Journal of the South East Asia Glaucoma Interest Group

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Goniotomy in Iridocorneal Endothelial Syndrome

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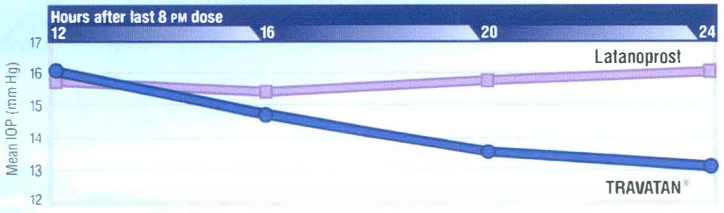

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TRAVATAN® (travoprost 0.004%) Ophthalmic Solution Sterile **DESCRIPTION** Travoprost is a highly selective, potent agonist for the FP prostanoid receptor Its chemical name is isopropyl (Z)-7-[(1R,2R,3R,5S)-3,5-dihydroxy-2-[(1E,3R)-3-hydroxy-4-[(α,α,α-trifluoro-m-tolyl)oxy]-1-butenyl]cyclopentyl]-5-heptenoate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

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* 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=0.011).

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

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SEAGIG
South East Asia Glaucoma Interest Group

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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
- to maintain and promote relationships with any organisation with similar goals.

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

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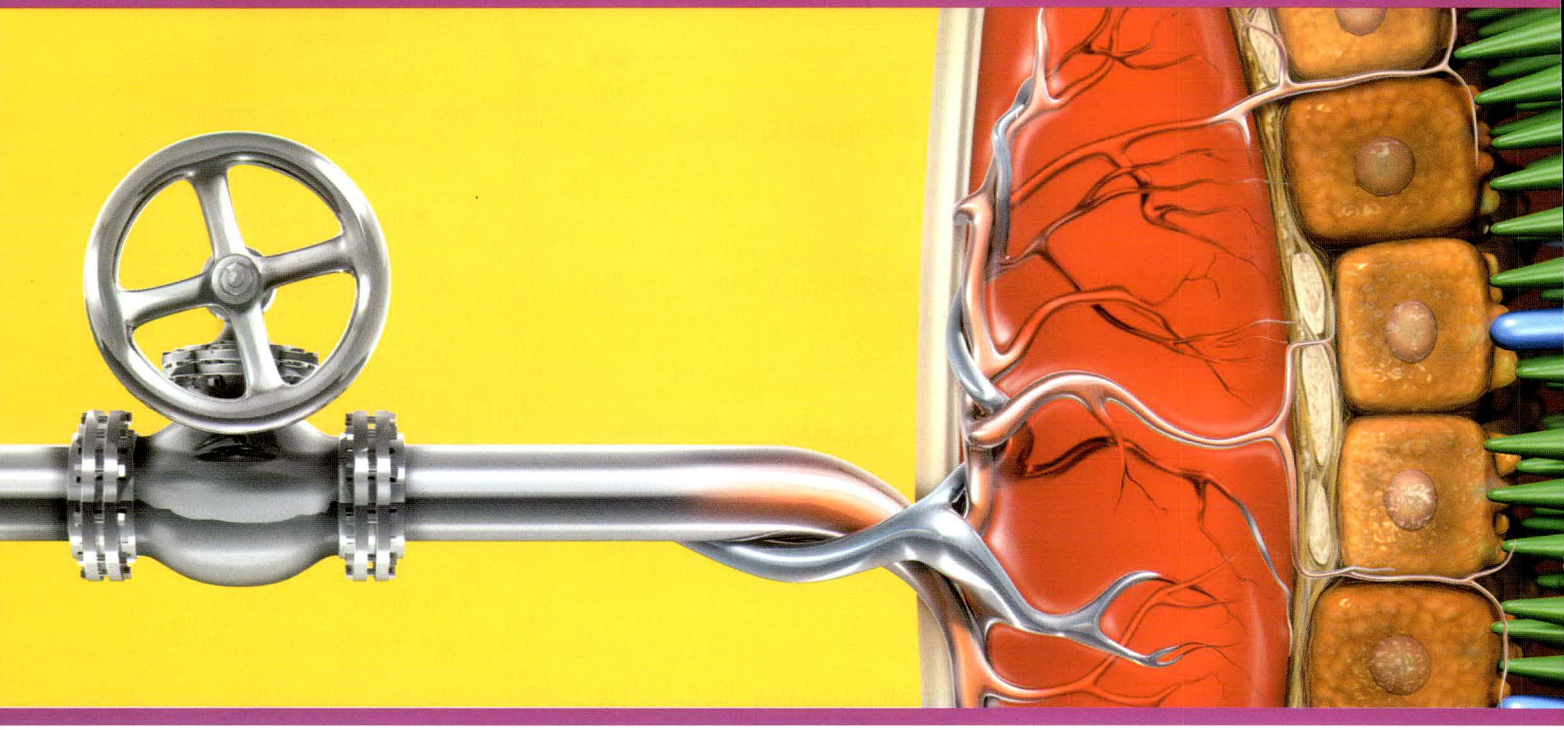

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* Age-related macular degeneration. † Vascular endothelial growth factor. ‡ Defined as <15 letters lost over 2 years.

References: 1. Data on file. Pfizer Inc, New York, NY. 2. Gragoudas ES, Adamis AP, Cunningham ET Jr, Feinsod M, Guyer DR, for the VEGF Inhibition Study in Ocular Neovascularization Clinical Trial Group. Pegaptanib for neovascular age-related macular degeneration. *N Engl J Med* 2004;351:2805-2816.

MACUGEN ABBREVIATED PACKAGE INSERT TRADE NAME: Macugen **PRESENTATION:** Macugen injection is supplied in a single use 1 mL glass syringe containing pegaptanib sodium 0.3 mg in a 90 µL deliverable volume. **INDICATIONS:** Treatment of neovascular (wet) age-related macular degeneration. **DOSAGE:** 0.3 mg administered once every six weeks by intravitreous injection into the eye to be treated. Macugen should be inspected visually for particulate matter and discoloration prior to administration. The injection procedure should be carried out under controlled aseptic conditions. Adequate anesthesia and a broad-spectrum microbicide should be given prior to the injection. **CONTRAINDICATIONS:** Patients with ocular or periocular infections. **WARNINGS & PRECAUTIONS:** FOR OPHTHALMIC INTRAVITREAL INJECTION ONLY. Intravitreous injections have been associated with endophthalmitis. Proper aseptic injection technique should always be utilized when administering Macugen. Patients should be monitored during the week following the injection to permit early treatment, should an infection occur. Intraocular pressure as well as the perfusion of the optic nerve head should be monitored and managed appropriately. **INTERACTIONS:** Pegaptanib is metabolized by nucleases and is generally not affected by the cytochrome P450 system. **PREGNANCY AND LACTATION:** Pregnancy Category B. Pegaptanib crosses the placenta in mice. There are no studies in pregnant women. The potential risk to humans is unknown. Macugen should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the fetus. It is not known whether pegaptanib is excreted in human milk; caution should be exercised when Macugen is administered to a nursing woman. **SIDE EFFECTS:** Anterior chamber inflammation, blurred vision, cataract, conjunctival hemorrhage, corneal edema, eye discharge, eye irritation, eye pain, hypertension, increased intraocular pressure (IOP), ocular discomfort, punctate keratitis, reduced visual acuity, visual disturbance, vitreous floaters, and vitreous opacities. Injection procedure related side effects include endophthalmitis, retinal detachment, iatrogenic traumatic cataract. **STORAGE:** Store in refrigerator at 2°C to 8°C. Do not freeze or shake vigorously. Reference: USPI (Dec 2004). **FULL PRESCRIBING INFORMATION IS AVAILABLE UPON REQUEST.**

MAC06003P

Does Goniotomy Have a Role in Adult Glaucomas?

