	1.50	2.25 (10.00)
1/L	-0.25	1.00	1.50	1.75 (1.50)
3/L	±	3.00	2.25	1.75 (13.00)
4/R	-1.25	3.25	3.00	2.00 (22.00)
4/L	-1.00	4.25	4.25	2.50 (18.00)
Mean	-0.55	2.45	2.50	2.05 (12.85)
SD	0.54	1.51	1.16	0.32 (7.95)

Abbreviations: L = left; R = right.

Recurrence of granular dystrophy is another well-known complication after lamellar or penetrating keratoplasty.[8] Lyons et al reported the recurrence of granular dystrophy in almost all grafts within 13 to 36 months of surgery and recommended lamellar keratoplasty as a primary procedure for patients with superficial deposits in granular dystrophies.[8] Dinh et al reported recurrence of granular dystrophy in 7 of 13 eyes after PTK at a mean follow-up period of 31.9 months.[9] No recurrence of granular dystrophy was observed in this study after a mean follow-up period of 8.8 months. The short follow-up may explain the lack of recurrence of granular dystrophy. If recurrence occurs, PTK can be safely repeated based on the thickness of the residual stromal bed.

The limitations of this study are that it is retrospective and enrolled only a small number of patients. Larger prospective case-control studies are required to validate these results.

PTK is safe and effective for the management of granular dystrophy. PTK can be the first-line management for this disease, particularly in countries where there is a scarcity of optical-grade corneal tissue and a long waiting list for keratoplasty. PTK is a repeatable procedure and can delay, or even obviate, the need for keratoplasty.

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Risk Factors for Low Vision in Elderly People in a Rapidly Developed Society

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Aim: To determine the prevalence of low vision and its correlation with associated risk factors in an elderly population in a rapidly developed Arabian society.
Methods: A prospective descriptive study enrolled all patients older than 50 years who were referred from the Department of Endocrinology outpatient clinics to the Department of Ophthalmology at the Hamad General Hospital, Doha, Qatar, from January 2003 to December 2006. All patients underwent visual acuity testing, using the Snellen E chart, and an eye examination, using a slit lamp, to ascertain the prevalence of visual impairment among elderly people, as well as associated comorbidities and demographic characteristics.
Results: The prevalence of low vision was higher among women (52.7%) than among men (43.7%). Overall, 47.6% of the patients had low vision. Most patients were in the 50 to 59 years age group (men, 45.5%; women, 51.4%). Nearly 40% of the patients with low vision had consanguineous marriages. Only 32.2% had a family history of visual impairment. Patients with type 2 diabetes mellitus (relative risk, 1.32; 95% confidence interval, 1.13-1.54), hypertension (relative risk, 1.30; 95% confidence interval, 1.11-1.52), and retinopathy (relative risk, 1.71; 95% confidence interval, 1.39-2.10) were at significantly higher risk for low vision than were patients without these comorbidities ($p < 0.0001$). Nearly half of the patients with low vision had diabetes mellitus (44.7%).
Conclusions: The prevalence of low vision was high in this elderly population, especially in women. Type 2 diabetes mellitus, hypertension, and retinopathy were significant risk factors for low vision.

Key words: Aged, cohort studies, Epidemiology, Vision disorders, Vision, low

Asian J Ophthalmol. 2008;10:126-9

Introduction

Visual impairment is a growing concern for people aged 70 years and older. According to the World Health Organization, there are an estimated 45 million blind people worldwide, with an additional 135 million individuals who are visually impaired.[1] Globally, cataract is the leading cause of blindness, with approximately 16 to 20 million people having a blinding cataract.[1-4] It has been estimated that more than 50% of people aged 60 years and older experience visual impairment.[2-10] Ocular morbidity increases steadily with age and it has been estimated that 4% to 16% of people in the USA have visual impairment.[3] Visual impairment can disrupt interpersonal relationships and limit an individual's ability to perform routine daily activities. However, visual function changes with age and most changes are amenable to correction with spectacles and do not affect daily activities.

One in 9 people older than 65 years experiences serious vision loss, with the rate increasing to 1 in 4 people older than 85 years.[11] Many people aged 70 years or older experience significant vision loss as a natural consequence of ageing. Visual problems occur in 21% to 50% of older adults. However, visual problems are often not detected in older people, and 25% of elderly people use inappropriate visual correction aids.[12]

Visual impairment among elderly people receives minimal attention. The association between vision loss and type 2 diabetes mellitus, hypertension, and other various health conditions is

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well documented.[13-17] The aim of this study was to determine the prevalence of low vision and associated risk factors in a rapidly developed Arabian society.

Methods

Patients

In this prospective descriptive study, all patients older than 50 years who were referred from the Department of Endocrinology outpatient clinics to the Department of Ophthalmology at the Hamad General Hospital, Doha, Qatar, were enrolled between January 2003 and December 2006. The Hamad General Hospital (HGH) is the main academic medical institution in Qatar, providing comprehensive tertiary health care services for the residents of Qatar, and is therefore a suitable institution for population-based studies. Ninety percent of all eye health outpatient visits in Qatar occur at the HGH. In 2006, there were 84,925 people in Qatar older than 50 years.

Since the majority of elderly patients with ocular morbidity in Qatar are treated at the Ophthalmology outpatients clinic, this study focused on individuals referred from the Endocrinology outpatients clinic to determine the prevalence of low vision and its associated risk factors. 1000 elderly patients with ocular morbidity were referred to the Ophthalmology outpatients clinic during the study period. All patients were screened to identify the major risk factors associated with low vision.

Of 1000 patients referred to the Ophthalmology outpatients clinic, 851 (85%) consented to participate in the study. The 15% of patients who did not participate in the study were unable to attend scheduled appointments, were lost to follow-up, or had no time or interest in participating in the study. Data on consanguinity, family visual history, type 2 diabetes mellitus, hypertension, retinopathy, nephropathy, and neuropathy were recorded.

Approval for the study was obtained from the Research Ethics Committee of the Hamad Medical Corporation. The study adhered to the tenets of the Helsinki declaration and written informed consent was obtained from the participants after explanation of the aims and nature of the study.

Design

The *International Statistical Classification of Diseases and Related Health Problems*[18] was used for the definitions of the visual impairment categories. Eye examination was performed using a slit lamp (Topcon, Tokyo, Japan) and visual acuity was tested using tumbling E letters at a distance of 6 m (20 ft). The participants' uncorrected visual acuity was measured separately for each eye, followed by best spectacle-corrected visual acuity (BSCVA). Visual acuity was recorded as the smallest line at which patients could read the 4 letters correctly. If a patient was unable to read the largest E letters in the chart (20/400 E letters) at 6 m, then finger counting and 'hand movement' was done at 1 m or more. Low vision and blindness were defined as BSCVA in the better eye of worse than 20/60 to 20/400 and worse than 20/400, respectively.

Statistical Analysis

Student *t* test was used to ascertain the difference between means of 2 continuous variables and confirmed by non-parametric Mann-Whitney test. Fisher exact test and chi-squared test were used to compare frequencies between 2 or more categorical variables. Spearman's correlation coefficient was used to evaluate the strength of concordance between variables. A p value of <0.05 was taken as the cut-off for significance.

Results

There were 483 men and 368 women. The mean ages of the men and women were similar at 62.4 years (SD, 13.0 years) and 63.5 years (SD, 10 years), respectively. Table 1 shows the demographic characteristics of the patients and the prevalence of low vision by sex. The prevalence of low vision was higher among women (52.7%) than among men (43.7%). Most of the patients were in the 50 to 59 years age group; 45.5% were men and 51.4% were women.

More than 65% of the patients watched television from a short distance away, 39.7% were in a consanguineous marriage, 32.2% had family history of visual impairment, 11.5% had severe low vision, 4.0% had profound low vision, and 1.3% were nearly blind. Near-to-normal vision (21.2%) and moderate low vision (16.3%) were higher in women, while severe low vision (12.2%) and profound low vision (4.6%) were higher in men. A significant difference was found in the vision evaluation between men and women ($p = 0.014$).

Table 2 shows the evaluation of low vision and its risk factors in patients older than 50 years. Patients with low vision had type 2 diabetes mellitus (44.7%), hypertension (41.0%), or retinopathy (40.7%). Patients with type 2 diabetes mellitus (relative risk [RR], 1.32; 95% confidence interval [CI], 1.13-1.54), hypertension (RR, 1.30; 95% CI, 1.11-1.52), or retinopathy (RR, 1.71; 95% CI, 1.39-2.10) were at significantly higher risk for low vision ($p < 0.0001$). Type 2 diabetes mellitus, hypertension, and retinopathy were the major contributors to low vision. Nearly half of the patients with low vision (44.7%) had type 2 diabetes mellitus, which was likely to have been causative of nephropathy and neuropathy.

The correlations between the severity of low vision and age ($r = 0.418$, $p < 0.01$), hypertension ($r = 0.734$, $p < 0.01$), type 2 diabetes mellitus ($r = 0.540$, $p < 0.01$), retinopathy ($r = 0.316$, $p < 0.01$), nephropathy ($r = 0.337$, $p < 0.01$), and neuropathy ($r = 0.349$, $p < 0.01$) were statistically significant.

Table 1. Demographic characteristics of elderly patients and the prevalence of low vision by sex (n = 851).

Variable	Men (SD) [n = 483]	Women (SD) [n = 368]	p Value
Age group (years)			
50-59	220 (45.5)	189 (51.4)	
60-69	167 (34.6)	129 (35.1)	0.025
70-79	79 (16.4)	44 (12.0)	
≥80	17 (3.5)	6 (1.6)	
Nationality			
Qatari	260 (53.8)	277 (75.3)	<0.001
Non-Qatari	223 (46.2)	91 (24.7)	
Occupation			
Retired	196 (40.6)	80 (21.7)	
Business	147 (30.4)	35 (9.5)	
Clerical	81 (16.8)	31 (8.4)	<0.001
Police/military	59 (12.2)	17 (4.6)	
Housewife	0 (0.0)	205 (55.7)	
Near television watching			
Yes	313 (64.8)	254 (69.0)	
No	170 (35.2)	114 (31.0)	0.196
Consanguineous marriage			
Yes	197 (40.8)	141 (38.3)	0.255
No	286 (59.2)	227 (61.7)	
Vision impairment			
Vision loss	211 (43.7)	194 (52.7)	
Normal vision	272 (56.3)	174 (43.3)	0.010
Family history of vision impairment			
None	329 (68.1)	248 (67.4)	
Mother	47 (9.7)	47 (12.8)	
Father	44 (9.1)	33 (9.0)	0.596
Both parents	35 (7.2)	24 (6.5)	
Siblings	28 (5.8)	16 (4.3)	
Vision evaluation			
Normal (20/20)	272 (56.3)	174 (47.3)	
Near normal (20/30 to 20/60)	68 (14.1)	78 (21.2)	
Moderate low vision (20/70 to 20/160)	56 (11.6)	60 (16.3)	0.014
Severe low vision (20/200 to 20/400)	59 (12.2)	39 (10.6)	
Profound low vision (20/500 to 20/1000)	22 (4.6)	12 (3.3)	
Near blindness (20/10000)	6 (1.2)	5 (1.4)	

Discussion

Low vision and blindness are important public health problems. This study supports the increasing level of visual impairment with age as a social concern. The prevalence of low vision in this study was higher among elderly women (52.7%) than among elderly men (43.7%). A similar result was found by Campbell et al, in that men were less likely to report visual impairment than women.[4] In this study, 47.6% of patients were affected by some type of ocular morbidity. Nearly half the patients had low vision, which is similar to the findings in other studies.[1-8,12-17] Both men and women were at risk for age-related low vision. Although comparisons of prevalence rates are difficult because of different methods of assessment and age grouping, the findings of this study are consistent with rates reported elsewhere.[1-4,6-8,16,17]

A study by Wallhagen et al reported that 12.3% of the participants experienced moderate or severe visual impairment;[19] a higher rate of moderate or severe visual impairment (29.2%) was noted in this study population. Crews and Campbell, in the National Health Interview Survey on Disability (NHIS-D), documented 22.4% of patients with fair vision and 15.3% with poor vision in their study population.[7] The prevalence rates for low vision were similar for the NHIS-D study[7] and current study.

This study found that 1.3% of patients were nearly blind, which is similar to the rate of 1.0% found in an eye survey conducted among South Indians.[20] In the Tehran eye study, the prevalence rate for blindness was low (0.28%).[21]

In this study, nearly half the patients with low vision had type 2 diabetes mellitus (45%). Diabetes mellitus was the primary cause of low vision in 7.3% of patients attending an eye clinic in Melbourne, Australia.[22] In a community-based study conducted in Ankara, Turkey,[23] the prevalence of low vision in the population with diabetes mellitus was 10.8%. The low vision rate in this study population was higher than the rates in the Australian and Turkish studies.

In this study, type 2 diabetes mellitus, hypertension, and retinopathy were the major contributors to low vision. Diabetes was associated with nephropathy and neuropathy in many of these patients, but these conditions were not associated with vision loss. Recent population studies from western countries have shown that age-related macular degeneration, glaucoma, and retinal vessel diseases, including diabetic retinopathy and retinal vein occlusion, are the most common causes of visual impairment in an elderly population.[24]

Many elderly people accept low vision, believing that there is no effective treatment, attributing it to the ageing process, or denying

Table 2. Evaluation of low vision and its risk factors in patients older than 50 years.

Variable	Normal vision (n = 446)	Low vision (n = 405)	Relative risk	95% confidence interval	p Value
Type 2 diabetes mellitus	110 (24.7)	181 (44.7)	1.32	1.13-1.54	<0.0001
Hypertension	104 (23.3)	166 (41.0)	1.30	1.11-1.52	<0.0001
Retinopathy	68 (15.2)	165 (40.7)	1.71	1.39-2.10	<0.0001
Nephropathy	58 (13.0)	154 (38.0)	1.83	1.46-2.29	<0.0001
Neuropathy	44 (9.9)	142 (35.1)	2.11	1.63-2.75	<0.0000

its existence. This study has reported population-based data for the prevalence of low vision and its correlation with type 2 diabetes mellitus and other associated factors.

The study findings indicate that the prevalence of low vision is high among elderly people, especially among women. The prevalence of low vision was greater among patients with type 2 diabetes mellitus and hypertension. Type 2 diabetes mellitus, hypertension, and retinopathy were significant risk factors for low vision. This survey indicates the need for the development and implementation of a national registry for screening and delivery of effective eye care services and visual impairment prevention programmes.

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Ocular Tuberculosis with Cerebral Tuberculoma

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Tuberculosis has re-emerged as a serious public health problem, raising the possibility that tuberculous eye disease may also become more prevalent. Although ocular tuberculosis associated with central nervous system tuberculoma has rarely been reported in the literature, prompt treatment can save sight. This report is of a 28-year-old man with ocular tuberculosis associated with subparietal tuberculoma who lost sight in one eye.

Key words: *Isoniazid, Tuberculoma, intracranial, Tuberculosis, ocular*

Asian J Ophthalmol. 2008;10:130-2

Introduction

Recently, tuberculosis has re-emerged as a serious public health problem, raising the possibility that tuberculous eye disease may also become more prevalent. Ocular TB, involving any tissue of the eye, is a rare event, occurring in 1% of all cases of TB.[1] The ophthalmic manifestations of tuberculosis are well described in the literature. However, ocular tuberculosis associated with central nervous system (CNS) tuberculoma has rarely been reported in the literature. This report is of a patient with ocular tuberculosis associated with subparietal tuberculoma.