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Iridocorneal endothelial (ICE) syndrome is an important and unusual cause of acquired glaucoma, and encompasses a spectrum of diseases that include progressive essential iris atrophy, Cogan-Reese syndrome, and Chandler's syndrome.[1] The pathophysiology of these conditions is well established, namely an endothelial cell abnormality capable of expression of epithelial cell-like characteristics with the ability to proliferate and migrate across the anterior chamber angle and iris.[2] The aetiology is less clear, but a role for herpes simplex virus and/or Epstein-Barr virus is suspected.[3]

Glaucoma in patients with ICE syndrome is often very difficult to control, and medical treatment is almost always inadequate. Trabeculectomy, even with anti-metabolites, is associated with a relatively high risk of failure, presumably because of continued growth of the abnormal cells over the sclerostomy site.[4] Glaucoma drainage implants are now advocated, but many patients with ICE syndrome need penetrating keratoplasty and the proximity of the tube to the corneal endothelium may risk survival of the graft.[5] In this issue, Espana et al describe the use of goniotomy to treat glaucoma in patients with ICE syndrome with good medium-term results.[6] Whilst this is not the first description of a goniotomy-type procedure to treat ICE syndrome, it is certainly the largest series to date.[7]

Espana et al hypothesise that ICE syndrome is potentially analogous to congenital glaucoma.[6] This has previously been proposed. Wilson suggested that both primary congenital glaucoma (PCG) and ICE syndrome are an abnormality of anterior segment development of neural crest cell origin.[8] This author proposed that PCG is an arrest of development, whereas ICE syndrome is an arrest of final differentiation. In PCG the defect was initially thought to be an imperforate membrane (Barkan's membrane) lining the anterior chamber angle based on gonioscopic findings,[9] but this membrane has never been demonstrated histologically, unlike the membrane in ICE syndrome, which has been demonstrated both histologically and on high frequency ultrasound.[10,11]

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Whether goniotomy works in PCG by releasing the reportedly taut trabeculae, by allowing a backward fall of the anteriorly inserted iris (thereby revealing the angle recess), by creating a cleft, or by a combination of these mechanisms is unclear. In ICE syndrome, obstruction to aqueous outflow presumably results from the membrane covering the trabecular meshwork, and it is therefore not surprising that goniotomy may be effective. However, recurrence of the membrane or development of anterior synechiae are likely to compromise the outcome in the longer term. It seems reasonable to suggest that goniotomy should be considered early in the management of secondary glaucoma in ICE syndrome, before peripheral anterior synechiae develops, much like the rationale for prophylactic goniotomy in aniridia.[12]

Goniotomy has been shown to have a favourable outcome in conditions other than PCG, including juvenile open angle glaucoma, glaucoma complicating anterior uveitis,[13] Axenfeld's anomaly and iris hypoplasia. In cases of adult glaucoma, where the pathophysiology necessitates incision of a membrane or obstruction to the trabecular meshwork (e.g., chronic anterior uveitis), goniotomy most certainly should be considered. Goniotomy is a relatively safe and effective procedure with no conjunctival disruption. Goniotomy deserves to be considered in the treatment of glaucoma associated with the ICE syndromes, either as a first-line treatment or as a temporising measure before more invasive procedures are needed.

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Goniotomy for Uncontrolled Intraocular Pressure in Iridocorneal Endothelial Syndrome

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Aim: To report the clinical outcome of 3 patients with iridocorneal endothelial syndrome who underwent goniotomy for the management of elevated intraocular pressure.
Methods: This was a single-centre retrospective case series of adult patients with uncontrolled glaucoma. Three female patients with iridocorneal endothelial syndrome underwent goniotomy.
Results: Goniotomy successfully reduced intraocular pressure in all 3 patients for a mean follow-up period of 52.3 months (SD, 38.4 months; range, 8 to 77 months). One patient eventually required a glaucoma drainage device for intraocular pressure control.
Conclusion: Goniotomy is a potentially useful surgical technique for reducing intraocular pressure in eyes with iridocorneal endothelial syndrome.

Key words: Glaucoma, Intraocular pressure, Trabeculectomy

Asian J Ophthalmol. 2007;9:107-10

Introduction

Iridocorneal endothelial (ICE) syndrome is a disorder in which the corneal endothelium and Descemet's membrane migrate over the trabecular meshwork, iridocorneal angle, and iris surface. Normal corneal endothelial cells develop characteristics of epithelial lineages, including the expression of cytokeratins, desmosomal attachments, and cell stratification.[1-3] Clinically, ICE syndrome is associated with progressive corneal oedema, anterior chamber narrowing, and iris changes that eventually lead to glaucoma, which results from obstruction of the anterior chamber angle. Closure of the angle by broad-based peripheral anterior synechiae (PAS) is common. Glaucoma occurs in 50% to 82% of patients with ICE syndrome and responds poorly to medications or surgical procedures to lower intraocular pressure (IOP).[4,5]

Goniotomy is a safe and effective treatment for the control of infantile glaucoma. There is a low complication rate and the conjunctiva remains untouched. These authors hypothesised that ICE syndrome is a potentially analogous situation to congenital glaucoma, and that if the Descemet's-endothelial membrane could be incised, goniotomy might allow aqueous egress from the anterior chamber. This study investigated the long-term outcome of 3 patients with ICE syndrome in whom goniotomy was the primary surgical procedure to control IOP.

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Methods

This study was approved by the New York Eye and Ear Institutional Review Board and was conducted in accordance with the tenets of the Declaration of Helsinki of 1975. Each patient gave written informed consent after explanation of the nature, risks, and possible adverse consequences of the procedure. Patients were seen between February 1999 and August 2002 and had high IOPs with progressive visual field loss. A diagnosis of ICE syndrome was based on the unilateral clinical features, low endothelial counts, and endothelial pleomorphism on specular microscopy. Follow-up ended when another IOP-lowering procedure was performed.

Surgery was performed under local anaesthesia by one surgeon using a standard goniotomy technique. In brief, a paracentesis track was made temporally. Acetylcholine, lidocaine, and a viscoelastic agent were injected into the anterior chamber through the entry site. A direct-view gonioscopy lens was placed on the cornea and

a Worst goniotomy knife was used to enter the mid-portion of the trabecular meshwork. A trabecular incision was created under direct visual control for approximately 4 clock hours. The same procedure was performed for 4 more clock hours using a paracentesis site superiorly. Finally, the viscoelastic was washed from the anterior chamber with balanced saline solution.

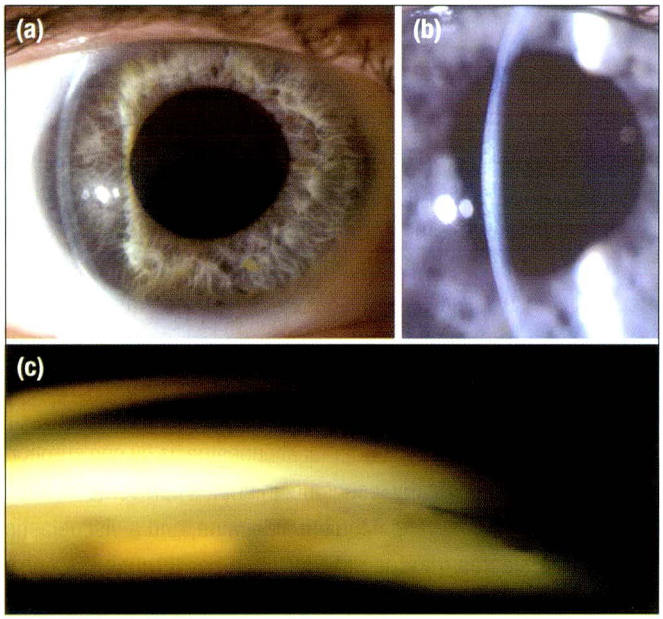
Results

All 3 patients were women (mean age, 46 years [SD, 4 years]) with Chandler's syndrome. In patient 1, medical treatment was inadequate. Patients 2 and 3 had previous failed trabeculectomies prior to goniotomy. All 3 patients initially had controlled IOP after goniotomy. Mean follow-up was 52.3 months (SD, 38.4 months; range, 8 to 77 months). In patient 1, the IOP decreased 20 mm Hg and was considered acceptable until the end of follow-up. Additional topical medications were progressively added to attain an acceptable IOP for patients 2 and 3. Patient 2 had an acceptable IOP even after undergoing 4 corneal transplants and a retinal detachment repair. Patient 3 finally required a glaucoma drainage implant due to visual field deterioration.

Patient 1

A 39-year-old woman with best-corrected visual acuity (BCVA) of 20/20 in both eyes had uncontrolled IOP ≥30 mm Hg in the right eye despite maximally tolerated medical therapy. After goniotomy, her IOP has remained in the teens for 7 years, although she continues to require 3 medications. No other surgical interventions have been performed since the goniotomy.

Figure 1. A 48-year-old woman presented with unilateral uncontrolled glaucoma. (a) Slit-lamp examination demonstrated a distorted pupil in the eye with high intraocular pressure; (b) minimal corneal stromal oedema was also noted; and (c) dark-room gonioscopy showed the compromise of the anterior chamber angle.



Patient 2

A 48-year-old woman had had a failed trabeculectomy and an Ahmed drainage implant in the left eye. BCVA was 20/20 in the right eye and 20/30 in the left eye. Her IOP was >30 mm Hg with 4 medications. Slit-lamp examination of the right eye was unremarkable. In the left eye, there was a superior flat scarred bleb, moderate corneal oedema, scattered PAS, and a drainage tube in the anterior chamber (Figure 1). The cup-disc ratios were 0.1 in the right eye and 0.6 in the left eye. A goniotomy was performed with reduction of IOP and, despite cataract surgery performed 8 months after goniotomy and a corneal transplant performed 10 months after that, the IOP remained in the low teens with the same medications. Three subsequent keratoplasties were performed because of progressive graft failure, beginning 30 months after the goniotomy, with maintenance of IOP in the low teens.

Patient 3

A 51-year-old woman was referred for management of elevated IOP in the left eye despite pilocarpine and betaxolol therapy. Examination of the right eye was normal. She had corneal oedema and variable PAS in the left eye. The cup-disc ratios were 0.25 in the right eye and 0.6 in the left eye. Trabeculectomy in the left eye failed despite multiple bleb needlings and antifibrotic agents. Combined corneal transplant and cataract extraction were performed for visual purposes. Following the postoperative period, her IOP was in the mid-twenties with 4 medications. Goniotomy was performed, after which the IOP fluctuated between the high teens and the low twenties with the same medications. Visual acuity progressively decreased due to corneal graft failure. Finally, a pars plana Ahmed implant was inserted for IOP control and a repeat keratoplasty was performed.

Discussion

Despite new medications and surgical devices, the management of glaucoma in ICE syndrome continues to be difficult and poorly effective, with the majority of patients not attaining long-term IOP control while corneal deterioration and visual impairment progresses.[6-8] It is thought that trabeculectomy fails because of continued membrane growth over the filtration site. Besides the complications of trabeculectomy, the use of antifibrotic agents may further impair the corneal endothelium.[9-11]

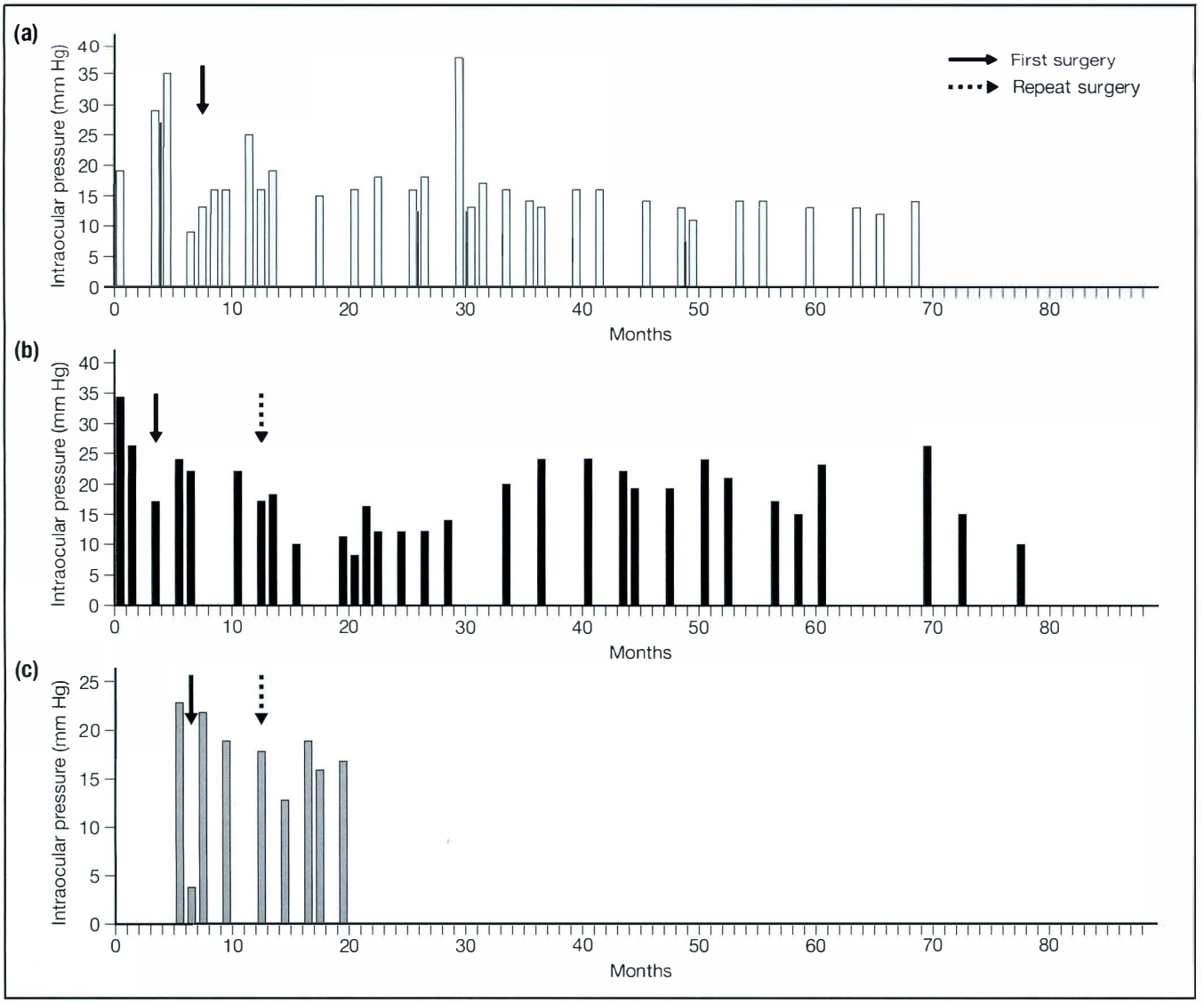
Glaucoma drainage implants have been advocated for the surgical management of patients with ICE syndrome. Kim et al[12]

reported adequate IOP control in 4 of 10 patients after a median follow-up of 4 years, and Doe et al[7] found a 53% control rate at 3 years. Nevertheless, the long-term outcome is not yet well established. The silicone tube in the anterior chamber may further endanger the survival and function of the compromised endothelium. A high proportion of patients undergo corneal transplantation after seton implantation.[13] Finally, the tube lumen may become obstructed by the ICE membranous outgrowth.[12]

Two of the 3 patients in this report had a persistent response lasting for more than 6 years after goniotomy (patients 1 and 2; Figure 2). Goniotomy provided sustained IOP control after failed trabeculectomy and drainage implant and maintained IOP control even after subsequent surgical procedures. A major advantage of goniotomy is the possibility of treating another area of trabecular meshwork in case of failure, or even treating the same area, presuming that the endothelial-Descemet's membrane has regrown. In trabeculectomy, aqueous flow is limited to the small area where the ostium is located and growth of ICE cells over that limited area can compromise aqueous outflow.

Although goniotomy is a common surgical procedure for congenital glaucoma, it has not been reported for the treatment of ICE syndrome in adults to the authors' knowledge. Goniotomy has potential advantages over the standard surgical procedures. A greater circumference of the trabecular meshwork is involved in the drainage of aqueous humor compared to a limited filtering sclerotomy opening or a smaller tube ostium. The use of antifibrotic agents and their detrimental effect on the endothelium is avoided. If goniotomy is ineffective in controlling IOP, the conjunctiva is preserved and remains available for other drainage procedures.

Figure 2. Intraocular pressure course of (a) patient 1; (b) patient 2; and (c) patient 3.