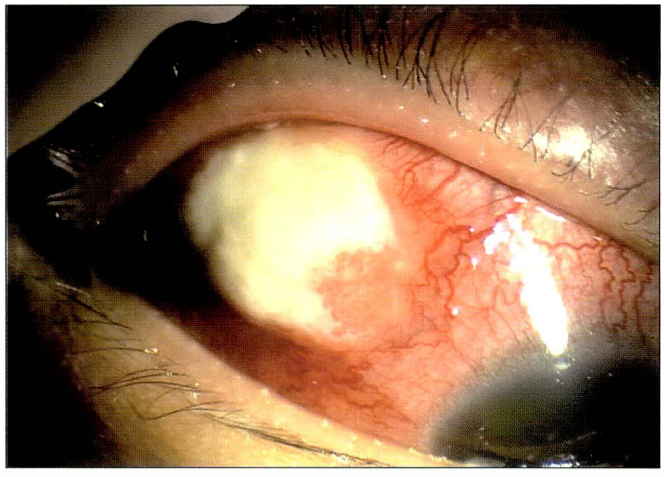
Case Report

A 28-year-old Chinese man presented to the Beijing Tongren Eye Center, Beijing Tongren Hospital, Beijing, China, in 2006 with complaints of progressive loss of vision in the right eye during the preceding 7 months, with red eye, severe pain, photopsia, and floaters. He did not have night sweats or weight loss.

He had previously attended a local hospital, where ultrasonography showed a mass in the right choroid, measuring 15 x 7 x 11 mm, with no blood vessel signal. Fundus fluorescein angiography revealed an elevated choroid mass with many yellowish exudates, mostly located at the posterior pole and the temporal side of the fundus, with slightly dilated retinal vessels and haemorrhage. He was suspected to have ocular tuberculosis. Unfortunately, he did not undergo an isoniazid therapeutic test because of the inconvenient transport to hospital.

Three months before presentation to the Beijing Tongren Eye Center, the visual acuity in his right eye decreased to counting fingers and, 10 days later, he had no light perception in the right eye. One month before his consultation, the patient found a yellowish solitary elevated lesion, measuring 10 x 7 mm in the temporal side of his right eyeball (Figure 1). He had no other known medical conditions.

Figure 1. Ocular tuberculosis presenting as a yellowish solitary elevated lesion, measuring 10 x 7 mm.



At examination, the patient was blind in the right eye, with obvious proptosis. Visual acuity was normal in the left eye. At slit-lamp examination of the right eye, a clear lens, normal iris, and anterior chamber flare (+) were found (Figure 2). A clear view of the fundus was not possible because of opaque vitreous. Ultrasonography revealed retinal detachment and a mass located under the detached retina. The patient had no palpable cervical or axillary lymphadenopathy. C-reactive protein was 10.8 mg/L (normal range, 0-80 mg/L). Complete blood cell count was normal. A tuberculin skin test and sputum culture for TB were negative, but a chest radiograph showed bilateral diffuse infiltration with some calcification foci in the upper lobe of the lung. As the tuberculosis

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Figure 2. Anterior segment showing anterior chamber flare (+).

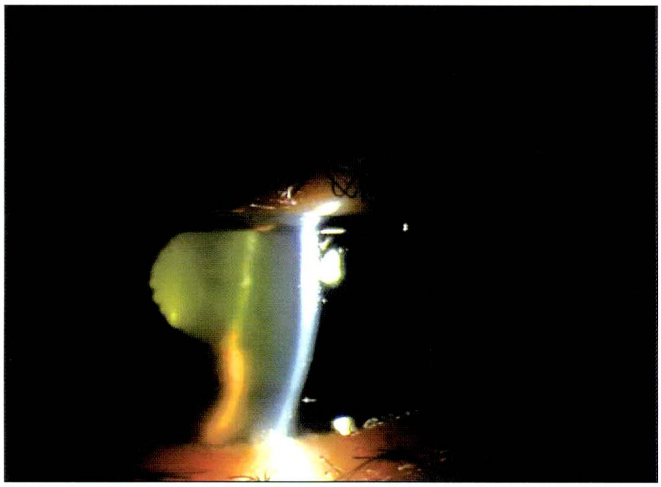


Figure 3. Enhanced magnetic resonance imaging of the brain showing high-density lesions with a ring enhancement consistent with cerebral abscesses located under the right lobes (arrow).

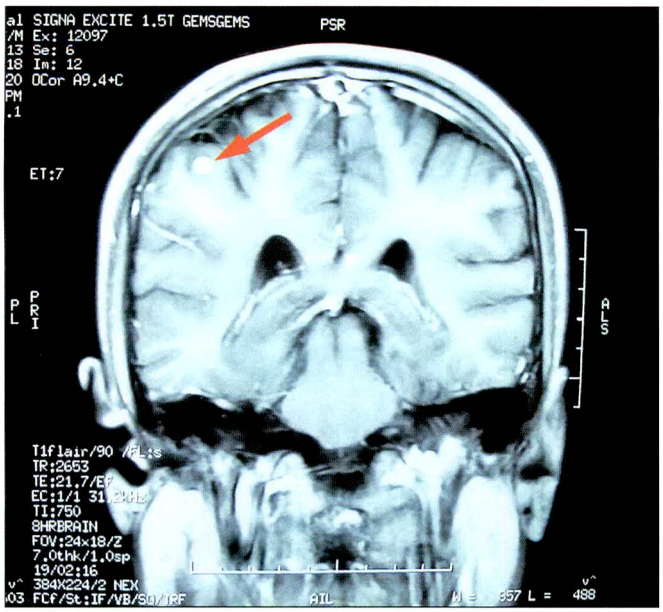
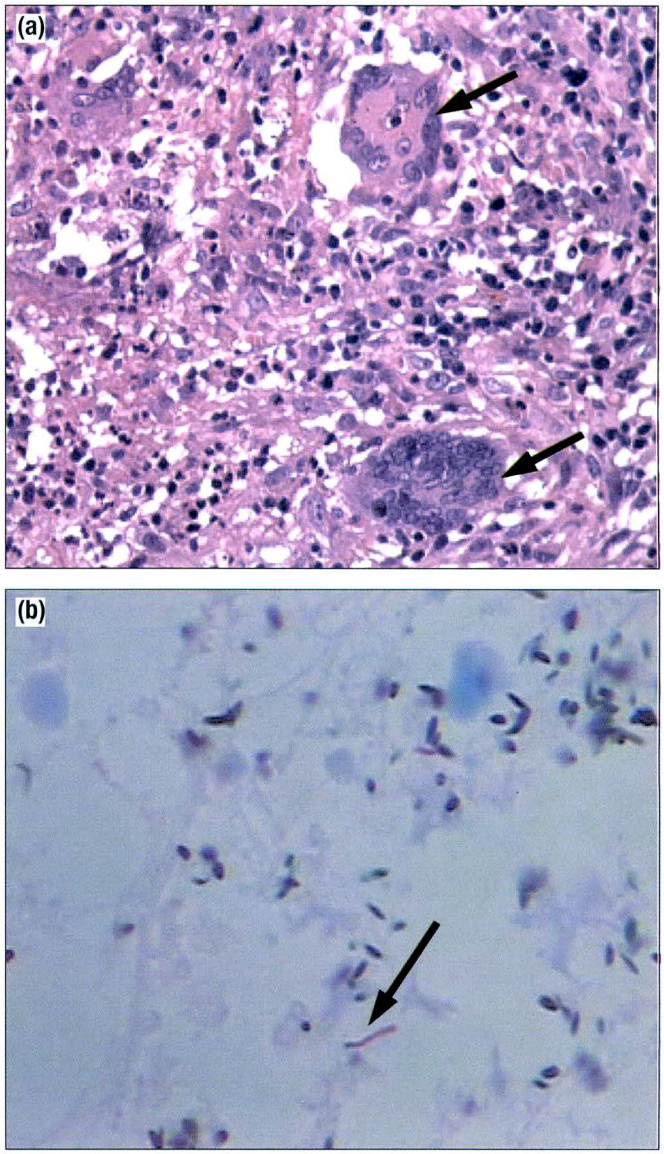


Figure 4. Histopathology showing (a) granuloma with epithelioid cells, lymphocytes, Langhans giant cells (arrow), and a necrotic centre without caseation; and (b) acid-fast bacilli (arrow).



of the orbit may have arisen from haematogenous spread, it was essential to rule out tuberculoma in the brain. Cerebral magnetic resonance imaging showed a sub-parietal lesion of the right lobe, measuring approximately 6 mm (Figure 3). Abdominal ultrasonography showed no enlarged lymph nodes along the aorta, inferior vena cava, and portal and mesenteric veins. Polymerase chain reaction (PCR) detection for *Mycobacterium tuberculosis* DNA in the aqueous humour was negative.

The symptoms and examination results strongly indicated ocular TB. The right eye could not be saved, and was enucleated. Histopathological results showed an eyeball full of necrotic tissue extending to the iris and ciliary body. A granuloma involved the sclera, choroid, and retina, with lymphocytes, epithelioid cells, giant cells, and acid-fast bacilli (Figure 4). Other causes, including toxoplasmosis, human immunodeficiency virus infection, and syphilis, were excluded by serological tests.

Systemic antituberculosis chemotherapy of isoniazid 300 mg once-daily, ethambutol 750 mg once-daily, thioacetazone 100 mg twice-weekly, and pyrazinamide 500 mg 3 times daily was started. The patient has been followed up to assess the cerebral tuberculoma and the possible ocular toxic effects of ethambutol.

Discussion

This patient had a mass similar to that reported by Grosse et al.[2] Also, coexistent CNS tuberculosis has been noted in 2 of 15 patients with acquired immunodeficiency syndome.[3]

In this patient, all examinations, including sputum examination, tuberculin skin test, and PCR detection of tuberculosis DNA in the aqueous humour, had negative results. Therefore, false-negative results are a concern. In 2 reports of patients with presumed tuberculous granulomatous uveitis, aqueous humour PCR–positivity for *M tuberculosis* was noted only in one-third of patients.[4,5]

Treatment for tuberculosis is relatively effective and cost-effective, and prompt treatment can save sight.[6,7] A clinical trial in Japan involved 10 patients who had presumed intraocular tuberculosis and were treated with antituberculosis therapy consisting of isoniazid, with or without rifampicin, 9 of whom exhibited decreased intraocular inflammation with treatment.[8] If the patient reported here had been administered an isoniazid therapeutic test at the start of his symptoms, his vision would probably have been saved. Therefore, the isoniazid therapeutic test is recommended for patients with presumed tuberculosis to avoid preventable visual damage.

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Diffuse Uveal Melanoma ex Oculodermal Melanocytosis in an Asian Woman

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This report is of a 38-year-old woman with oculodermal melanosis who presented with painless gradual visual loss for 8 months. Ocular examination showed visual acuity of 20/200 in the affected eye. Dilated fundus examination revealed a large superotemporal choroidal mass with overlying retinal detachment. Histopathology showed epithelioid cell–type melanoma occupying the choroid, ciliary body, and iris. Most of the tumour mass was in the posterior choroid. There was some infiltration of the tumour cells into the inner layers of the sclera without extrascleral extension. Systemic examination did not reveal any other organ involvement. During 14 months of follow-up, there was no evidence of metastasis.

Key words: *Asian continental ancestry group, Melanoma, Melanosis, Nevus of Ota, Uvea*

Asian J Ophthalmol. 2008;10:133-5

Introduction

Uveal melanoma is the most common primary intraocular malignancy in adults. The disease usually affects middle-aged to elderly patients, and is more common in fair-skinned individuals. Known risk factors for developing uveal melanoma include light skin pigmentation, dark choroidal pigmentation,[1] and sun exposure.[2]

Most uveal melanomas occur as a single lesion. Multifocal melanoma[3,4] and simultaneous bilateral melanoma[5] have previously been reported. Only a few patients with diffuse choroidal melanoma have been reported in the literature.[6,7] However, a diffuse lesion affecting the whole uvea, that is, continuously from the iris and ciliary body to the choroid, has been reported only once, in a 5-year-old Caucasian boy.[6]

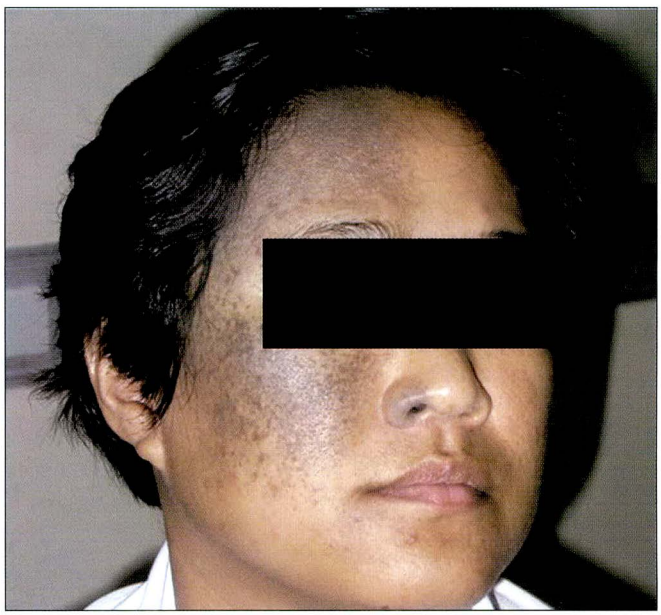
Oculodermal melanosis, also known as nevus of Ota, presents with congenital ipsilateral hyperpigmentation of the eyelids, periorbital skin, and sclera. Uveal melanoma arising from oculodermal melanosis has been found mostly in Caucasians. Several instances of the tumour occurring in association with oculodermal melanosis have been reported in black,[8] Hispanic,[9] and Indian patients.[10] A study of Caucasians suggested that a patient with 2 uveal melanomas in a single eye has an approximately 1000-fold likelihood of having underlying oculodermal melanosis than the general population.[4]

This report is of a Thai woman with underlying oculodermal melanosis since birth, who later developed a diffuse uveal melanoma.

Case Report

A 38-year-old Thai woman with oculodermal melanosis presented in 2004 with painless gradual visual loss in her right eye during

Figure 1. Hyperpigmented macules on the right side of the face.



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The paper was presented in part as a poster at the Asia-ARVO meeting held in Singapore, 2-5 March 2007.

Figure 2. Fundus photograph of the right eye showing a large choroidal mass with overlying retinal detachment at the superotemporal area.

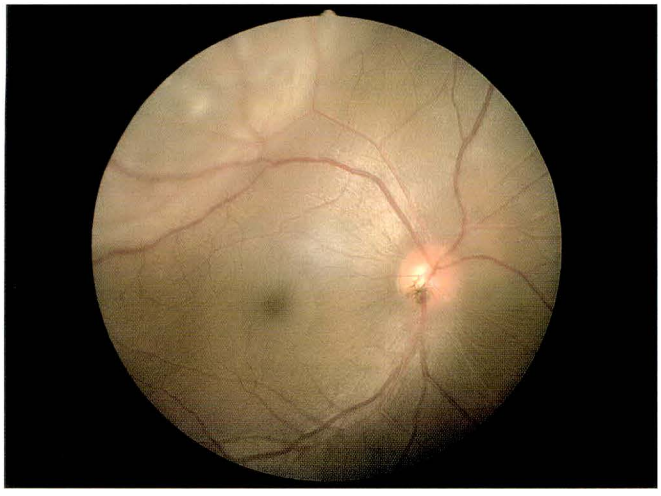


Figure 3. Gross pathology examination showing a melanotic posterior choroidal mass and hyperpigmented thickening of the ciliary body and the iris.