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Non-penetrating Deep Sclerectomy with Deroofing of Schlemm's Canal with Mitomycin C for Primary Open Angle Glaucoma

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Aim: *To report the results of non-penetrating deep sclerectomy with deroofing of Schlemm's canal with intraoperative mitomycin C in eyes with primary open angle glaucoma.*
Methods: *This prospective study included 33 eyes of 33 patients with newly diagnosed primary open angle glaucoma. Non-penetrating deep sclerectomy with deroofing of Schlemm's canal with intraoperative mitomycin C was performed for all patients. Visual acuity, intraocular pressure, anterior chamber depth measurement, and slit-lamp examination were performed preoperatively and postoperatively at 1 and 5 days and 1, 3, 6, 9, 12, 15, 18, and 21 months.*
Results: *The complete success rate, defined as an intraocular pressure ≤21 mmHg and ≥30% intraocular pressure reduction without medication, was 96.9% at 15 months. Visual acuity remained stable. No significant change in anterior chamber depth occurred. Complications included microperforations (9%), shallow dissection (3%), haemorrhage in the bleb region (9%), and conjunctival wound gape without leak (6%).*
Conclusion: *Non-penetrating deep sclerectomy with deroofing of Schlemm's canal with mitomycin C appears to be a safe and highly effective technique for primary open angle glaucoma, without serious complications.*

Key words: *Glaucoma, open angle, Surgery*

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Introduction

Non-penetrating deep sclerectomy (NPDS) is gradually evolving as an attractive surgical option for the management of primary open angle glaucoma (POAG). NPDS has been practiced in its various forms since the reports of Epstein[1] and Krasnov.[2] Besides deep sclerectomy,[3] other non-penetrating filtering surgeries are sinusotomy,[2] trabeculectomy ab externo,[4-6] and viscocanalostomy.[7] NPDS has been claimed to circumvent various complications of conventional penetrating trabeculectomy, which still remains the most popular and commonly performed glaucoma filtering surgery with a success rate ranging from 60% to 96%.[8-10] However, the procedure is associated with potentially sight-threatening complications such as flat anterior chamber, hypotony, choroidal detachment, anterior segment inflammation/uveitis, initiation or hastening of cataractogenesis,[11] intraoperative haemorrhage (hyphaema, suprachoroidal, or expulsive), iris incarceration, cystoid macular oedema, bleb-related problems, and an increased risk of endophthalmitis.[12]

By maintaining an intact trabeculo-Descemet's membrane, NPDS avoids the serious complications of conventional trabeculectomy. Non-penetration of the anterior chamber increases the safety of NPDS. Several studies have reported the safety and efficacy of NPDS in short- and medium-term follow-up.[3,13-17] The procedure has been modified by various investigators to improve its success. NPDS has been combined with use of collagen implant,[18] reticulated hyaluronic acid implant,[19] 5-fluorouracil (5-FU),[17,20-22] and mitomycin C (MMC)[16,23-25] to prevent fibrosis and closure of the filtration site. Use of MMC in NPDS has been restricted to failed glaucoma filtering surgery.[16,23-25] This study prospectively investigated the success rate and complications of NPDS with deroofing of Schlemm's canal with mitomycin C for newly diagnosed patients with POAG.

Methods

Patients

Thirty three patients with POAG attending the glaucoma service at the Department of Ophthalmology, University College of Medical

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Sciences, Delhi, India, from February 2001 to September 2002 were enrolled in this prospective study. Local ethical committee approval was obtained and informed consent was given by all patients. Inclusion criteria were newly diagnosed POAG, age 45 years or older, absence of previous intraocular pressure (IOP)–lowering or glaucoma surgery, and superior conjunctiva devoid of chronic inflammatory or cicatricial disorder. Exclusion criteria were angle closure glaucoma, normal tension glaucoma, severe ocular trauma, secondary open angle glaucoma, argon laser trabeculoplasty, rheumatoid arthritis, and collagen vascular disorders. All patients underwent detailed ophthalmic evaluation consisting of best corrected visual acuity assessment, biomicroscopy, gonioscopy, Goldmann's applanation tonometry, anterior chamber depth measurement (pachymetry), fundus examination, and visual field testing. Preoperatively, IOP was controlled with antiglaucoma medication. All the surgeries were performed by one surgeon under peribulbar anaesthesia.

Surgical Technique

A superior rectus bridle suture was passed. A superior limbal-based conjunctivo-tenon flap 8 mm away from the limbus, approximately 10 to 15 mm from the limbal arc was raised to expose the sclera. Haemostasis was achieved using wet-field bipolar cautery. A 5- x 5-mm limbal-based superficial scleral flap of approximately one-third scleral thickness was dissected 1 mm into clear cornea. MMC was applied over the scleral bed underneath the superficial scleral flap using a 5- x 5-mm merocel sponge soaked in freshly prepared MMC 0.02% solution. Contact of the MMC-soaked sponge with the conjunctival flap was avoided. The sponge was applied for 1 minute and washed with 20 mL normal saline. A second 5- x 5-mm deep scleral flap of approximately 90% scleral thickness was then dissected off the scleral bed. While approaching the corneoscleral junction, the plane of dissection was kept superficial to the roof of Schlemm's canal. The dissection continued forward, involving 1 mm of clear cornea. Schlemm's canal was identified as a bluish line at the corneoscleral junction. In the absence of any tear, the roof of Schlemm's canal was incised vertically and a 30 G angulated cannula was gently passed into the lumen of the canal. The roof of the canal was gently excised with Vannas scissors and a dark glistening deroofed canal was isolated and identified as the floor of Schlemm's canal, with the aqueous appearing as a glistening reflex. The tissue between Schlemm's canal and the base of the deeper flap was further dissected, leaving a thin trabeculo-Descemet's membrane through which aqueous was seen to be percolating in the dissected area. The deeper flap was approximated using 2 x 10-0 monofilament sutures at the corners of the flap. The conjunctiva was sutured with 10-0 monofilament in a continuous fashion. Subconjunctival injection of gentamicin 20 mg with dexamethasone 2 mg was given. Possible intraoperative problems included failure to identify and deroof Schlemm's canal, non-percolation of aqueous while dissecting Schlemm's canal, microperforation, loss of anterior chamber, hyphaema, shallow/deep dissection, and exposure of choroid. Postoperative treatment included topical dexamethasone sodium phosphate 0.1% with neomycin 0.5% eye drops 4 times a day for 3 to 4 weeks and oral ciprofloxacin 500 mg twice daily for 5 days.

Postoperatively, the following parameters were evaluated at each follow-up visit: visual acuity, status of the bleb, slit-lamp biomicroscopy, condition of the cornea, anterior chamber depth (ACD), IOP, and fundus examination. Patients were examined daily for 5 days, weekly for 4 weeks, monthly for 3 months, and 3 monthly to July 2003. Postoperative complications included hypotony, defined as a postoperative IOP ≤4 mm Hg, and cataract developing or progressing as a direct consequence of NPDS. The surgery was defined as a complete success if the postoperative IOP was ≤21 mm Hg without antiglaucoma drugs; a qualified success if the postoperative IOP was ≤21 mm Hg with antiglaucoma medication; and a failure when the postoperative IOP was >21 mm Hg with antiglaucoma medication.

Statistical Analysis

Statistical analyses were performed using paired Student's *t* test for comparisons of means, repeated measure analysis of variance design for analysis of IOP and ACD using both simple contrast and repeated contrast.

Results

NPDS with deroofing of Schlemm's canal with intraoperative MMC application was performed on 33 eyes of 33 patients with POAG. There were 18 men and 15 women. The mean age was 62.4 years (SD, 9.0 years; range, 60 to 79 years). Preoperatively, IOP was controlled by antiglaucoma medications, which included timolol maleate 0.5% eye drops twice daily, pilocarpine nitrate 2% eye drops 4 times daily, and oral acetazolamide 250 mg 6 hourly either alone or in combination. A single drug (timolol) was used for 9 eyes (27.3%), 2 drugs (timolol plus acetazolamide) was used for 15 eyes (45.5%), and 3 drugs (timolol, pilocarpine, plus acetazolamide) in 9 eyes (27.3%).

The mean preoperative baseline IOP was 42.2 mm Hg (SD, 12.6 mm Hg; range, 24 to 80 mm Hg) [Table 1]. Postoperatively, IOP ranged from 8 to 22 mm Hg. Table 1 shows the mean postoperative IOP values. The mean IOP reduction was 85.3% on day 1, 75.3% at 3 months, 75.2% at 6 months, 74.8% at 12 months, 72.5% at 18 months, and 76.3% at 21 months (Table 1). There

Table 1. Comparison of preoperative and postoperative intraocular pressure.

	Mean intraocular pressure (SD) [mm Hg]	Percent reduction
Preoperative	42.2 (12.6)	
Postoperative		
1 day	6.1 (1.2)	85.3
1 month	9.6 (1.9)	77.1
3 months	10.4 (2.6)	75.3
6 months	10.4 (2.6)	75.1
12 months	10.6 (2.6)	74.7
18 months	11.6 (3.8)	72.5
21 months	10.0 (0.0)	76.3

was no statistically significant difference amongst the mean IOPs and percentage IOP reduction at 3, 6, 12, 15, 18, and 21 months, indicating that the reduction in IOP was stable during the follow-up period. An IOP of 4 mm Hg was recorded in 4 eyes (12%) at day 1 and 1 eye (3%) at day 2.

The mean follow-up duration was 21.5 months (SD, 3.3 months; range, 18 to 27 months). Thirty three eyes completed follow-up of 18 months, of which only 1 eye (3%) had an IOP >21 mm Hg, which was controlled with topical timolol. This eye had had shallow dissection of the trabeculo-Descemet's membrane. The complete success rate at mean follow-up of 21.5 months was 96.96% and the qualified success rate was 100%.

The mean preoperative ACD was 2.69 mm (SD, 0.29 mm) while the mean postoperative ACD was 2.66 mm (SD, 0.28 mm) at day 1 ($p = 0.001$), 2.68 mm (SD, 0.29 mm) at day 3, and 2.69 mm (SD, 0.29 mm) at day 5; the difference was only statistically significant at day 1 (Table 2). No change in ACD occurred in 15 eyes (45.5%). Table 3 shows the postoperative bleb grade.

There was no change in visual acuity in 28 eyes (84.8%), but visual acuity improved from 0.14 (SD, 0.09) preoperatively to 0.21 (SD, 0.11) postoperatively in 5 eyes (15.2%) [Table 4]. In the immediate postoperative period, there was an average improvement in visual acuity from 0.33 (SD, 0.28) preoperatively to 0.34 (SD, 0.28) on postoperative day 9, and at the end of 18 months,

Table 2. Comparison of preoperative and postoperative anterior chamber depth.

	Anterior chamber depth (SD) [mm]
Preoperative	2.69 (0.29)
Postoperative	
Day 1	2.64 (0.29)
Day 2	2.67 (0.29)
Day 5	2.69 (0.29)

Table 3. Bleb grade at 12 months.

Grade	Number of patients (%)
I	1 (3.03)
III	6 (18.75)
IV	12 (37.50)
V	14 (43.75)

Table 4. Change in visual acuity.

Visual acuity	Mean (SD)
Preoperative	0.24 (0.17)
Postoperative	0.25 (0.16)
No change	84.8%
Improved	15.2%

Table 5. Intraoperative and postoperative complications.

Complication	Number of eyes (%)
Microperforation in the floor of Schlemm's canal	2 (6)
Microperforation of trabeculo-Descemet's membrane	1 (3)
Shallow dissection	1 (3)
Haemorrhage in bleb region	3 (9)
Conjunctival wound gape	2 (6)

the mean visual acuity was 0.29 (SD, 0.29). Sixteen eyes (48.5%) had immature senile cataract. Cataract progressed and required surgery in 4 eyes. Disc and field changes remained stable. The operative and postoperative complications are listed (Table 5).

Operative complications included 3 eyes (9%) with microperforations that did not require conversion to trabeculectomy — 2 (6%) had microperforation in the floor of Schlemm's canal and 1 (3%) had microperforation of the trabeculo-Descemet's membrane and shallow dissection of the trabeculo-Descemet's membrane, providing insufficient percolation of aqueous. Postoperatively, 2 eyes (6%) developed conjunctival wound gape 12 days after surgery without any evidence of aqueous leak and healed uneventfully. Three eyes (9%) had haemorrhage under the conjunctival flap from the first postoperative day that resolved completely in 2 weeks.

There was no significant difference in change in IOP (preoperative versus postoperative value) and ACD between patients with microperforation and those without microperforation. Two patients had IOPs <4 mm Hg on day 1; these patients had microperforation in Schlemm's canal.

None of the eyes had persistent hypotony, choroidal detachment, anterior chamber inflammation, thin large cystic bleb, bleb fibrosis, bleb-related endophthalmitis, hyphaema, iris incarceration, malignant glaucoma, scleral ectasia, and/or surgically-induced cataract. Four eyes (12%) that showed cataract progression underwent extracapsular cataract extraction with endocapsular posterior chamber intraocular lens implantation through corneal section 21 months after NPDS.

Discussion

Trabeculectomy was described by Sugar in 1961[8] and Cairns in 1968,[9] and remains the standard technique for glaucoma filtering surgery. Despite several modifications, it is still associated with many serious postoperative complications.[11,12] The quest for an effective, safe, and reproducible glaucoma filtering operation

has revived interest in various techniques of non-penetrating filtering surgery (NPFS), including sinusotomy,[2] deep sclerectomy,[3] ab externo trabeculectomy,[4-6,26,27] and viscocanalostomy.[7] Epstein[1] described paralimbal deep sclerectomy and Krasnov described sinusotomy,[2] both of which were performed without an overlying scleral flap as the opened Schlemm's canal was directly covered by conjunctiva. Although sinusotomy had minimal complications, the success rate was 50% to 83%.[2,28] In deep sclerectomy, first described by Fyodorov et al,[3] after raising a superficial scleral flap, a second deep scleral flap of 90% depth is dissected, and the corneoscleral trabeculae and the roof of Schlemm's canal are removed leaving a thin trabeculo-Descemet's membrane for outflow of aqueous. Fyodorov et al's deep sclerectomy was not exactly non-penetrating as they had also performed a basal iridectomy.[3] Kozlov et al[17] and Fyodorov[13] described the use of a collagen drainage device within the scleral bed at the end of deep sclerectomy. Further modifications to improve the success of NPFS include the use of high viscosity hyaluronic acid,[7] reticulated hyaluronic acid implant,[18] 5-FU,[19-21] and MMC.[16,22-24] The non-penetrating filtering technique used in this study consisted of a rectangular superficial scleral flap, intraoperative MMC 0.02% application, and rectangular deep scleral flap with deroofing of Schlemm's canal. NPDS was done as a first-line treatment, as all patients had newly diagnosed POAG. Moreover, no patient had medically uncontrolled glaucoma or was receiving maximal medical therapy. The indications for NPDS in most of the studies were uncontrolled glaucoma with maximal medical therapy, drug intolerance, or advanced glaucomatous disc damage.[16,22,29] Indications for primary surgery for the patients in this study included anticipated poor compliance, inability to attend for regular follow-up, poor financial resources, and low educational level. A low complication rate and encouraging short- and mid-term success rates for NPDS prompted these authors to perform primary NPDS. The complete success rate at the mean follow-up of 21.5 months was 96.96%. Low mean IOPs, in the range of 10 to 11 mm Hg were maintained for 6 to 21 months postoperatively. A target pressure of 10 to 11 mm Hg may be considered sufficiently low, even for patients with advanced glaucomatous disc damage.[30]

Various studies of deep sclerectomy have reported a complete success rate of 44.5% to 92.3% without collagen implant,[16,24,31-34] and 44.6% to 89% with collagen implant.[14,21,29] NPDS, as performed by Chiselita,[31] Massy et al,[32] and El Sayyad et al,[34] had success rates of 44.5% , 81.0%, and 92.3%, respectively. These 3 studies used a success criteria of IOP <21 mm Hg. Kozlov et al reported a success rate of 85%, although no details of the criteria for success or follow-up were provided.[17] Other authors reported the short- and medium-term success for deep sclerectomy with collagen implant to be good: Demaily et al[14] reported a complete success rate of 89% at 6 months and 75.6% at 16 months, and Welsh et al[29] reported success rates of 87.5% at 6 to 12 months. Sanchez et al[15] showed similar success rates after deep sclerectomy with or without collagen implant; better surgical outcome was achieved in terms of decreased bleb fibrosis, lower need for postoperative antiglaucoma medication, and increased success rate when a collagen implant was used.[15] However, in a non-randomised comparative study of deep sclerectomy with or without collagen implant, Demaily et al found no significant difference between the 2 groups.[14] Intraoperative use of 5-FU in deep sclerectomy has been found to be safe and effective, and use of a collagen implant does not lead to better IOP control. Demaily et al reported a complete success rate of 90% at 12 months in the 5-FU group and 58% in the group receiving deep sclerectomy with collagen implant.[14] Hamard et al reported comparable mean postoperative IOPs for patients receiving 5-FU or collagen implants.[20]