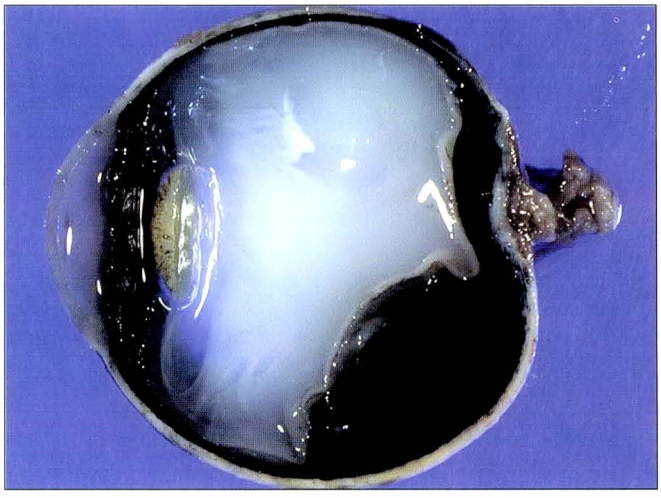
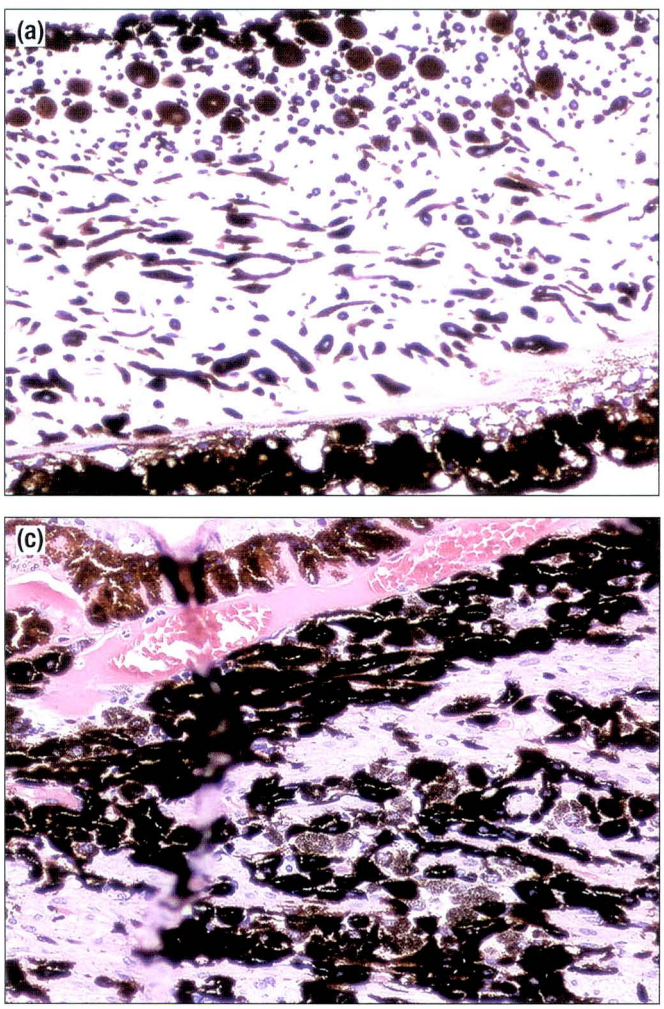


Figure 4. Photomicrograph of (a) the iris showing plump non-cohesive melanocytic cells infiltrating into the anterior iris stroma (haematoxylin and eosin stain; original magnification, x 200); (b) the junction between the ciliary body (pars plana) and the anterior choroid showing hyperpigmentation and thickening of the uveal stromal layers (haematoxylin and eosin stain; original magnification, x 100); (c) the pars plicata area of the ciliary body showing tumour cells occupying the uveal stromal layers (haematoxylin and eosin stain; original magnification, x 200); and (d) polyhedral large tumour cells filled with melanin pigment granules — the nuclei are large with prominent, occasionally multiple, magenta-coloured nucleoli (haematoxylin and eosin stain; original magnification, x 400).



the previous 8 months. General examination showed extensive hyperpigmented spots and patches on the right side of her forehead, upper cheek, eyelids, and ala nasi (Figure 1). Ocular examination displayed patches of hyperpigmentation on the sclera. Vision testing showed a visual acuity of 20/200 for the affected eye. The anterior eye segment was unremarkable. The iris appeared normal and the colour was dark brown in both eyes. Dilated fundus examination revealed a large superotemporal choroidal mass with overlying retinal detachment (Figure 2). B-scan ophthalmic ultrasonography showed a large choroidal mass with low internal reflectivity. Systemic examination did not reveal any other organ involvement.

The patient underwent enucleation. Gross examination of the eye showed a large melanotic choroidal mass with diffuse thickening of the uveal tissues (Figure 3). Histopathology showed epithelioid cell–type melanoma occupying the choroid, ciliary body, and iris (Figure 4). The majority of the tumour mass was in the posterior choroid. There was some infiltration of the tumour cells into the inner layers of the sclera, but without any extrascleral extension. During 14 months of follow-up, there was no evidence of intraorbital tumour extension or distant metastasis.

Discussion

Uveal melanomas usually present as intraocular masses. The most common area is at the choroid. Patients may be diagnosed quite late in the course of the disease if the tumour does not primarily affect the vision. Tumour masses are nodular in shape. After time, when the malignancy grows and breaks through the overlying Bruch's membrane, it may form a typical 'mushroom-shaped' mass. Iris and ciliary body melanoma may present as an anterior eye segment mass, glaucoma or, occasionally, intraocular inflammation.

Most uveal melanomas are solitary lesions. Multifocal discrete lesions are not common and are usually found to arise from an oculodermal melanosis.[4] Diffuse melanoma often refers to non-prominent lesions, presenting as infiltrating plaques or uveal thickening.[7,11] Only 1 previous incidence of a 5-year-old child with a diffusely located uveal melanoma has been reported.[6] Even though a histopathological study of a series of patients has been reported,[12] the prognosis of and treatment options for diffuse melanomas have never been broadly discussed due to the scarcity of the tumour type.

Oculodermal melanosis is described as hyperpigmented macules over the face and periorbital areas. Review of the literature has found that there are reports of malignant melanocytic transformation in multiple organs, for example, conjunctiva, skin, uvea, choroid, and meninges. However, most patients have been Caucasian. The association is rarely reported in blacks and Asians. This patient illustrates the association of oculodermal melanosis with uveal melanoma in an Asian population. Moreover, the diffuse lesions seen in this patient are very rare. These authors postulated that, with the underlying hyperpigmentation, the patient was prone to develop extensive disease. Fortunately, there has been no systemic involvement of the malignancy for this patient.

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Acute Multifocal Posterior Placoid Pigment Epitheliopathy in Association with Erythema Nodosum and Group A *Streptococcus* Infection

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A 22-year-old woman presented with a 2- to 3-day history of positive scotomas in both eyes, preceded by a 2-week episode of influenza-like symptoms, sore throat, and erythema nodosum. Ocular examination revealed multiple pale yellow lesions at the level of the retinal pigment epithelium in both eyes. Fluorescein angiogram confirmed features of acute multifocal posterior placoid pigment epitheliopathy with early hypofluorescence and late hyperfluorescence over the lesions. Blood test revealed raised antistreptolysin O titre and erythrocyte sedimentation rate. This report highlights that patients with acute multifocal posterior placoid pigment epitheliopathy may have a significant systemic disorder associated with the ocular findings.

Key words: *Acute multifocal posterior placoid pigment epitheliopathy, Antistreptolysin, Erythema nodosum, Pigment epithelium of eye,* Streptococcus

Asian J Ophthalmol. 2008;10:136-9

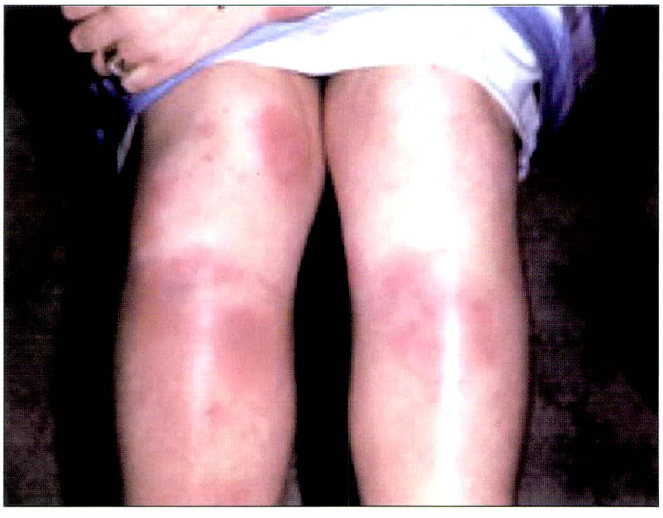
Introduction

Acute multifocal posterior placoid pigment epitheliopathy (AMPPPE) is grouped as part of the white dot syndromes, characterised by multiple whitish-yellow inflammatory lesions located at the level of the outer retina, retinal pigment epithelium (RPE), and choroid. The diagnosis is mainly clinical, based on presentation and characteristic fluorescein angiogram features. Viral, bacterial, and systemic inflammatory aetiologies have all been implicated, but for most patients, the associations are unclear. This report is of a patient with AMPPPE following proven group A *Streptococcus* spp infection in association with erythema nodosum.

Case Report

A 22-year-old woman was referred to the eye clinic in 2006 with symptoms of positive scotomas in both eyes for the preceding 2 to 3 days. She had a history of feeling unwell for the previous 2 weeks with influenza-like symptoms and a sore throat. She also developed painful erythematous nodules on both shins (Figure 1). A diagnosis of erythema nodosum was made by her general practitioner. Throat culture disclosed the presence of group A *Streptococcus* spp. Blood tests showed a raised antistreptolysin O titre of 1356 U/mL (normal range, <160 U/mL), an erythrocyte sedimentation rate of 62 mm/hour (normal range, 0-20 mm/hour) and C-reactive protein of 130 mg/L (normal range, 0-80 mg/L). She was given a 1-week course of oral penicillin 1 g daily.

Figure 1. Multiple painful nodules on both shins characteristic of erythema nodosum.



At presentation her visual acuities were 6/6 in the right eye and 6/9 in the left eye. She had 1+ cells in both anterior chambers and occasional vitreous cells in the left anterior vitreous. Dilated

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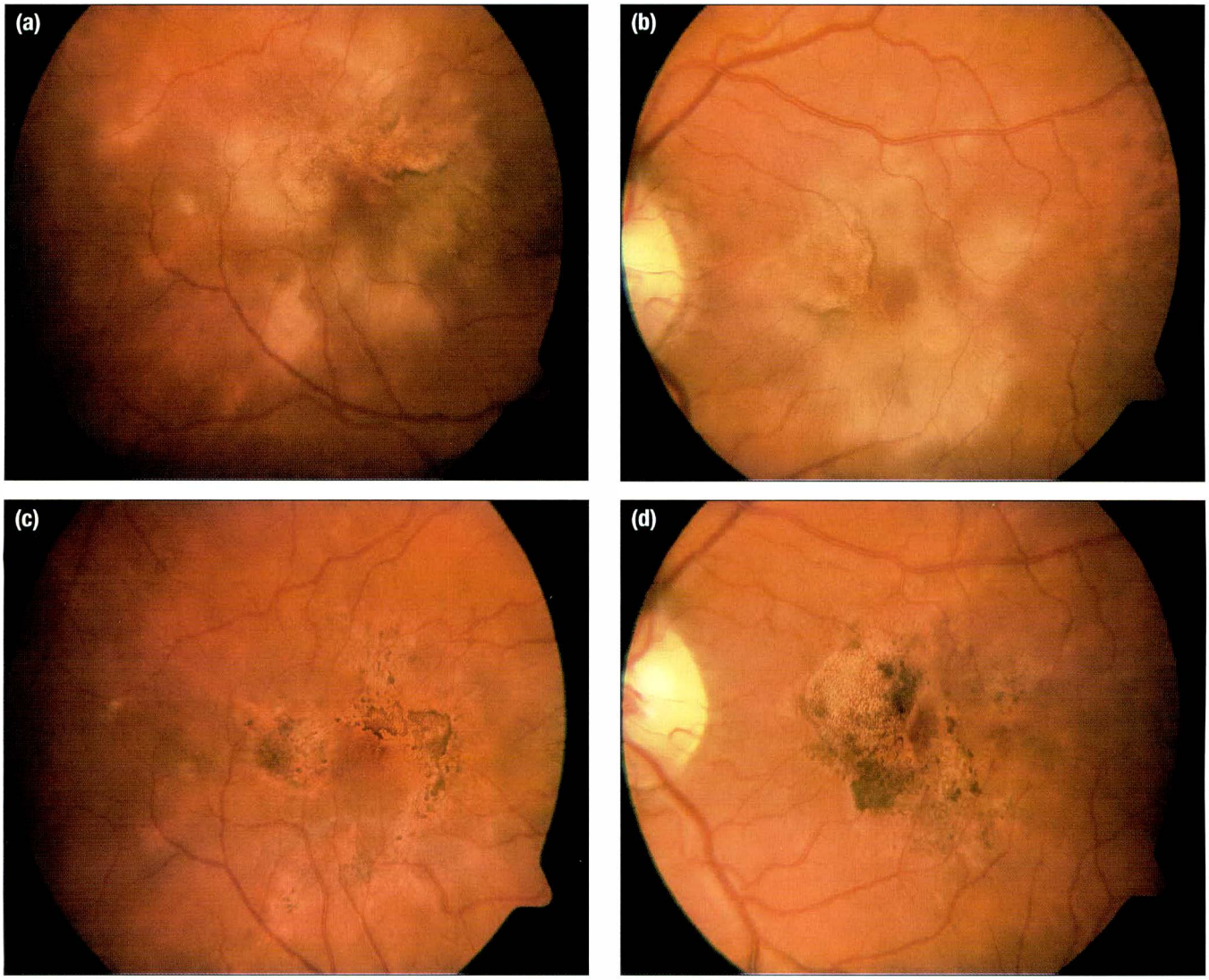
Figure 2. Fundus photographs of the (a) right and (b) left eyes showing multiple pale yellow placoid lesions over the macula area; and fundus photographs taken 2 weeks later showing areas of hyperpigmentation over the (c) right and (d) left macula.



fundoscopy showed multiple pale yellow placoid lesions at the level of the RPE, concentrated mainly at the posterior poles in both eyes (Figure 2). A provisional diagnosis of AMPPPE was made.

Fluorescein angiogram showed early hypofluorescence and late hyperfluorescence in the affected areas (Figure 3), which corresponded with the diagnosis of AMPPPE. The lesions were mainly concentrated over the posterior pole and were coalescing together near to the macula.