In this study, no collagen implant was used. Instead, MMC 0.02% solution was applied over the scleral bed and under the superficial scleral flap prior to dissecting the deep sclerectomy flap. Contact of MMC with the conjunctival flap was avoided to limit formation of avascular blebs as in Dahan and Drusedau's study.[16] Intraoperative MMC was used to achieve better surgical outcome by preventing postoperative scleral fibrosis. Short duration of MMC application (1 minute) and its application before dissection of the deep scleral flap was done to avoid intraocular penetration of MMC, if any, through the thin trabeculo-Descemet's membrane and Schlemm's canal. The use of MMC was simple and inexpensive compared with an expensive collagen implant. MMC has been used to improve the surgical outcome of conventional filtering surgery in patients with high-risk factors such as young age, black race, and previous surgical procedures. Recently, MMC has been used in deep sclerectomy in previously operated eyes. Dahan and Drusedau applied MMC 0.5% solution with a 27 G cannula for 1 minute under the scleral flap in the deep sclerectomy area just before Schlemm's canal was reopened in 28 failed NPFS patients.[16] Postoperatively all eyes had an IOP <21 mm Hg. Yamin and Quentin performed deep sclerectomy with MMC 0.1 mg/mL solution application for 2 minutes on the sclera in 12 previously operated eyes.[24] Seven eyes (58%) needed antiglaucoma treatment. Nakaizumi et al have used MMC 0.4% for 3 minutes with sinusotomy in patients with advanced glaucomatous damage, and obtained IOPs of 11 to 13 mm Hg up to 18 months postoperatively.[22] Kozobolis et al have reported a case of haemorrhagic Descemet's membrane detachment following deep sclerectomy with MMC 0.3 mg/mL under the conjunctival flap for 2.5 minutes.[23]

In this study, MMC was used for primary NPDS. To the best of the authors' knowledge this is the first report of primary NPDS with intraoperative MMC application for POAG. Major factors contributing towards the highly successful results in this study include primary NPDS, intraoperative use of MMC, and absence of high-risk factors such as young age, black race, and previous surgical procedures.[30] The operative and postoperative complications were infrequent in this series. The main intraoperative complications were microperforations of the floor of Schlemm's canal and trabeculo-Descemet's membrane, and shallow dissection of deep scleral flap (9%). The eyes with microperforation had good blebs without any overfiltration or shallowing of the anterior chamber. Perforation of trabeculo-Descemet's membrane is common in the learning phase of NPDS and the incidence decreases with increased surgical experience.[17] The eye with shallow dissection of the deep scleral flap had a flat bleb with IOP >21 mm Hg. Due to shallow dissection of the deep scleral flap, the corneoscleral trabeculae and roof of Schlemm's canal remain in situ leading to insufficient aqueous percolation. Shallow dissection of the deep scleral flap appears to be the major cause of failure of NPDS. These authors suggest that it would be better to err on the side of microperforation rather than shallow dissection in NPDS.

The postoperative complications were haemorrhage in the bleb region (9%) and conjunctival wound gape (6%). Although it is difficult to pinpoint the exact aetiology of haemorrhage, it could be secondary bleeding from the vessels of the conjunctival flap, episclera, newly formed scleral bed, or reflux from deroofed Schlemm's canal. The haemorrhage resolved without any adverse effects on the bleb. Conjunctival wound gape without aqueous leak occurred 12 days postoperatively and healed uneventfully. Despite the use of MMC, none of the eyes showed postoperative worsening of visual acuity, corneal erosions, conjunctival leaks, shallow anterior chamber, choroidal detachment, persistent hypotony, surgically induced cataract, overfiltration, large cystic thin walled bleb, scleral thinning, anterior uveitis, or endophthalmitis.

This study indicates that NPDS with intraoperative MMC application for patients with newly diagnosed POAG provides a complete success rate of 96.96% at 21 months. Two main factors are likely to have contributed to the high success rate: sufficiently low mean IOP and absence of bleb fibrosis. The absence of late postoperative IOP elevation appears to be due to the primary nature of the procedure and the intraoperative use of MMC. The operative and postoperative complication rate was low and no potentially sight-threatening complications were encountered despite use of MMC.

Primary NPDS with intraoperative application of MMC appears to be a safe and effective procedure for POAG without any risk of potentially vision-threatening complications. Considering the minimal complications, encouraging success rate, and reasonably low postoperative IOPs this procedure may be offered as first-line treatment for POAG.

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Endonasal Dacryocystorhinostomy — an Australian Perspective

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Aim: *To evaluate the outcome of 100 primary endonasal dacryocystorhinostomy operations.*
Methods: *A retrospective study was conducted at 3 hospitals in Sydney, Australia, by reviewing patients' medical records. Ninety eight patients with epiphora or chronic dacryocystitis underwent endonasal dacryocystorhinostomy between 2001 and 2005. Two patients had bilateral surgery. The mean age of the patients was 62 years. Mean follow-up was 13 months.*
Results: *The overall success rate was 91% (objective and subjective criteria) or 95% (objective criteria). Complications included epistaxis, surgical emphysema, and formation of fibrous adhesions. Early silicone tube dislodgement occurred in 7 patients, but all of these had successful outcomes.*
Conclusion: *Similar to the traditional external approach, endonasal dacryocystorhinostomy was found to be a safe operation with a high success rate.*

Key words: *Dacryocystitis, Dacryocystorhinostomy, Lacrimal apparatus diseases, Lacrimal duct obstruction*

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Introduction

Chronic obstruction of the lacrimal drainage system manifests itself by means of epiphora, inflammation, or infection (dacryocystitis). External dacryocystorhinostomy (EX-DCR) was first introduced by Toti in 1904.[1] The procedure has been modified over the years, but remains the gold standard for the treatment of nasolacrimal duct obstruction. Although the endonasal approach was introduced in 1893 before EX-DCR,[2] there were difficulties in visualising the operation site. With the development and refinement of nas-endoscopy, endonasal dacryocystorhinostomy (EN-DCR) has become an alternative to the traditional EX-DCR. In 1988, Rice reported a cadaver study demonstrating the feasibility of EN-DCR[3] and the first clinical study of EN-DCR was published in 1989.[4]

The principle of DCR is to create a functioning conduit from the lacrimal sac to the lateral wall of the nose. For many years EX-DCR has been shown to be a more successful procedure than EN-DCR with success rates of 85% to 95% and 68% to 85%, respectively,[5] but due to limitations and variations in study design it has been difficult to make evidence-based determinations regarding the relative efficacy of these methods. Only 1 randomised controlled trial has been conducted comparing the 2 methods and the results favoured EX-DCR.[6,7]

EN-DCR offers many potential advantages over the traditional external approach. The advantages cited include avoidance of a cutaneous incision and scar, less disruption of the medial canthal anatomy and lacrimal pump function, decreased intraoperative haemorrhage, quicker recovery from surgery, and the ability to address nasal and/or paranasal sinus pathology during the operation.[7,8]

Complications of EN-DCR include bleeding from the nasal mucosa, ethmoid air cells, or nutrient vessels of the anterior lacrimal crest.[9] Potential disadvantages include the difficulty of detecting nasolacrimal sac or duct pathology, difficulty in dealing with canalicular pathology, the cost of instrumentation, and the need for meticulous haemostasis essential for endoscopic visibility.

Most failures in DCR relate to 2 main factors.[10] Firstly, there are anatomical failures, in which the surgeon is unable to create an adequate ostium. The second cause relates to scarring, where granulation tissue may grow over the surgical ostium. Studies have attempted to decrease this early fibroblastic response by the intraoperative application of mitomycin C.[11,12] Other reasons for

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The data in this study has been presented at the 38th Annual Scientific Congress of The Royal Australian and New Zealand College of Ophthalmologists in November 2006.

failure include preoperative misdiagnosis, inadequate haemostasis, inadequate resection of the nasal mucosa, granulation tissue formation around the silicone tubes, synechiae between the lateral nasal wall and the middle turbinate, and an atonic or fibrotic lacrimal sac.[13] It is thought that the fewer failures reported with EX-DCR relate to this procedure being technically easier, with an unimpaired view in a larger working space.

The aim of this study was to evaluate and report the success rate of EN-DCR in 98 patients (100 procedures) who presented with epiphora or dacryocystitis.

Methods

Medical records of patients who underwent EN-DCR between 2001 and 2005 were reviewed. Data were collected for 100 eyes of 98 patients. Two patients had bilateral symptoms and underwent bilateral primary EN-DCR. The study included all the EN-DCR procedures that were performed by 1 ophthalmologist and 1 otorhinolaryngologist at 1 of 3 hospitals in Sydney, Australia. During this time, the 2 surgeons performed many more EN-DCR operations, but not necessarily as co-surgeons, or not at 1 of the 3 hospitals. No patients were excluded from the study. Ethics approval to collect patient data was granted by the Hospital Ethics Committees at all hospitals.