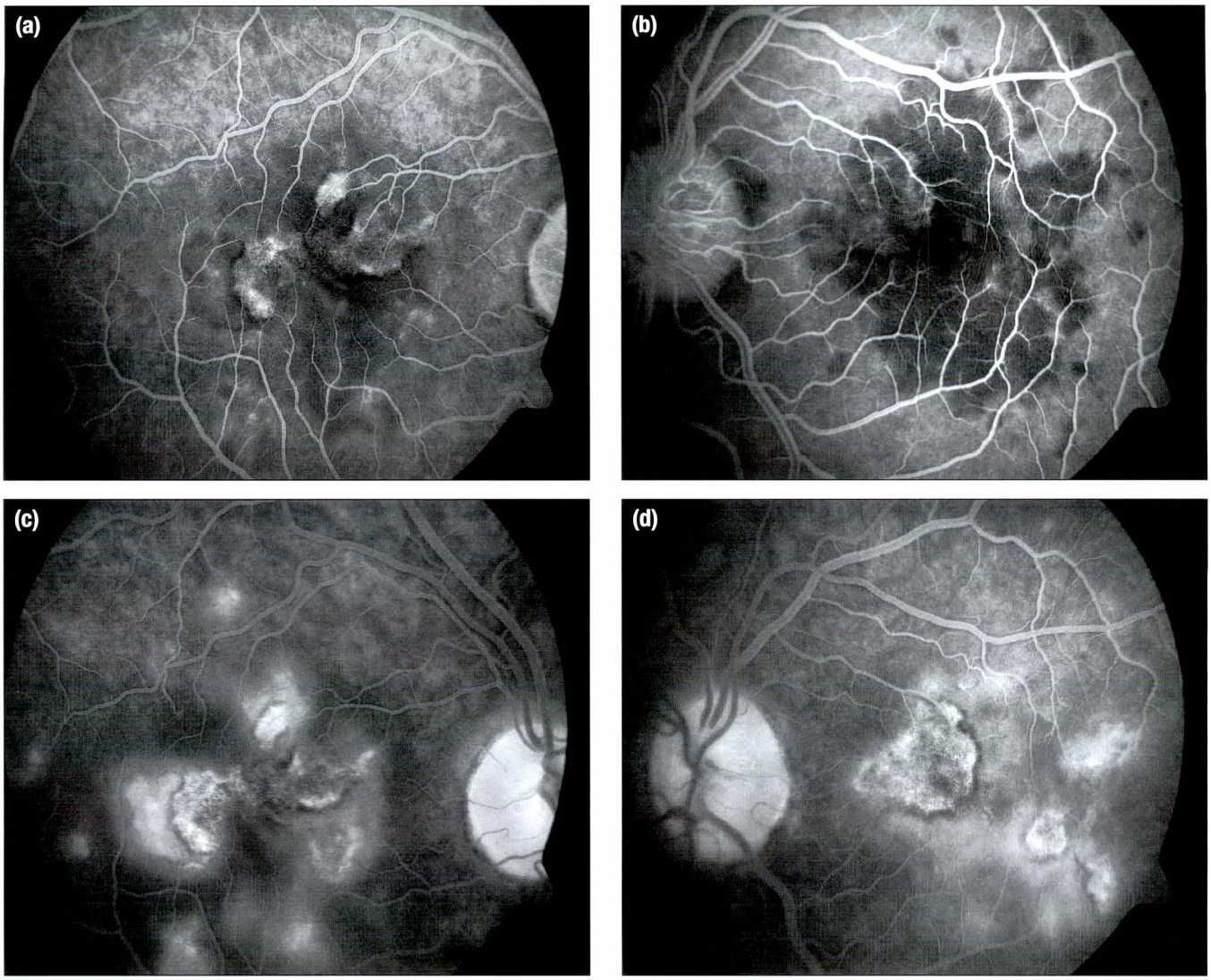
At review 2 weeks later, the patient complained of a further reduction in vision. Her visual acuities had decreased to 6/9 in the right eye and 6/36 in the left eye. Examination of the fundus showed bilateral macular scarring with pigmentary changes over both maculas and reduced anterior chamber inflammation (Figure 2). At a subsequent follow-up visit 3 months later, her visual acuities were 6/12 in the right eye and 6/9 in the left eye. However, the macular appearance remained the same, with RPE mottling over the macula area, which was more extensive in her right eye.

Discussion

AMPPPE was first described by Gass in 1968.[1] AMPPPE typically affects healthy men and women between the ages of 20 and 50 years. Classic lesions are yellowish-white placoid lesions at the level of the RPE in the posterior poles, which rarely extend beyond the equator. The lesions tend to fade after a few days and, after 2 weeks, they are partly replaced by hypotrophy and hypertrophy of the RPE.

A prodromal illness has been described in approximately one-third of patients with AMPPPE. Usually, this involves a febrile episode, myalgia, athralgia, and night sweats. For this patient, the prodromal illness was attributable to acute infection with group A

Figure 3. Fluorescein angiogram showing typical early hypofluorescence over the lesions in the (a) right and (b) left eyes; and late hyperfluorescence over the lesions in the (c) right and (d) left eyes.



Streptococcus spp. This patient also described classical lesions of erythema nodosum on both shins prior to the onset of her visual symptoms. Erythema nodosum is present in a variety of conditions, including streptococcal infection, use of drugs (sulphonamides, oral contraceptive, aspirin), sarcoidosis, tuberculosis, leprosy, and inflammatory bowel disease. All the causative factors for erythema nodosum, except for streptococcal infection, could be ruled out for this patient.

The association between erythema nodosum and uveitis has been described in the literature.[2-4] For most patients, erythema nodosum is associated with recurrent anterior uveitis. Mert et al found that, of 50 patients with erythema nodosum, 16% were attributed to post-streptococcal infection.[5] Several reports suggest that recurrent anterior uveitis may be a part of the post-streptococcal syndrome, which is an autoimmune disorder whose manifestations include acute rheumatic fever (characterised by fever, rheumatic heart disease, arthritis, and cutaneous lesions) and acute glomerulonephritis.[2-4] AMPPPE has been associated with group A *Streptococcus* infection in 2 reports,[2,6] although erythema nodosum was only a feature in 1 report.[2]

The aetiology of AMPPPE is uncertain, but it is thought to originate in the choriocapillaries. The postulated mechanism through which damage to the choriocapillaries occurs could be similar to the mechanism for glomerulonephritis in post-streptococcal syndrome. Immune complex–mediated activation, as well as cross-reactive antigens — whereby antigens on the surface of the organisms resemble antigens on the glomerular endothelial cells — sensitise lymphocytes to the cross-reactive antigens, which leads to cell-mediated cytotoxicity. This may, in turn, cause small vascular occlusions in the choriocapillaries, resulting in the

clinical appearance of AMPPPE, and may explain the hypofluorescence in the fluorescein and indocyanine green angiography studies.[2] Associations with systemic vasculitis such as polyarteritis nodosa, Wegener's granulomatosis, and sarcoidosis support this hypothesis.

There is no specific treatment for AMPPPE. Most cases are self-limiting and have a good visual prognosis if the fovea remains uninvolved. However, treatment with systemic steroids is suggested for patients with foveal involvement and evidence of central nervous system (CNS) involvement.[6] This is especially important for patients with CNS involvement, as mortality may occur from CNS vasculitis, which has been reported to develop several weeks after the onset of AMPPPE.[7] There is also an argument for administering long-term antibiotic prophylaxis against streptococcal infections in the presence of acute rheumatic fever to prevent severe cardiac damage should inflammation occur with repeat infections. However, due to the limited course of the disease, lack of ongoing ocular complications, and absence of non-ocular disorders, it is thought that the risks of long-term antibiotic therapy outweigh the potential benefits.

In summary, although AMPPPE in most individuals is a 'benign' condition with a good visual prognosis, patients for whom this condition is diagnosed should undergo a thorough systemic evaluation to check for secondary causes.

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Inappropriate Use of the Term 'Glaucoma'

Dear Editor,

Re: the article by Narayanaswamy et al,[1] although the title of the article is nice and concise, it is misleading. Since there is no optic nerve damage involved, the term 'glaucoma' should not have been used. *Acetazolamide-induced Choroidal Effusion Causing Angle Closure* would perhaps have been a more appropriate title.

Reference

1. Narayanaswamy AK, Antrolikar M, Vijaya L. Acetazolamide-induced glaucoma. Asian J Ophthalmol. 2007;9:213-5.

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Author Reply

Dear Editor,

We appreciate the feedback on our article.[1] The suggested title could be an alternative, but we do differ in the view that the existing title is misleading. We hope the rationale explained below justifies our reasons for the title.

We do agree that the definitions of the glaucomas have evolved recently, and this is essential to standardise the use of the terminology. The recent change in terminology has been accepted mainly to describe 'primary entities' and not 'secondary entities'. Malignant glaucoma is a secondary entity and is accepted terminology. However, there need not be disc damage criteria for the term 'malignant glaucoma' to be used.

If we go by current definitions all secondary glaucomas without optic disc damage will have to be labelled 'secondary ocular hypertension' — this is not yet the norm.

The published report[1] belongs to a unique group of drug-induced secondary glaucoma. On the basis of its secondary nature, the current use of the title is not inappropriate or misleading, unless the terminology norms change for secondary entities and the same are universally accepted.

Reference

1. Narayanaswamy AK, Antrolikar M, Vijaya L. Acetazolamide-induced glaucoma. Asian J Ophthalmol. 2007;9:213-5.

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Primary Hypopyon Herpetic Uveitis with Negative Serology

Dear Editor,

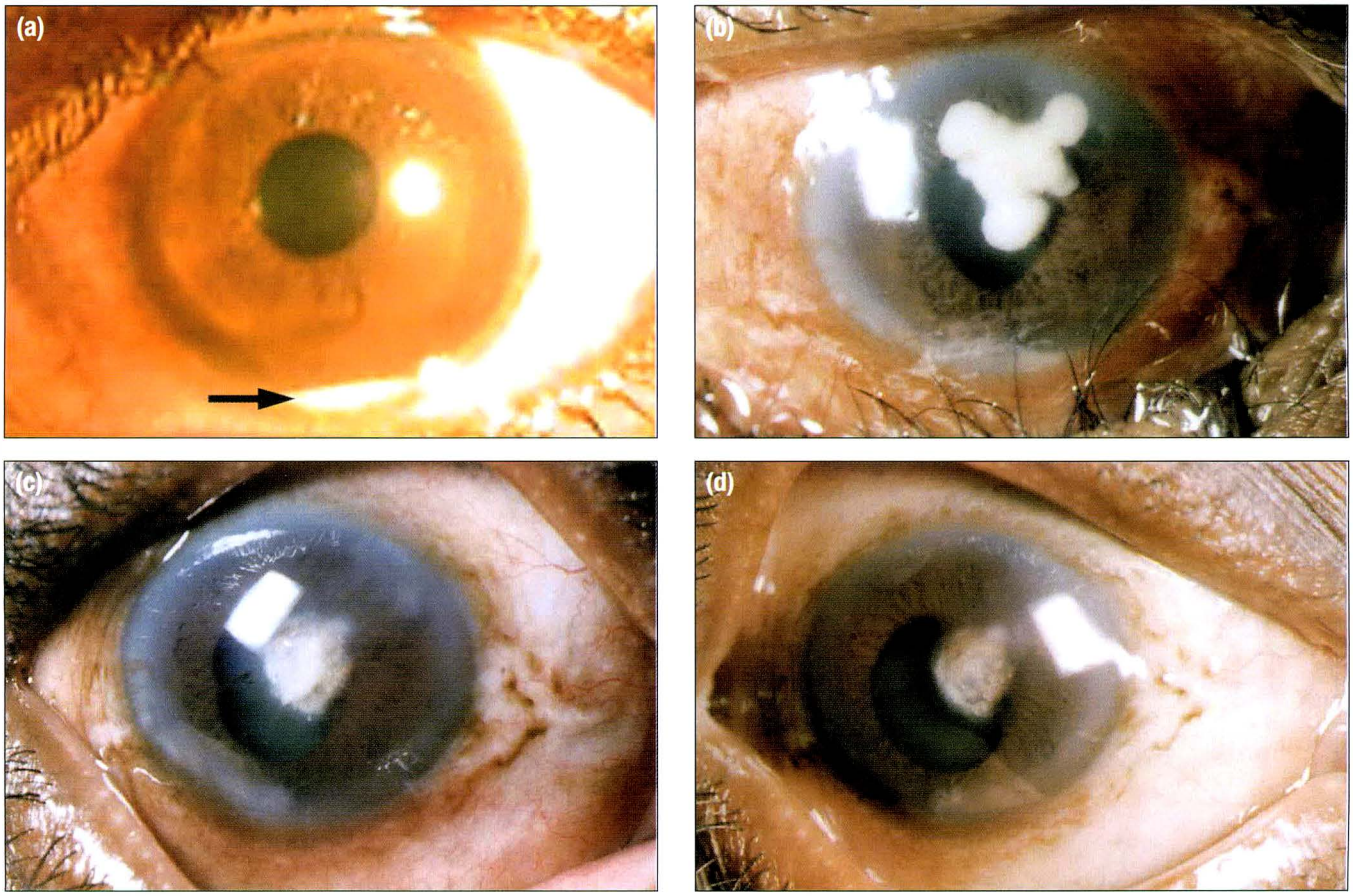
Herpetic uveitis (HU) without prior or concurrent corneal involvement is rare.[1,2] Negative serology for herpes virus rules out herpetic infection, although positive serology does not confirm herpetic infection.[3] This report is of a patient with primary hypopyon HU with negative herpetic serology but positive aqueous aspirate polymerase chain reaction (PCR) for herpes simplex virus-1 (HSV-1).

A 48-year-old woman presented with acute onset photophobia in the right eye for 4 days. Examination revealed circumcorneal congestion, a clear cornea with decreased sensation, diffuse fine keratic precipitates, and a 3-mm greyish-white hypopyon (Figure 1a). In the right eye, pupillary reaction was sluggish, the fundus was normal, intraocular pressure (IOP) was 20 mm Hg, and visual acuity was 6/12. The left eye was normal.

Systemic investigations were normal, and serology for syphilis, pulmonary tuberculosis, and *Varicella zoster* and HSV were negative. The patient was diagnosed with idiopathic hypopyon uveitis and prescribed prednisolone eye drops 2-hourly and cyclopentolate 3 times daily. The condition improved during the next 3 weeks.

One week later, she presented with recurrence of hypopyon uveitis. Her visual acuity was 3/60 and the IOP was 56 mm Hg (Figure 1b). An oedematous cornea precluded fundus evaluation. The hypopyon took the form of a multilobulated mass and adhered

Figure 1. Right eye showing (a) clear cornea with hypopyon in the anterior chamber (arrow) during the first episode; (b) hypopyon in the form of a multilobulated mass, adherent to the superonasal quadrant of the pupillary margin, at the time of recurrence; (c) resolving hypopyon, with patchy iris atrophy (at the site of initial hypopyon) with localised cataract and posterior synechiae 2 months after recurrence; and (d) iris atrophy with localised cataract and posterior synechiae after 2 years.



to the pupillary margin in the superonasal quadrant. Ultrasound-B scan showed a normal posterior segment.

Anterior chamber aspirate from the right eye was sent for bacterial culture and PCR for *Mycobacterium*, HSV-1, HSV-2, and *V zoster*. PCR of aqueous aspirate was positive for HSV-1 DNA.

The patient was given topical acyclovir 5 times daily and oral acyclovir 800 mg 5 times daily for 6 weeks, 1% prednisolone 3 times daily, and cyclopentolate 3 times daily, as well as timolol twice daily, and oral acetazolamide 250 mg 4 times per day until the IOP was controlled. During the next 2 months, the uveitis diminished and her IOP returned to normal, but patchy iris atrophy with posterior synechiae and localised cataract was seen (Figure 1c). Her visual acuity improved to 6/9 and fundus evaluation was normal. She has not had a recurrence and her vision is maintained at 6/9 after 2 years (Figure 1d).

HU almost exclusively occurs in patients with prior or concurrent herpetic corneal disease.[1,2] Primary herpes infection is usually mild and may be asymptomatic. Approximately 1% to 6% of all herpetic ocular diseases are associated with mild uveitis, although recurrent herpetic ocular disease may rarely cause hypopyon uveitis.[1] Associated trabeculitis may cause a secondary rise in IOP, but the IOP usually returns to normal with treatment of the infection.[4]

The pathogenesis of HU includes both hypersensitivity and active viral replication.[5] The initial response for this patient was likely to be due to suppression of the immune system by topical steroids. However, in the absence of acyclovir, the virus actively replicated and resulted in a severe recurrence. Topical application of acyclovir may not be sufficient to achieve an adequate concentration in the anterior chamber, so oral acyclovir should be given as well.[6]

In the presence of active ocular disease, serology is used to confirm the absence of ocular HSV.[3] In this patient, despite negative serology, aqueous aspirate PCR confirmed HSV-1 infection, and appropriate treatment led to resolution of the condition. This patient highlights the importance of aqueous aspirate investigations for the definitive diagnosis of hypopyon uveitis.

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Imaging and Risk Assessment for Glaucoma Management

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Primary open angle glaucoma (POAG) is a chronic progressive optic neuropathy associated with acquired atrophy of the optic nerve and loss of retinal ganglion cells (RGCs) and their axons. Although glaucoma is the second leading cause of blindness worldwide, the disease is under diagnosed, and many patients have severe visual field loss before diagnosis.

The glaucomatous process is initiated when there is an acceleration of RGC apoptosis. As the disease progresses, there are changes in the retinal nerve fibre layer (RNFL), optic disc, and visual field. The glaucoma continuum describes the progression of glaucoma in 3 stages of undetectable disease, asymptomatic disease, and functional impairment. Patients with asymptomatic disease are not aware of any visual field loss, but have changes in the RNFL, optic disc, or visual function.

Staging Glaucoma

Management involves staging the disease according to the glaucoma continuum, and measuring the rate of progression. Estimation of risk of progression is done using factors of intraocular pressure (IOP), central corneal thickness, age, cup-disc ratio, visual field loss, and exfoliation. IOP is a surrogate for measuring the rate of progression.

The World Glaucoma Association Consensus Statement recommendations for assessment of structural damage in glaucoma are as follows: a method for detecting abnormality and documenting optic nerve structure should be part of routine clinical management of glaucoma; according to limited evidence, available sensitivity and specificity of imaging instruments for detection of glaucoma are comparable to expert interpretation of stereophotography and should be considered when such expert advice is not available; digital imaging is recommended as a clinical tool to enhance and facilitate the assessment of optic nerve and RNFL in the management of glaucoma; automated analysis of the results using appropriate databases is helpful for identifying abnormalities consistent with glaucoma; different imaging technologies may be complementary, and detect different abnormal features in the same patients.

Imaging is an important part of making a diagnosis of glaucoma, providing documentation, disease staging, risk assessment, and confirmation of glaucoma damage or progression. Judicious use of imaging techniques such as scanning laser polarimetry, confocal scanning laser ophthalmoscopy, or optical coherence tomography will complement the clinical examination, assisting the decision-making process.

In Summary

Imaging can facilitate glaucoma diagnosis and disease staging. These findings have clinical implications that can affect treatment strategies. Each of the imaging technologies measures different features of the optic nerve and RNFL, and their use is complementary.

Imaging Methods for Optic Disc and Retinal Nerve Fibre Layer Assessment

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Imaging plays a central role in the management of patients with glaucoma and glaucoma suspects. However, imaging technologies that aid and support the clinical evaluation of the optic nerve do not replace clinical judgement, but augment the clinical decisions. Table 1 shows the currently available imaging technologies for patients with glaucoma and glaucoma suspects.

Stereophotography

Stereophotography enables clinicians to assess retinal and optic nerve head (ONH) reflectivity, surface topography, and RNFL thickness. However, evaluation with stereophotography is subjective, and has greater interobserver variability than the semi-automated scanning devices.

There are various forms of optic disc photography used for imaging the nerve, usually with a field of view of 15° to 30°. Stereophotography is the only form of imaging that provides full colour imaging of the optic nerve.

The mode of imaging can be monoscopic, although stereoscopic imaging is preferable to enable visualisation of contour changes in the optic nerve head. Simultaneous stereoscopic imaging is preferred over sequential imaging

Table 1. Currently available imaging technologies.

Technology	Parameters evaluated
Stereophotography	Retinal/optic nerve head reflectivity
	Surface topography
	RNFL thickness
RNFL photography	RNFL reflectivity
Confocal scanning laser ophthalmoscopy (HRT)	Rim area
	Surface shape
Scanning laser polarimetry	RNFL thickness
	TSNIT average
Optical coherence tomography	RNFL thickness
	Thickness variation

Abbreviations: HRT = Heidelberg retinal tomography; RNFL = retinal nerve fibre layer; TSNIT = temporal, superior, nasal, inferior, temporal.

for providing a stable depth representation.

Retinal Nerve Fibre Layer Photography

RNFL photography provides a clear image of the reflectivity of the RNFL. The field of vision is wide at 60°, and red-free monochromatic pictures are obtained. Detecting the subtle abnormalities shown in the image is subjective.

Confocal Scanning Laser Ophthalmoscopy

Confocal scanning laser ophthalmoscopy (CSLO; Heidelberg retinal tomography [HRT]) evaluates the neuroretinal rim area and surface topography of the retina and optic nerve head.

Various measurements of the rim and cup can be made, including area and volume, and software algorithms — usually the Moorfields Regression Analysis or the Glaucoma Probability Score — are used to compare the measurements to a normative database. All the technologies are associated with some degree of measurement variability, but CSLO is associated with imaging artefacts that confound the classification algorithms.

Scanning Laser Polarimetry

Scanning laser polarimetry (SLP; GDx VCC) measures the polarisation properties of the RNFL, which equate to RNFL thickness. The TSNIT (temporal, superior, nasal, inferior, temporal) values describe the retardation measurement in an annulus centred on the optic disc (Figure 1). TSNIT parameters are calculated from within the calculation circle. The limitations of SLP include atypical scans and unreliable corneal compensation in the presence of macular disease.

Optical Coherence Tomography

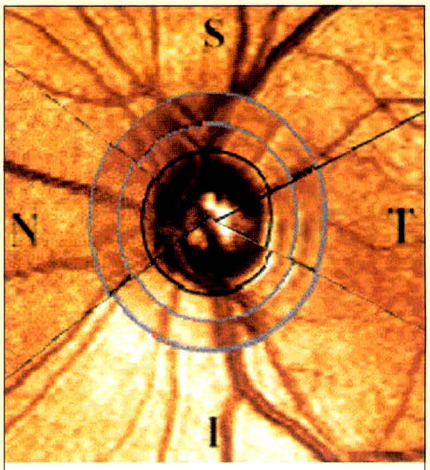
Optical coherence tomography (OCT) quantifies RNFL thickness and evaluates RNFL thickness variation. There are 3 principal scan patterns for OCT, of which the RNFL thickness scan is recommended for glaucoma evaluation.

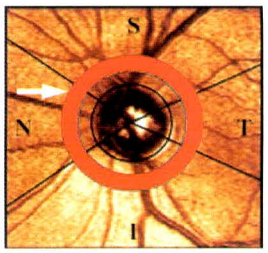
The limitations of this technology are that an experienced operator is required for quantitative data acquisition, signal strength may impact RNFL thickness measurement, the detection algorithm may fail, the ability to detect change needs validation, and the procedure is expensive.

In Summary

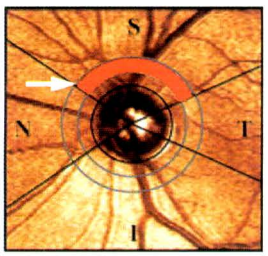
Each imaging device has advantages and disadvantages related to the specific technology applied. The devices augment the clinical assessment, but are not diagnostic on their own; the measurement data and classifications should be interpreted in the context of all available clinical data. The correct interpretation of images and device reports depends on an understanding of the technology and the potential sources of error for the devices.

Figure 1. TSNIT values. The TSNIT values describe the retardation measurements in an annulus centred on the optic disc. TSNIT parameters are calculated from within the calculation circle (red band within grey circles).
Abbreviations: TSNIT = temporal, superior, nasal, inferior, temporal; RNFL = retinal nerve fibre layer.

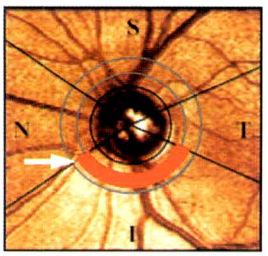




TSNIT average
Average RNFL thickness from the entire calculation circle

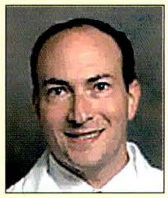


Superior average
Average RNFL thickness in the superior 120° of the calculation circle



Inferior average
Average RNFL thickness in the inferior 120° of the calculation circle

Assessment of Scan Quality and Identification of Imaging Artefact



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Imaging technology can facilitate the diagnosis of glaucoma, with the help of statistical classifications in the presence of normative data. However, imaging data may be associated with artefacts that are important to be able to identify. Reliability criteria are important for differentiating imaging techniques that are useful for making clinical decisions from those that should be avoided.

Specific Artefact

For HRT2, the pixel standard deviation (SD) on the standard printout provides quality assessment; the mean should be <40 µm. The images should be sharply focused, well centred around the optic nerve, and free of motion artefact. For the newer version, HRT3, an automated process generates a score based on pixel SD and image quality checks. The scores inform of the quality as follows: excellent, 9 µm; very good, 17 µm; good, 24 µm; or poor, 45 µm.

GDx also generates an automatic quality assessment, which should be ≥8 on a 10-point scale. Scans should be well centred and focused, and free of motion artefacts. Corneal birefringence should be adequately compensated (<13 nm). Qualitative features should also be assessed via the typical scan score.

For OCT, the 4.0 software generates an automatic quality assessment involving the centration of the OCT beam around the optic nerve and a well-centred disc. Assessment of the RNFL segmentation to ensure that the algorithm correctly identifies the borders of the RNFL is important. There is also an automated assessment of signal strength related to signal-to-noise ratio; the signal strength should be ≥6 on a 10-point scale.

Various artefacts are common to all types of imaging technology (Table 2). However, some artefacts are more likely to be associated with a particular technology (Table 3).

Table 2. Artefacts common to all types of imaging technology.

Artefact	Photography	Confocal scanning laser ophthalmoscopy	Scanning laser polarimetry	Optical coherence tomography
Eye movement	+	+	+	+
Ocular surface disruption	+	+	+	+
Media opacity	++	+	+	++
Inadequate pupillary dilation	++	+	+	++
Poor focus	+	+	+	+
Poor centration	+	+	+	+

Abbreviations: + = moderate; ++ = high.

Table 3. Factors contributing to imaging artefact.

Confocal scanning laser ophthalmoscopy	Scanning laser polarimetry	Optical coherence tomography
Uncorrected refractive error	Atypical birefringence images	Parapapillary atrophy
Vitreous opacities	Vitreoretinal pathology	Media opacity
Incorrect contour line placement	Corneal pathology/surgery	Vitreoretinal pathology

In Summary

A variety of imaging techniques enable the generation of relevant information about damage that occurs at the level of the optic nerve and the RNFL. Each of these technologies plays an independent role and provides complementary information, and no single technology is appropriate for all patients.

Integrating Imaging Technology with Case Management

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Assessment of the optic disc is an integral part of the examination of a patient with glaucoma in addition to a clinical examination. Stereophotography is recommended for baseline assessment, although standard photography or imaging are useful alternative approaches. At follow-up examinations, repeat photography or imaging is required, as indicated by the stage and progression of the disease.

Case Study 1

Case studies show the value of imaging for refining the clinical diagnosis. A 59-year-old woman presented with visual acuity of 20/20, IOP of 18 mm Hg, a thin cornea of 437 µm, plano refraction, a large cup-disc ratio, an RNFL defect superiorly, and normal visual field.

Based on the clinical data, it was unclear whether the patient had early glaucoma or was glaucoma suspect. The initial management plan was to monitor the patient and initiate treatment, if required. However,

imaging studies added to the information gathered. HRT showed a borderline RNFL defect, both inferiorly and superiorly; GDx identified a structural defect superiorly, and a mild RNFL defect was noted inferiorly; OCT demonstrated an RNFL defect superiorly; frequency doubling technology demonstrated an RNFL defect inferiorly; and short wavelength automated perimetry demonstrated a severe inferior hemifield defect and a mild superior hemifield defect. Given this additional information, the diagnosis was revised to early-to-moderate glaucoma and therapy was initiated.

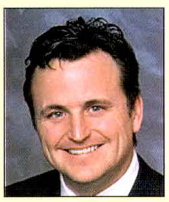
Case Study 2

Similarly, the diagnosis can be revised downwards, as in the case of a 46-year-old man, whose clinical examination suggested glaucoma suspect. The treatment plan was for monitoring and treatment, if required. While GDx demonstrated a light RNFL attenuation superiorly and inferiorly, OCT, FDT, and SWAP were normal. The diagnosis was therefore revised to normal or low-risk glaucoma suspect. While the patient will continue to be monitored, follow-up can be done less frequently.

In Summary

Imaging can facilitate glaucoma diagnosis and disease staging. The findings have clinical implications that can affect treatment strategies. Each of the imaging technologies measures different features of the optic nerve and RNFL, and their use is complementary.

Subjective and Objective Glaucoma Progression in the Optic Disc



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Subjective signs of glaucoma progression include neuroretinal rim thinning and excavation of the optic cup; expansion or appearance of new RNFL defects; expansion of β-zone peripapillary atrophy (PPA); and development of optic disc haemorrhage.

Subjective Signs

Cup-disc ratio is a commonly used method to quantify the optic disc in clinical practice, but it is inadequate to identify the subjective signs of progressive disease. Changes in the RNFL over time can be subtle, and would be difficult to detect without optic disc photography.

Progressive β-zone PPA represents loss of the pigment epithelium and underlying choroidal atrophy that surrounds the optic disc. Increase in PPA is an indicator of eventual visual field progression and an important sign of glaucomatous progression. Photography is necessary to document PPA over time.

Imaging Technology

All of the available imaging technologies provide quantitative data with high reproducibility. The data is easier to use clinically, and is less time-consuming than examining photographs, with less operator dependence. The main disadvantage of these techniques for defining progressive glaucoma is that there are currently few longitudinal data to define progression.

Disease Progression Prediction

Disease progression prediction using HRT shows that abnormal Moorfields Regression Analysis is strongly predictive of progression, while normal Moorfields Regression Analysis has a strong negative predictive value. Methods for progression detection with the HRT include topographic change analysis, linear regression of the rim over time, and serial comparison of individual parameters or Moorfields Regression Analysis classifications (Table 4). These are similar to the progression techniques for visual field testing. HRT has the most longitudinal data of any imaging instrument, it is backward compatible, and has progression algorithms.

Table 4. Methods for progression detection.

Topographic change analysis
Linear regression of rim over time
Serial comparison of individual parameters
Moorfields Regression Analysis classifications

Disease progression prediction using GDx shows that patients with lower linear discriminant function scores are more likely to progress. However, change analysis software is currently only available on research instruments.

Disease progression prediction using the OCT II for glaucoma suspects shows that reduction in RNFL is predictive for development of glaucomatous damage. Change detection for the OCT is being developed, but is not currently available.

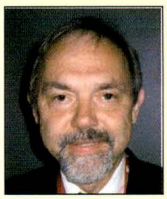
In Summary

Periodic optic disc examination is critical to detect glaucomatous structural progression. While imaging is recommended as a clinical tool to enhance and facilitate optic nerve and RNFL assessment, it does not replace photography.

Different imaging techniques may serve complementary roles in glaucoma management. However, there is limited validation of imaging methods to define progression in glaucoma, and more longitudinal studies are needed.