All patients underwent a complete ophthalmic and ear, nose, and throat (ENT) examination prior to surgery. All the DCRs were performed using the following standardised technique. The operation was performed under general anaesthesia. A topical decongestant (200 mg cocaine) was applied to the nasal cavity via neuropathies. The lateral nasal wall was infiltrated with 2 to 3 mL of 1% lidocaine and 1:100 000 epinephrine. No local anaesthetic was injected transcutaneously. The operation was performed using Wormald's technique.[14] The entire procedure was performed endoscopically using a 30° angled 4-mm rigid endoscope. The bone overlying the lacrimal sac was removed using a combination of Kerrison rongeurs, Hajek Koeffler punches, and a Xomed Medtronic 2.9 mm coarse diamond burr drill to uncover the body of the lacrimal sac. The sac was then opened with the use of a sickle knife and an 'H-shaped' incision was made into the sac creating a large anterior flap and a smaller posterior flap. The raised mucosal flaps were then trimmed to approximate with the cut edges of the exposed sac (in an attempt to marsupialise the sac). The flaps were lifted with a Priya periosteal elevator attached to suction. This elevator was then used to out-fracture the thin lacrimal bone. Bone was then removed sequentially by rongeurs and punches as required. Once the bony ostium was created, the nasal mucosa was replaced after a 'U-shaped' excision of mucosal tissue by a ThruCut instrument was made. One portion of the nasal mucosa was placed over the posterior lacrimal sac flap and one portion was placed over the anterior flap. Irrigation through both the superior and inferior canaliculi was assessed and an O'Donoghue silicone tube was placed in the newly created ostium and was fixed with 2 square knots.

Patients were instructed not to blow their nose during the first week after surgery. Postoperative care included chloramphenicol/prednisolone 0.1% eye drops, oral cephalexin 250 mg 4 times daily, saline and/or steroid nasal spray, and lacrimal irrigation. The average follow-up time was 13 months (range, 6 months to 3 years).

The data that was collected by reviewing patients' medical records included date of operation, age, sex, preoperative symptoms, primary or revision procedure, affected side, septoplasty, intraoperative findings, date of discharge from hospital, date of silicone tube removal, complications, repeat procedures, results of lacrimal irrigation and fluorescein testing, and subjective improvement or absence of epiphora.

Success was defined as patency of the lacrimal drainage system using the functional endoscopic dye test[15] whereby fluorescein was applied to the conjunctival fornix during postoperative endoscopy and dye was visualised at the osteotomy sight in a patent system (objective criterion) [Figure 1], accompanied by the subjective relief of symptoms as described by the patient at the time of their last visit — that is, reporting a significant decrease in or absence of epiphora or dacryocystitis and satisfaction with the procedure

Figure 1. View through the nasal endoscope of the opening of the nasolacrimal duct of a 37-year-old woman who presented with right-sided epiphora and underwent right endonasal dacryocystorhinostomy. Photograph taken with endoscopic-mounted blue filter 6 weeks after removal of an O'Donoghue silicone tube and instillation of 2% fluorescein. Photograph reproduced courtesy of R Chalasani and R Ghabrial of the Lacrimal Clinic, Concord Hospital, Australia.

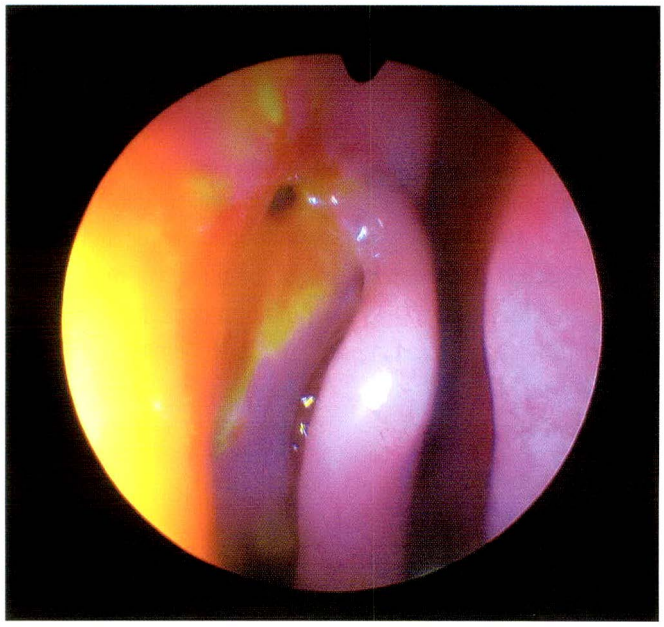

Table 1. Dacryocystorhinostomies and success rates from 2001 to 2005.

Year	Number of procedures	Successful procedures Number (%)
2001	14	13 (93)
2002	18	17 (94)
2003	31	26 (84)
2004	35	33 (94)
2005	2	2 (100)
Total	100	91

(subjective criterion). For the procedure to be recorded as successful, both the objective (endoscopic dye test) and subjective measures needed to be satisfied.

Results

Sixty five women and 33 men were recruited into the study. The patients' ages ranged from 8 to 87 years with a mean of 62 years. The reason for DCR surgery was epiphora (n = 93) or chronic dacryocystitis (n = 7). Septoplasty was performed by the otorhinolaryngologist during the procedure in 8 patients and 1 patient had previously undergone a septoplasty prior to the operation. Of the 98 patients who had the procedure, 92 went home the same day and the remaining 6 were all discharged the following day. Patients who remained in hospital overnight usually had their procedure performed late in the day or resided a long distance from the hospital. Two of the 6 patients stayed in hospital overnight as their operation was converted to EX-DCR (1 patient had distal canalicular pathology not accessible by nasendoscopy and the other patient had multiple stones in the lacrimal sac — both patients underwent successful external procedures) and 1 patient who stayed overnight had epistaxis. Silicone tubes were removed, on average, 6.45 weeks after the procedure (range, 1 to 22 weeks).

Of the 100 eyes that underwent EN-DCR, 91 operations (91%) were successful based on satisfying both criteria (lacrimal irrigation/fluorescein testing and significant reduction or absence of epiphora). However, 95% of patients satisfied the lacrimal irrigation and fluorescein testing, although 4 of these patients complained of epiphora. There were no patients who reported subjective improvement but failed fluorescein testing. The number of procedures and success rates from 2001 to 2005 are shown in Table 1.

Of the 9 patients for whom DCR failed, 6 had no intraoperative or postoperative complications. Intraoperative haemorrhage occurred in 2 patients whose procedures failed but haemostasis was rapidly achieved and both patients went home on the day of surgery. The details of the 9 patients considered to have failed treatment are summarised in Table 2.

No patients had serious complications such as periorbital oedema, orbital injury, thermal injury, or cerebrospinal fluid leakage, all of which have been reported in the literature.[9] There were also no episodes of diplopia, blindness, or soft tissue infection. One patient who had recurrent dacryocystitis was found intraoperatively to have had a previous nasal septal fracture but was not excluded from the study. Two other patients in the study also had facial fractures, but both patients underwent successful procedures. Postoperative complications amongst patients who underwent successful EN-DCR included epistaxis in 6 patients (defined as the passage of clots greater than spotting after leaving the recovery room), surgical emphysema in 1 patient, formation of fibrous tissue adhesions in 4 patients, and a low-grade fever overnight in 1 patient.

Discussion

The introduction of EN-DCR in the early 1990s provided hope for changing dacryocystorhinostomy into an elegant and minimally invasive procedure. However, lacrimal surgeons still regard EX-DCR as the gold standard due to the very high reported surgical success rates of between 85% to 95%.[5]

With the advent of improved technology and surgical skill in endoscopic nasal and paranasal sinus surgery, EN-DCR has become an accepted technique for the management of nasolacrimal duct obstruction.[16-19] The procedure is increasingly being performed by ophthalmic and ENT surgeons and, in many lacrimal clinics, is the preferred method of surgery. In this series, the most notable benefit was the quicker recovery and return to daily activities (in part due to decreased periorbital bruising and swelling), which has both social and economic implications.

Table 2. Complications of endonasal dacryocystorhinostomy.

Patient number	Complications	Date of surgery
1	Converted to external dacryocystorhinostomy	November 2001
2	Converted to external dacryocystorhinostomy	September 2002
3	Postoperative haemorrhage, recurrent epiphora and dacryocystitis	March 2003
4	Recurrent epiphora	April 2003
5	Recurrent epiphora	June 2003
6	Minor haemorrhage postoperatively and recurrent epiphora	June 2003
7	Recurrent dacryocystitis	November 2003
8	Recurrent epiphora	May 2004
9	Recurrent epiphora	May 2004

In this study, surgery was successful in 91% of patients undergoing primary EN-DCR overall. By only considering objective criteria (endoscopic dye test), surgery was successful in 95% of patients, but 4 patients with patent ostia and good irrigation still complained of epiphora and they were regarded as unsuccessful.