From the Pfizer satellite symposium Effective Glaucoma Management: An Imaging & Risk Assessment Workshop with the Experts *held at the American Academy of Ophthalmology (AAO) Annual Meeting, New Orleans, Louisiana, USA, 11 November 2007.*

Advances in Glaucoma Diagnostics and Evidence-based Therapy



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Glaucoma is a chronic *progressive* optic neuropathy. Therefore, progression is important for the diagnosis and follow-up of glaucoma.

Diagnosis and Documentation

Both structural and functional tests are required for the diagnosis of glaucoma. Standard automated perimetry, and optic nerve head (ONH) and retinal nerve fibre layer (RNFL) visualisation are required to make the diagnosis and baseline documentation. Perimetry printout and ONH/RNFL photograph or ONH drawing is important for monitoring progression.

Patients with early glaucoma or ocular hypertension are not usually aware of any visual field defects. As the fellow eye compensates for visual field loss, patients may not present until any visual field defect is advanced or binocular.

Once glaucoma is diagnosed, the rate of progression must be ascertained to determine the target pressure or range. Event analysis, or baseline comparison, is a quick method for determining progression. However, trend analysis is a more accurate method for measuring the rate of progression.

In standard automated perimetry, the Glaucoma Progression Analysis (GPA) software for the Humphrey Field Analyser (HFA 2i) will generate a new graphic analysis. The GPA plots the visual field index, an improved metric of visual field loss, against a patient's age. The GPA also provides a projection of the amount of additional field loss that would occur in up to 5 years if therapy is not changed and the disease continues to progress. The GPA software and its new enhancements are based on algorithms pioneered and developed by Bengtsson, and Heijl.[1]

Frequency doubling perimetry is an alternative to white-on-white perimetry. Frequency doubling technology is a fast efficient method for diagnosis.

Digital imaging is recommended as a clinical tool to augment and facilitate the visualisation of the ONH and RNFL for the management of glaucoma. Measuring structure and function in glaucoma involves assessment of the RNFL and the optic disc using ophthalmoscopy and optic disc photography. Imaging technologies include confocal scanning laser ophthalmoscopy such as Heidelberg retinal tomography (HRT) and nerve fibre layer analysis (NFA-1, NFA-2; GDx), optical coherence tomography (OCT II, OCT III), and retinal thickness analyser. These are useful tools for detecting change in the ONH and RNFL.

HRT and GDx provide printouts by which comparison with baseline (or normal) will indicate progression. For HRT, the Moorfields Progression Analysis is used for progression analysis and, for GDx, the GDx Review and Guided Progression Analysis will be available soon.

Stratus™ OCT objectively finds the margin of the disc using signal from the edge of the retinal pigment epithelium. The test measures the TSNIT (temporal, superior, nasal, inferior, temporal) values, and compares these with normative data. The Stratus GPA, a new program for measuring glaucoma progression, will soon be available.

For some of these technologies (OCT and GDx), the software is updated more rapidly than glaucoma progresses; therefore, programmes to calculate differences between older and newer versions are needed.

Comparative studies have so far failed to show large differences between the imaging technologies' abilities to distinguish between normal and glaucomatous eyes. However, stereoscopic disc photography is still recommended, as it is the only imaging method that captures full colour images.

Evidence-based Therapy

Although research into improving blood supply and neuroprotection continues, there is no evidence showing a benefit for these strategies to date. Therefore, the primary goal of glaucoma therapy is to lower intraocular pressure (IOP). Several trials have investigated IOP-lowering for glaucoma,[2-6] and are useful for determining a target IOP. Table 1 shows the target IOPs used in these trials.

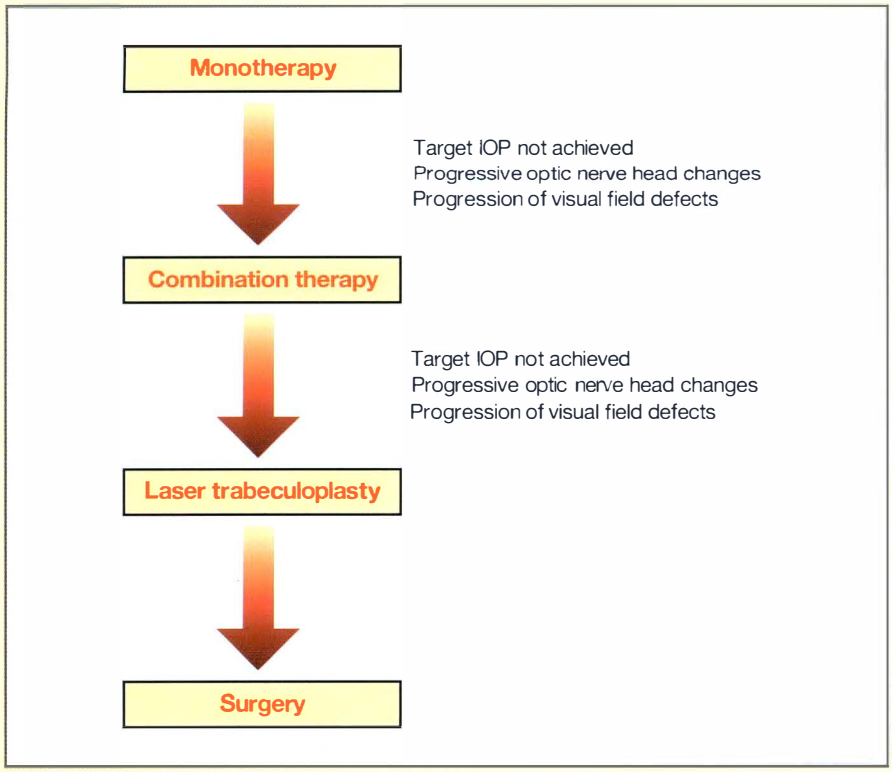
The first-line therapy is usually medical treatment (Figure 1). However, there are many medical treatment options, incorporating topical or systemic drugs, prostaglandin analogues, β-blockers, sympathomimetics, and carbonic anhydrase inhibitors (CAIs). Topical prostaglandin analogues are usually prescribed first, although they are not available for first-choice therapy in some countries and β-blockers will be prescribed instead.

Although monotherapy is recommended, if prostaglandins are not sufficient to achieve

Table 1. Target intraocular pressure (IOP) in various trials.

Trial	Target IOP
Ocular Hypertension Treatment Study[2]	20% reduction
Early Manifest Glaucoma Trial[3]	25% reduction
Collaborative Normal-Tension Glaucoma Study[4]	30% reduction
Collaborative Initial Glaucoma Treatment Study[5]	>35% reduction
Advanced Glaucoma Intervention Study[6]	<18 mm Hg at 100% of visits

Figure 1. Glaucoma therapy.
Abbreviation: IOP = intraocular pressure.



the target pressure, then β-blockers such as timolol may be switched or added. To simplify the dosing schedule and reduce the amount of preservatives entering the eye, fixed combination drugs are preferred when adding to medical therapy.

For comprehensive IOP management, medical therapy must show IOP-lowering efficacy, long-term control, ocular tolerability, and long-term safety. Importantly, treatment should not have a negative impact on patients' quality of life. The criteria used to select the best drug include low side effect profile, high tolerability, and minimal effects of preservatives.

Laser trabeculoplasty (LT) may be considered if medical treatment fails. LT is a good option for many patients, especially elderly patients and those with pigment in the trabecular meshwork or pseudoexfoliation.

Selective LT (SLT) is easy to use, and results in fewer changes to the trabecular meshwork. It is thought that SLT is a repeatable procedure, although clinical trials have yet to confirm this. Comparison of IOP reduction for SLT and argon LT (ALT) show similar results in clinical trials. ALT has a 35% failure rate after 5 years, so is not recommended for young patients with juvenile glaucoma, who normally require surgery.

Deep sclerectomy or viscocanalostomy is non-penetrating surgery aimed at restoring aqueous outflow independent of external filtration. Use of YAG laser goniopuncture changes the technique to a 2-step filtering procedure. The procedure is safe, but does not result in the low IOP levels obtained with trabeculectomy, which is the preferred procedure for advanced glaucoma. The failure rate for trabeculectomy is <20% after 5 years.

Target Pressure

The normal physiological loss of retinal ganglion cells (RGCs) increases with age. This normal loss is increased in a slow, moderate, or advanced fashion in glaucoma, resulting in functional impairment. The rate of glaucomatous progression will help to determine the point at which visual disability will occur. The greater the rate of RGC loss, the lower the target pressure needs to be. Factors that need to be considered when determining the target pressure include the level of damage, life expectancy, and the IOP level at which damage occurred.

In Conclusion

Identification of the rate of change or progression is an important element in the treatment of glaucoma. Resources should be appropriately allocated for better identification and follow-up of individuals at risk for visual disability and blindness.

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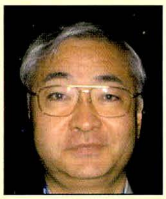
Glaucoma Risk Reduction in Primary Angle Closure Glaucoma and Normal Tension Glaucoma



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Glaucoma is the leading cause of blindness in Japan. However, there are various definitions of blindness and visual impairment, so the rate varies according to the criteria used. The rate of blindness in Japan is lower than that in countries such as Singapore, the USA, and India (Figure 2).[1-5]

Prognostic Factors

Acute primary angle closure (PAC) is usually treated by laser peripheral iridotomy (LPI) and/or laser iridoplasty as first-line therapy. Surgical peripheral iridectomy (PI) is selected when severe corneal oedema is present in acute PAC. Trabeculectomy with adjunctive mitomycin C is indicated for chronic primary angle closure glaucoma (PACG) when LPI/PI fails to control the IOP, and goniosynechialysis is required in the presence of extensive peripheral anterior synechiae (PAS).

A 10-year study to examine the prognosis for 246 patients with chronic PACG found an 80% success rate 3 months after laser iridotomy or surgical iridectomy. During the same period, 55 eyes with acute PAC were studied; 90% were successfully treated with laser iridotomy in addition to medication. However, some patients required additional trabeculectomy. The therapeutic outcome for patients with acute PAC suggests that treatment with laser or surgical iridotomy alone is sufficient for 50% of patients, while 19% require filtering surgery and 31% require antiglaucoma medication (Figure 3).

Comparison of the characteristics of patients requiring trabeculectomy with those who succeed with iridotomy alone suggests that duration of symptoms before appropriate care is a prognostic factor (Table 2). The presence of glaucomatous optic neuropathy and the extent of PAS are also important factors for determining the success of iridotomy alone.

Figure 2. Blindness rates.[1-5]
* Caucasian population.
† Black population.

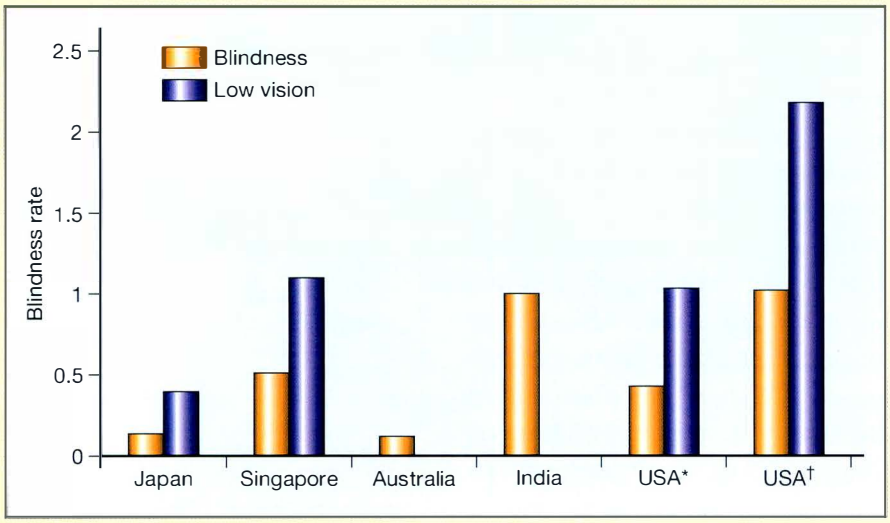
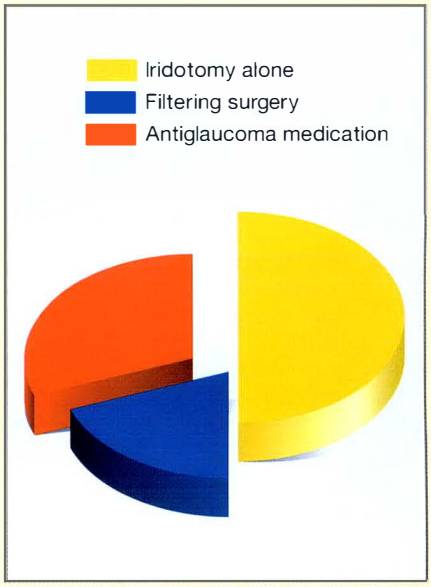


Figure 3. Therapeutic outcome after laser or surgical iridectomy.



A study to investigate the relationship between IOP reduction and visual field in 40 eyes of 40 patients with normal tension glaucoma (NTG) was performed. All eyes had undergone trabeculectomy, and had a preoperative AGIS score of <16. The preoperative IOP was 15 mm Hg, and the postoperative IOP was 8 to 10 mm Hg — 68.3% (SD, 7.8%) of patients maintained a postoperative IOP reduction of 20% and 56.2% (SD, 8.0%) of patients maintained a postoperative IOP reduction of 30% during 15 years of follow-up. The visual field remained stable (AGIS score deterioration <4) for 95.7% (SD, 4.3%) of patients who maintained a postoperative IOP reduction of 30%, and for 92.7% (SD, 5.0%) of patients who maintained a postoperative IOP reduction of 20%. However, all the patients who did not achieve a 20% IOP reduction progressed, suggesting that an IOP reduction of 20% is mandatory for management of NTG.

Although IOP is an important prognostic factor, there are many IOP-independent factors involved in the development and progression of NTG. Ishida et al identified

Table 2. Characteristics of patients requiring iridotomy alone or additional trabeculectomy.

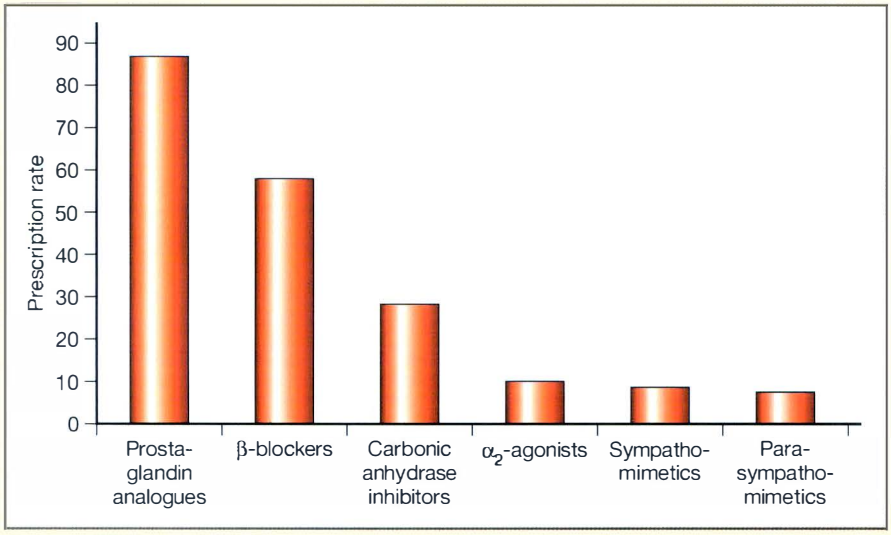
	Iridotomy alone	Trabeculectomy
Duration of symptoms (days)		
Mean (SD)	5.1 (14.4)	18.9 (47.3)
Glaucoma		
Present	4	5
Absent	34	5
Extent of peripheral anterior synechiae (hours)		
Mean (SD)	3.4 (4.2)	11.4 (1.4)

Table 3. Clinical factors significant for progression of normal tension glaucoma.

Factor	Hazard ratio	p Value
Disc haemorrhage*	3.043	0.0001
Use of calcium channel blockers	0.371	0.0001
Maximum intraocular pressure (per mm Hg)	1.172	0.0035
Cold provocation test recovery (per %, 7 minutes)	0.981	0.0249

* Per eye; n = 218.

Figure 4. Most frequently prescribed glaucoma medications in Japan.



clinical factors significant for progression of NTG as disc haemorrhage, use of calcium channel blockers, maximum IOP, and cold provocation test recovery (Table 3).[6] In this study, 46.6% (SD, 8.1%) of patients with disc haemorrhage progressed compared with 12.3% (SD, 9.0%) without disc haemorrhage.

Glaucoma Management

Surgical IOP reduction for NTG slows or stabilises progression of visual field loss. To achieve the low target pressure required for long-term management of NTG, antimetabolites such as mitomycin C are needed. The Japan Glaucoma Society Guidelines for Glaucoma recommend IOP reduction for all patients with glaucoma, suggesting that, based on the evidence, the only reliable therapy for glaucoma is to lower intraocular pressure.[7] The intention of treatment is to achieve the maximum effect with the minimum number of drugs and minimum adverse effects.

The principles of setting an individual target pressure for open angle glaucoma include consideration of the baseline IOP, glaucoma stage, and other risk factors. After setting a target pressure, monotherapy should be initiated. If the target pressure is reached, monotherapy should be continued, but if the target pressure is not reached, the treatment strategy should be reconsidered. This strategy is also applicable to PAC/PACG after laser iridotomy has been performed.

In Japan, prostaglandins are the most frequently prescribed medications for glaucoma, followed by β-blockers and CAIs (Figure 4).

In Conclusion

For PAC/PACG, early diagnosis and early surgical or laser intervention is necessary. If the IOP is not controlled, medical therapy is required after releasing pupillary block. For NTG, before starting treatment, it is necessary to establish a baseline, after which long-term medical management is required.

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From the Pfizer satellite symposium **Evidence-guided Practice in Glaucoma** *held at the Asian Oceanic Glaucoma Society (AOGS) Conference 2007, Bangkok, Thailand, 2 December 2007.*

Brimonidine/Timolol Fixed Combination Therapy in Glaucoma Management

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Elevated intraocular pressure (IOP) is the main risk factor for disease progression in glaucoma. IOP-lowering can slow or halt the progression of visual loss in glaucoma, and this is currently the only target for treatment of all types of glaucoma.

IOP-lowering with monotherapy is the ideal treatment, and the newer drugs can provide 30% IOP-lowering. Use of monotherapy reduces the risk for adverse events, drug interactions, and preservative-induced corneal damage compared with multi-drug therapy. Monotherapy is also more convenient and cost-effective, and can increase compliance. However, monotherapy is often insufficient to control IOP.

In the Collaborative Initial Glaucoma Treatment Study, 75% of patients required 2 or more medications after 2 years of treatment. In the Ocular Hypertension Treatment Study, 49% of patients required 2 additional medications after 5 years to achieve a 20% reduction of IOP.

When combination therapy is needed, medications with complementary mechanisms of action should be considered to provide maximal IOP-lowering. As therapy tends to be long term, selection of agents with favourable safety and tolerability profiles is required.

Approaches to Combination Therapy

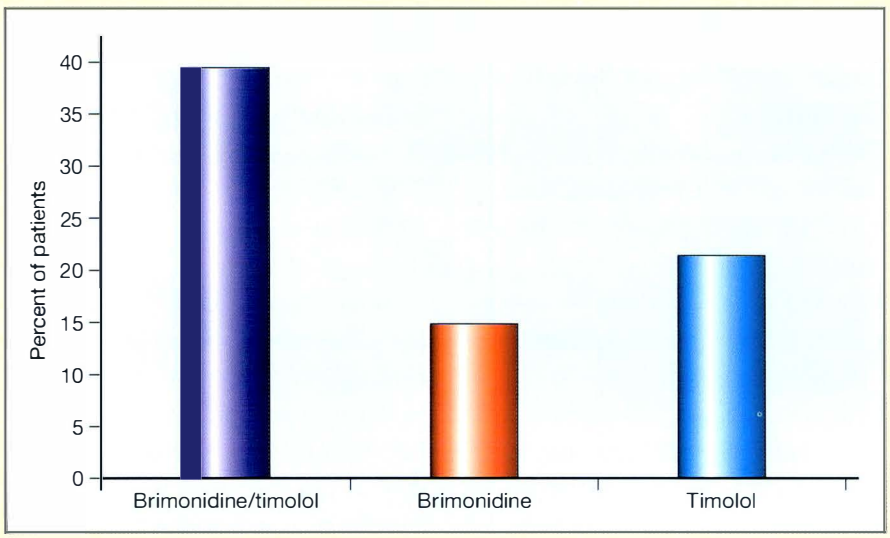
Administration of 2 drugs from a single bottle has the following advantages over 2 drugs administered separately:

- more convenient dosing
- may improve compliance
- diminished risk of washout from the second drug
- limits exposure to potentially damaging preservatives

There are several different combination therapies available. Combigan® is a combination of timolol 0.5% and brimonidine 0.2% in benzalkonium chloride 0.005%. A 12-month safety and efficacy trial compared brimonidine/timolol fixed combination, brimonidine, and timolol in 1159 patients. The primary outcome measure was IOP throughout the day (8 am, 10 am, 3 pm, and 5 pm). The peak effect occurred at 10 am, when the combination resulted in lower IOP than brimonidine or timolol alone. Mean change in IOP from baseline was highest in the group receiving combination therapy at all time points; this difference was greatest at 10 am (peak effect). The number of patients with mean diurnal IOP <18 mm Hg at all visits was greater in the combination therapy group than in the other 2 groups (Figure 1). Allergic conjunctivitis was decreased in the combination group compared with the brimonidine group. This study concluded that the fixed combination provided superior IOP-lowering efficacy compared with brimonidine or timolol alone. No additional adverse events were noted with the fixed combination.

Subsequently, a comparison of the efficacy and safety of brimonidine/timolol fixed combination with brimonidine and timolol given concomitantly was performed. The IOP-lowering was equal between the 2 groups after 12 weeks. This study found that the fixed combination was as safe and effective as concomitant treatment with the individual components. This simplified dosing regimen has the potential to improve compliance.

Figure 1. Mean diurnal intraocular pressure <18 mm Hg at all visits.



Combigan in Clinical Practice

A phase 4 multicentre open-label study was conducted in Canada to investigate the efficacy, safety, and tolerability of Combigan in clinical practice. The CEED II (Combigan Early Experience Data) study enrolled 2133 patients who required additional IOP-lowering or who would benefit from the improved convenience and compliance of combination therapy. Combigan was given either as adjunctive (50%) or replacement (50%) therapy. The primary outcomes were mean IOP and tolerability/patient satisfaction.

After 2 months, the overall mean IOP decreased from 20.2 mm Hg to 16.1 mm Hg ($p < 0.0001$) [Table 1]. The number of patients achieving an IOP ≤18 mm Hg increased from 41% to 77%. For all patients receiving Combigan, the additional IOP-lowering was 11% ($p < 0.0001$) [Table 2], while patients switching from Cosopt monotherapy to Combigan monotherapy achieved an additional 10.8% IOP reduction ($p < 0.0001$) [Table 3]. The comfort/tolerability profile was positive, with patients experiencing less burning, stinging, metallic taste, and itchiness with Combigan than with Cosopt ($p < 0.0001$).

Overall, Combigan provided an additional 4.1 mm Hg (17.8%) reduction in mean IOP. Target pressures of ≤18 mm Hg were achieved by 77% of eyes treated with Combigan. Fifty four percent of eyes achieved ≥15% reduction in IOP from baseline.

In the 12-month safety and efficacy trial, Combigan resulted in a lower allergy rate than brimonidine, particularly among patients who had not previously been exposed to brimonidine (5.5% and 10.9% for Combigan and brimonidine, respectively). A review of 102 patients prescribed Combigan who had not previously been prescribed brimonidine found that the allergy rate for Combigan was approximately half that for brimonidine.

Table 1. Mean intraocular pressure reduction with Combigan.

	Intraocular pressure (mm Hg)	Intraocular pressure reduction (%)
Baseline	20.2	
1 month	16.5	15.8
2 months	16.1	17.8

Table 2. Intraocular pressure reduction for all patients receiving Combigan.

	Intraocular pressure (mm Hg)	Intraocular pressure reduction (%)
Baseline	18.6	
1 month	16.6	9.0
2 months	16.1	11.0

Table 3. Intraocular pressure reduction for patients switching from Cosopt monotherapy to Combigan monotherapy.

	Intraocular pressure (mm Hg)	Intraocular pressure reduction (%)
Baseline	18.8	
1 month	16.6	10.2
2 months	16.1	10.8

Indications for Combination Therapy

Fixed combination therapy is indicated for patients who are already using both medications in the combination, as the more convenient dosing regimen may increase compliance. The traditional glaucoma treatment paradigm is to start with one medication and add further drugs according to the IOP-lowering achieved. However, when aggressive IOP-lowering is required, combination therapy may be used as first-line treatment; therapy can be reduced if side effects occur. Care must be taken not to overmedicate patients when using combination therapy, but the benefits exceed the risks and careful follow-up for side effects will enable dose reduction or a change of medications if necessary.

In Summary

Combigan is effective when used as replacement or adjunctive medication. There is a place for Combigan as initial therapy in some instances, and combination therapy may be tried instead of step-wise increases in therapy.

Diagnosis and Management of Glaucoma — European Perspective

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The European Glaucoma Society (EGS) guidelines were first published in 1998, with a second edition published in 2003. The guidelines contain sections on recent randomised trials, flow charts, patient examination, classification and terminology, and treatment.

European Glaucoma Society Guidelines

Guidelines are necessary to:

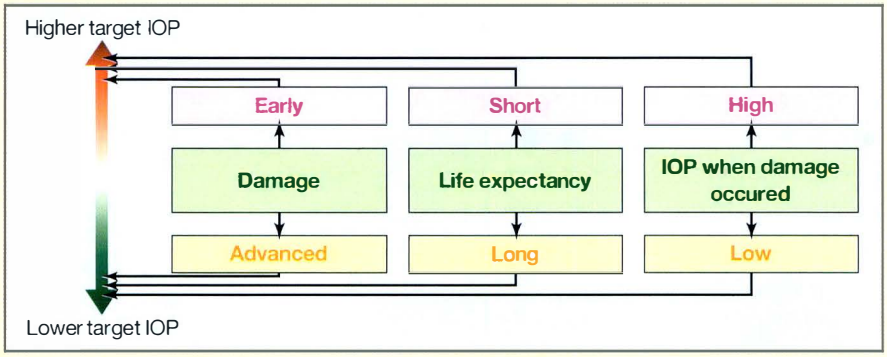
- improve the understanding of a disease
- provide a rational approach to the diagnosis and management
- augment health care systems
- justify examinations and treatments in a stepwise manner
- provide help for insurance reimbursement.

Guidelines are used by a variety of individuals, including trainee doctors, general ophthalmologists, glaucoma specialists, and health care economists. Approximately 65% of ophthalmologists follow the EGS guidelines, and they are now widely accepted.

The EGS guidelines suggest the type of questions to ask patients with glaucoma, diagnostic criteria (intraocular pressure, visual field, optic nerve head appearance), frequency of visual field testing (annual follow-up if there is no change, and more frequently if change is noted), follow-up assessment, and gonioscopy assessment.

Gonioscopy is highly recommended by the EGS, although it is not performed as frequently in Europe as in Asia, possibly because there is less angle closure in Europe. Educational video kits have been produced by the EGS to improve knowledge and awareness of gonioscopy, as well as the optic nerve

Figure 2. Target intraocular pressure (IOP).



head and visual field. Another tool for angle structure differentiation is the van Herrick test, which uses a slit lamp to measure the peripheral anterior chamber depth and ascertain the likelihood of angle closure.

Applanation tonometry is a widely accepted examination for glaucoma. Non-contact tonometry is more usually associated with optometry and is not recommended for glaucoma follow-up. Stereophotography is recommended by the EGS guidelines as the first test to document the optic disc, but a large number of ophthalmologists prefer to rely on detailed drawings of the optic disc. However, this is inferior to photography, Heidelberg retinal tomography, or scanning laser polarimetry documentation. Pachymetry is widely accepted throughout Europe.

Glaucoma Treatment

The EGS guidelines contain flow charts showing when and how to treat glaucoma. The concept of target pressure is explained as being dependent on the IOP level at which damage occurred and the life expectancy, resulting in a higher or lower target pressure (Figure 2). The EGS guidelines contain a 'treatment stepladder' guiding when to start treatment for different types of glaucoma. The first step is usually medical therapy, followed by laser trabeculoplasty, and surgery. A therapeutic trial of monotherapy will determine how effective a drug is for a particular patient. If the first drug is not effective, it is recommended to change to another drug; if the drug is effective, but the IOP is not lowered sufficiently, than another drug may be added. When combination therapy is used, a fixed combination is preferred.

The first-line medical therapy is usually a prostaglandin analogue or prostamide, β-blocker, α_2-agonist, or carbonic anhydrase inhibitors. Adrenergic and cholinergic medications are rarely used. Newly diagnosed patients are most likely to receive a prostaglandin analogue or prostamide as first-line therapy, although β-blockers are used as first-line therapy in some countries. If the first-line treatment is not sufficiently effective, more than 60% of patients receive combination therapy. β-blockers tend to be used earlier in the glau-coma continuum (for glaucoma suspects), with prostaglandin analogues or prostamides usually given for more progressive disease.

The average IOP threshold at which treatment for ocular hypertension is initiated tends to be at 25 mm Hg, if no risk factors are present. If there is an abnormal cup-disc ratio, then treatment tends to start at 20 to 22 mm Hg.

In Summary

In Europe, there are challenges in the diagnosis of glaucoma, with clinical diagnosis predominating. There is an increase in use of diagnostic equipment, although access to this equipment remains a barrier. There is a significant educational need for diagnostic approaches, particularly for gonioscopy.

β-Blockers are still widely used in Europe, but are decreasing in importance with the increasing use of prostaglandin analogues, and fixed combination use is increasing. Guidelines are necessary to clarify the treatment options, and the EGS guidelines have become widely accepted in Europe.

Glaucoma: an Asian Perspective

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The majority of people affected by glaucoma live in developing countries. Of the 33 million people with primary angle closure (PAC) and glaucoma (PACG), almost all of them live in Asia. Visual impairment is more severe in PACG than in primary open angle glaucoma (POAG), and the risk for blindness from PACG is 3 times that of POAG. With increases in population and longevity, PACG will become a greater public health problem. PAC and PACG should be detected early in the course of the disease; if PAC and PACG are detected and treated early, blindness from this form of glaucoma is preventable.

Detection Strategies

Strategies for detection include population-based screening and case-based detection. There are several reasons for avoiding population-based screening. The positive predictive value (PPV) of the screening test depends on the prevalence of the disease in the population. As the prevalence of glaucoma is low, most tests will have a

poor PPV, resulting in a low number of true-positive results and a large number of false-positive results. Individuals with false-positive results use up valuable clinic time, need to be characterised, and there is the problem of 'labelling' an individual. Once screening is implemented, the disease needs to be diagnosed and managed in a modern manner, and this is not possible in many clinics.

One method to 'increase' the prevalence of the disease in the population — and therefore the PPV — is to target the high-risk population. Screening only clinic patients who have sought out an ophthalmologist is different to screening the general population, as at least 5% of patients in the clinic will have angle closure (AC) requiring intervention to prevent blindness. Therefore, every clinic patient should be considered a glaucoma suspect, and examined accordingly. This involves a complete eye examination consisting of slit lamp, applanation tonometry, gonioscopy, and disc assessment. This complete examination will also reveal any other pathology that needs treatment. The Advanced Glaucoma Intervention Study consensus on ACG concludes that indentation gonioscopy is the gold standard for diagnosis of PAC and is mandatory in a clinic situation. There are several types of gonioscopy lens available. The Magna View lens provides an excellent view and photographs, but in the over-the-hill position, in expert hands at least, the lens seems to artifactually open the angle. Therefore, most clinicians use the indentation lens, which shows whether an angle is occludable and allows true indentation. Gonioscopy is associated with a long learning curve to develop the skill, but κ agreement of 0.9 can be achieved over time. Gonioscopy is not more difficult to learn than modern techniques of cataract surgery.

Anterior segment imaging may be the way of the future. Angle imaging is needed to achieve results similar to gonioscopy in a standardised, valid, and reliable manner. If angle imaging can be performed by a technician, it is not time-consuming for the clinician. Angle imaging can detect PAC suspect, identify cyclodialysis and foreign body if the entire angle is scanned, and perform angle measurement. However, there are disadvantages to angle imaging. All measurement parameters are dependent on spur localisation; specialists could identify the spur 70% of the time. It is not possible to check the entire angle at one time, and critical angle details such as peripheral anterior synechiae and blotchy pigment cannot be visualised. Angle imaging therefore cannot yet be used clinically or for screening.

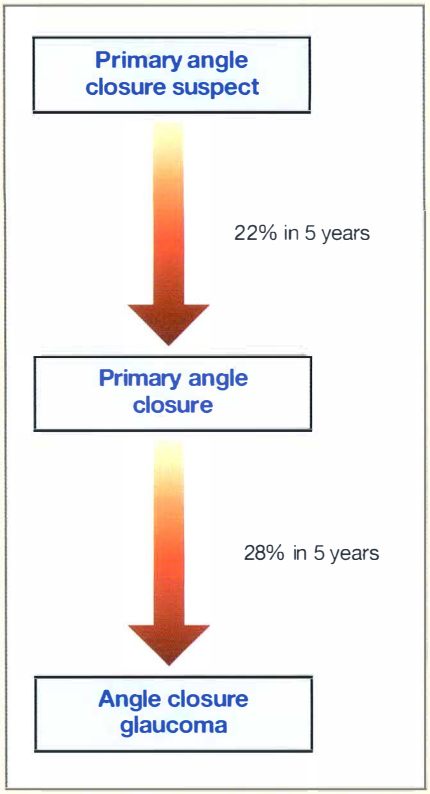
Management Philosophy

Measures to guide treatment include consideration of the number of patients needed to treat (NNT) to obtain 1 benefit, particularly in developing countries. The NNT for ocular hypertension is 20 patients, while the NNT for early glaucoma is 5. If the IOP is lowered sufficiently, the NNT decreases to 2. As the NNT for medical and surgical treatments are equivalent, primary surgery may be justified in some underdeveloped regions.

The number of patients needed to harm (NNH) is the number treated to produce 1 side effect. If cataract formation is considered, the NNH for medical treatment is 33, while the NNH for surgery is only 9. Therefore, although the beneficial results of medicine and surgery are equivalent, consideration of the NNH and other complications of surgery will help to guide the treatment decision.

The management of angle closure depends on the natural history of the disease (Figure 3). Currently, laser peripheral iridotomy (LPI) is not recommended for all PAC suspects. The procedure may be reserved for PAC suspects known to be at high risk for progression. LPI is an accepted treatment for patients with PAC and PACG, with a success rate of 90%. After LPI, the treatment for PAC and PACG is the same as for POAG. As far as medical treatment is concerned, all else being equal, the first line of therapy should be a prostaglandin analogue or prostamide.

Figure 3. Natural history of angle closure.



In Summary

Indentation gonioscopy is currently the gold standard for detection of angle closure, but angle imaging may play a role in the future. NNT and NNH are useful concepts for making management decisions. LPI is the mainstay of treatment for PAC and early PACG, but overtreatment of PAC suspects should be avoided. To prevent blindness, disease must be detected early. The key is to integrate glaucoma care with comprehensive eye care, as part of a comprehensive response to blindness.

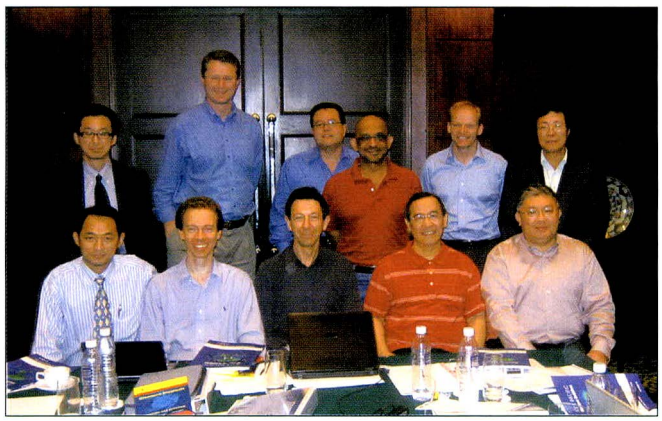
From the Allergan satellite symposium Brimonidine/Timolol Fixed Combination Therapy in Glaucoma Management *and the Plenary Session II* Diagnosis and Management of Glaucoma — an International Perspective *held at the Asian Oceanic Glaucoma Society (AOGS) Conference 2007, Bangkok, Thailand, 2-3 December 2007.*

Asia Pacific Glaucoma Guidelines Second Edition

The Asia Pacific Glaucoma Guidelines (APGG) were first published by the South East Asia Glaucoma Interest Group (SEAGIG) in 2003.[1] As understanding about glaucoma has increased and new technologies have become available, periodic updating of the guidelines has become necessary. New information can be added and outdated techniques that are no longer recommended can be removed. To discuss how best to update the APGG for a second edition, members of SEAGIG met in Bangkok, Thailand, on 29 November 2007.

The meeting started with a presentation on the value and development of guidelines. The key message was that evidence-based medicine unites medical research and clinical practice by translating the results of randomised clinical trials into accepted practice patterns. However, it is difficult to translate randomised clinical trials performed in the West to the different context in Asia due to the varying patterns of glaucoma in the region. Variation in practice patterns due to geography, socioeconomic status, culture, and patient differences is necessary to individualise treatment in Asia, confirming the need for glaucoma guidelines specific to South and East Asia.

Figure 1. Members of the Asia Pacific Glaucoma Guidelines Core Working Group in Bangkok, Thailand, 29 November 2007.
Front row, sitting: Prin RojanaPongpun, Paul Healey, Ivan Goldberg, Manny Agulto, Paul Chew
Back row, standing: Hidenobu Tanihara, Paul Foster, Aung Tin, Ravi Thomas, Jonathan Crowston, Ningli Wang



The primary aim is for future editions of the APGG to remain practical, accessible, and user-friendly. Feedback on the first edition of the guidelines has been invaluable to verify the requirements of guideline users and to ensure that their needs are again met in the second edition.

SEAGIG is aiming to launch the second edition of the APGG at the SEAGIG/AACGC Joint Congress in Seoul, Korea, 25 to 27 September 2008.

Acknowledgements

With grateful thanks to the members of the Asia Pacific Glaucoma Guidelines Second Edition Working Group: Prof Ivan Goldberg, Australia; Dr Manuel Agulto, The Philippines; Prof Paul Chew TK, Singapore; Prof Prin Rojanapongpun, Thailand; Dr Paul Healey, Australia; Prof Ravi Thomas, India; Dr Paul Foster, UK; Dr Aung Tin, Singapore; Dr Ningli Wang, China; Dr Jonathan Crowston, Australia; Dr Hidenobu Tanihara, Japan; Dr Clement Tham, Hong Kong; Dr Ki Ho Park, Korea; Dr Makoto Araie, Japan.

Reference

1. South East Asia Glaucoma Interest Group. Asia Pacific Glaucoma Guidelines. Singapore: SEAGIG, 2003-2004. Available at: www.sea-gig.org/pdf/APGGuidelinesNMview.pdf Accessed: 28 April 2008.

2008 SEAGIG/ AACGC Joint Congress

Seoul, Korea, 25-27 September 2008

SEAGIG 2008 Seoul, Korea

AACGC

The 5th Congress of the South East Asia Glaucoma Interest Group (SEAGIG 2008) and the 6th Meeting of the Asian Angle-Closure Glaucoma Club (AACGC) will take place in Seoul, Korea, from 25-27 September 2008. SEAGIG was established to facilitate contact between glaucoma specialists in the region, to encourage collaborative research and service projects, to increase the opportunities for exchange of skills and knowledge in this rapidly advancing field, and to assist comprehensive ophthalmological colleagues and other eye care workers (whether medically trained or not) to keep up to date with advances in all aspects of glaucoma diagnosis and management. The aim of the AACGC is to establish a scientific network for Asian glaucomatologists who are interested in exchange of knowledge about angle closure glaucoma.

The conference organising committee plans to introduce an educational and scientific programme that will cover cutting-edge basic and clinical research topics in the field of glaucoma. You are invited to make the scientific programme more dynamic and stimulating by submitting abstracts and registering for the conference.

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- Glaucoma Screening and Awareness in Asia
- Medical Treatment
- Surgical and Laser Treatment
- Imaging and Diagnosis
- Controversies/Future Trends
- Neuroprotection in Glaucoma
- Angle-Closure Glaucoma

Important Dates

Abstract submission deadline	6 June 2008
Early registration	30 June 2008
Abstract acceptance notice	11 July 2008

For further details, contact the website at:
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Enquiries should be directed to:
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Chennai, India, 12-13 July 2008

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- Refractive surgery nightmares
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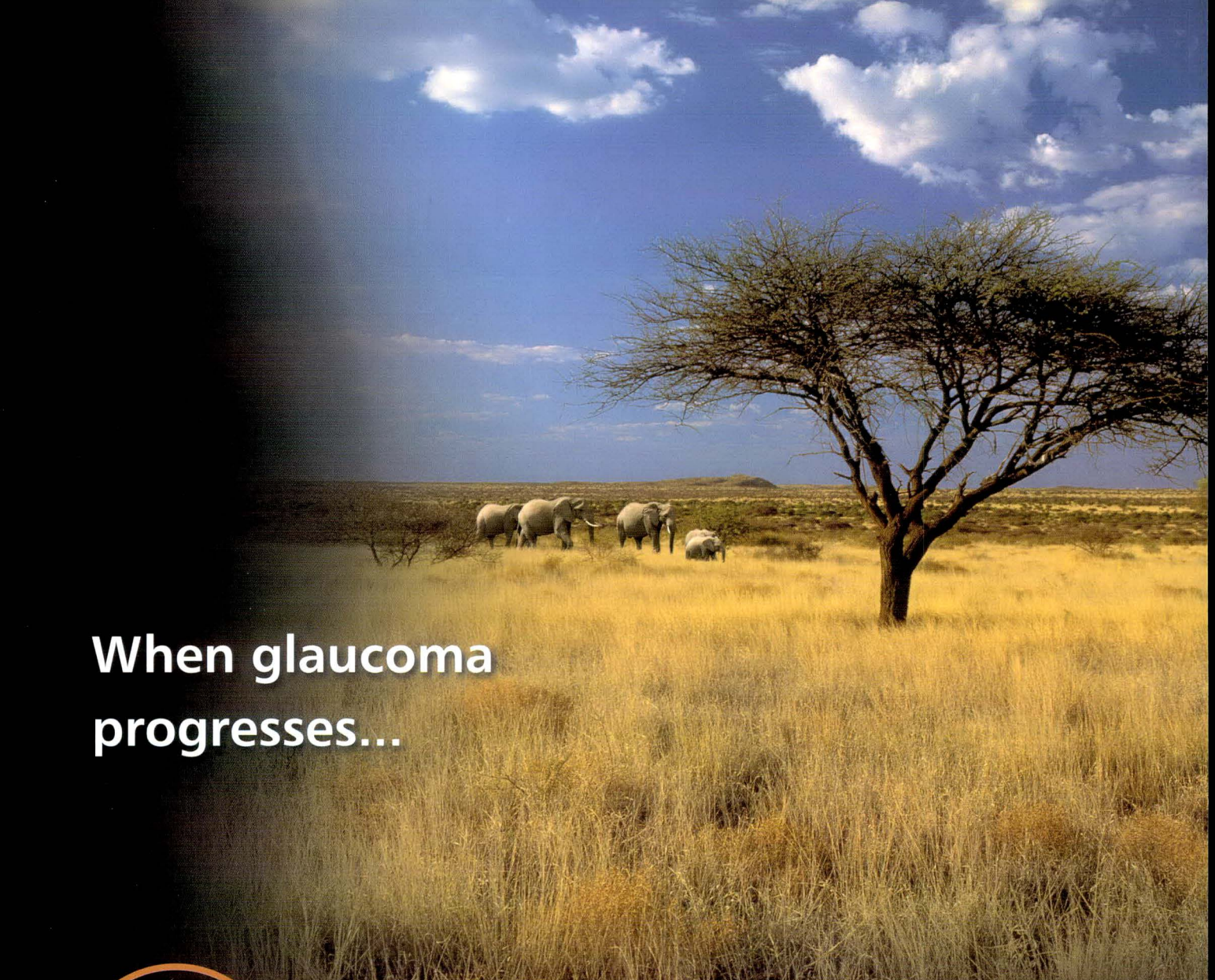

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RÉFERENCES: 1. Larsson L-I, *et al*. The effect on diurnal intraocular pressure of the fixed-combination of latanoprost 0.005% and timolol 0.5% in patients with ocular hypertension. *Acta Ophthalmol Scand*. 2001;79:125–8. 2. Konstas AGP, *et al*. Twenty-four hour control with latanoprost-timolol-fixed combination therapy *vs* latanoprost therapy.*Arch Ophthalmol*. 2005;123:898–902. 3. Diestelhorst M and Larsson L-I, for the European-Canadian Latanoprost Fixed Combination Study Group. A 12-week, randomized, double-masked, multicenter, study of the fixed combination of latanoprost and timolol in the evening versus the individual components. Ophthalmology. 2006;113:70–6. 4. Shin DH, *et al*. Efficacy and safety of the fixed combinations latanoprost/timolol versus dorzolamide/ timolol in patients with elevated intraocular pressure. Ophthalmology. 2004 Feb;111:276–82. 5. Topouzis F, *et al*. A 1-year study to compare the efficacy and safety of once-daily travoprost 0.004%/ timolol 0.5% to once-daily latanoprost 0.005%/timolol 0.5% in patients with open-angle glaucoma or ocular hypertension. *Eur J Ophthalmol*. 2007;17:183–90. 6. Martinez A and Sanchez M. A comparison of the safety and intraocular pressure lowering of bimatoprost/timolol fixed combination versus latanoprost/timolol fixed combination in patients with open-angle glaucoma. *Curr Med Res Opin*. 2007;23:1025–32.

In the 6-month registration trials, the most frequent adverse events were eye irritation, including stinging, burning, and itching (12.0%); eye hyperemia (7.4%); corneal disorders (3.0%); conjunctivitis (3.0%); blepharitis (2.5%); eye pain (2.3%); headache (2.3%); and skin rash (1.3%)[1].

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