The success rate reported in this series is similar to that reported in other large published case series. Ben Simon et al recently reported success rates of 84% (86 patients) for EN-DCR and 70% (90 patients) for EX-DCR.[15] Dolman reviewed 354 DCR operations — 153 external (EX-DCR) and 201 non-endoscopic endonasal (EN-DCR).[20] This author found success rates of 90.2% and 89.1%, respectively, with no statistical difference between the 2 groups. Interestingly, 5 patients had bilateral procedures with alternative techniques performed on opposite sides, and all 5 patients reported retrospectively that they preferred the endonasal approach.

While complications can occur with EX-DCR (e.g., intraoperative or postoperative bleeding, poor wound healing, and infection at the incision site[19]), the current literature suggests that EX-DCR should remain the preferred procedure in certain circumstances. The procedure is indicated if a lacrimal sac tumour is suspected, if medial canthal repositioning is required after trauma, or if bone removal is not possible during attempted EN-DCR.[20,21]

There is a difference of opinion as to whether silicone tubes should be used in DCR surgery. It is thought that intubation may help increase the patency of the new rhinostomy[22] and thus all of the 98 patients in this study were intubated. However, silicone may cause peripunctal granulation and chronic infection and therefore some lacrimal surgeons warn against its use.[23,24] In this study, silicone tubes dislodged early in 7 of the 100 operations (mean time of dislodgement was 18 days), but all of these were successful procedures. It is thought that a possible cause of early tube dislodgement may be eye-rubbing after the operation and patients need to be warned against this. Tubes were not replaced in these patients.

It has been suggested that the success rate of EN-DCR is influenced by the extent of lacrimal sac exposure during the procedure and the size of the newly created bony ostium.[7,14] This may be an explanation for the high success rate in this case series, as the entire body of the lacrimal sac was exposed. Mucosal flaps were then created to approximate with the cut edges of the exposed sac in order to prevent cicatrisation and ostial closure. The technique described by Wormald[14] creates the largest possible bony ostium to increase patency rates. Tsirbas and Wormald also reported a high success rate using the same method of lacrimal sac exposure.[25] These authors report a 95% anatomic success rate (defined as anatomical patency with fluorescein flow on nasendoscopy and patency to lacrimal syringing) and an overall success rate of 89% (includes subjective symptom relief).

This study has limitations in that it is a retrospective case series reporting the success rate of EN-DCR. To reliably measure whether this procedure is as successful as the gold standard, definitions of success and failure need to be standardised, and more randomised controlled trials comparing the 2 procedures need to be undertaken.

The success rate in this case series was similar to other high success rates achieved with EN-DCR, and also comparable to quoted success rates of EX-DCR. Inspection of the intranasal anatomy and direct access to the rhinostomy site are major advantages of EN-DCR. If it is established that the 2 procedures have equal success rates for primary surgery, then patient preference, surgeon preference, and availability of instrumentation will become important determining factors. Studies also need to establish which patients would benefit more from EN-DCR than EX-DCR as there will remain a significant number of patients for whom EX-DCR is preferable.

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Eyelid and Conjunctival Bacterial Flora and Antibiotic Resistance Patterns of Acne Rosacea with Ocular Involvement

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Aim: *To investigate the eyelid and conjunctival bacterial flora and antibiotic resistance patterns of ocular signs of acne rosacea.*
Methods: *Eighty randomly selected patients with acne rosacea underwent routine ophthalmic examination for ocular signs of rosacea. Samples from the eyelid and conjunctiva were obtained from all patients with acne rosacea with ocular signs and cultured aerobically. Bacterial isolates were identified and tested for antibiotic susceptibility.*
Results: *Fifty patients (62.5%) had ocular involvement, of whom 31 (62.0%) had coagulase-negative* Staphylococcus, *8 (16.0%) had no growth, 8 (16.0%) had* Staphylococcus aureus, *and 3 (6.0%) had* Streptococcus pneumoniae. *Of the coagulase-negative* Staphylococcus, *12.9% showed nodrug resistance. Among the drug-resistant coagulase-negative* Staphylococcus, *77.7% were resistant to bacitracin, 66.6% were resistant to polymyxin, 7.4% were resistant to tobramycin and gentamicin, and 14.8% were resistant to chloramphenicol, ofloxacin, ciprofloxacin, or norfloxacin; 59.2% were multi-drug resistant. Among* S aureus, *and 62.5% were resistant to bacitracin, 100% were resistant to polymyxin, and 12.5% were resistant to gentamicin and tobramycin; and 62.5% were multi-drug resistant. Among* S pneumoniae, *100% were resistant to polymyxin.*
Conclusions: *Coagulase-negative* Staphylococcus *was the most commonly isolated bacterium followed by* S aureus. *The high rate of bacitracin resistance and multi-drug resistance of coagulase-negative* Staphylococcus *and* S aureus *might adversely affect treatment of ocular rosacea.*

Key words: *Drug resistance, Rosacea*

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Introduction

Acne rosacea is a chronic inflammatory disease of unknown aetiology involving the skin and the eyes.[1,2] The most common ocular problems associated with acne rosacea are lid disease–related manifestations, including meibomian gland dysfunction, telangiectasis, and anterior blepharitis.[3] Less frequent ocular manifestations include chronic cicatrising conjunctivitis, marginal corneal infiltrates, corneal neovascularisation, thinning, ulceration or perforation, and episcleritis or scleritis.[4,5] Patients with blepharitis are more likely to have normal ocular flora but in greater quantities than patients without blepharitis.[6] Antibiotic susceptibility patterns of ocular flora have been reported to show variations in chronic inflammatory conditions.[7] The purpose of this study was to investigate the ocular bacterial flora and antibiotic resistance patterns of ocular involvement of acne rosacea.

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Methods

Patients with acne rosacea selected randomly by a dermatologist at the Community Health Care Center, Ankara, Turkey, were referred to the ophthalmology outpatient clinic to test for ocular signs of acne rosacea. The patients had not received any topical or systemic treatment for acne rosacea. All patients underwent routine ophthalmic examination including best-corrected visual acuity, intraocular pressure measurement, biomicroscopy, and fundus examination. Patients with acne rosacea were diagnosed as having ocular involvement on the basis of ocular signs,

including lid disease–related manifestations such as meibomian gland dysfunction, telangiectasis and anterior blepharitis, chronic cicatricial conjunctivitis, marginal corneal infiltrates, corneal neovascularisation, thinning, ulceration or perforation, or episcleritis or scleritis.

Eyelid and conjunctival samples were obtained at the initial visit. The swabs were inoculated on blood agar and MacConkey agar plates and incubated at 37°C aerobically for 18 to 24 hours. Following incubation, the identification of each isolate was done by API (bioMërieux, Marcy-l'Etoile, France) and tested for antimicrobial susceptibility according to the methods established by CLSI (formerly NCCLS). Bacitracin, polymyxin, tobramycin, gentamicin, chloramphenicol, ofloxacin, ciprofloxacin, and norfloxacin were used for antimicrobial susceptibility tests.

Results

Ocular involvement was found in 50 of the 80 patients with acne rosacea (62.5%). Meibomian gland dysfunction, telangiectasis, and anterior blepharitis were among the most common ocular signs detected. Less frequent ocular manifestations were marginal corneal infiltrates, corneal neovascularisation, thinning, and episcleritis.

The bacteria isolated and the number of patients with the bacteria are summarised in Table 1. The most common bacterium was coagulase-negative *Staphylococcus* (CNS), isolated from 31 patients (62.0%). *Staphylococcus aureus* was the second most common bacterium, isolated from 8 patients (16.0%). Eight patients (16.0%) had no growth. *Streptococcus pneumoniae* was the least common bacterium, found in 3 patients (6.0%).

Table 1. Bacterial isolates from eyelid and conjunctiva cultures of acne rosacea patients with ocular manifestations.

Bacterial isolate	Bacterial isolates (n = 50) Number (%)
Coagulase-negative *Staphylococcus*	31 (62)
Staphylococcus aureus	8 (16)
Streptococcus pneumoniae	3 (6)
No growth	8 (16)

Antibiotic resistance patterns of the isolated bacteria are summarised in Table 2. Four of the 31 CNS cultures (12.9%) showed no drug resistance. Among the 27 drug-resistant CNS culture samples, 21 (77.8%) were resistant to bacitracin, 18 (66.7%) were resistant to polymyxin, 2 (7.4%) were resistant to tobramycin, 2 (7.4%) were resistant to gentamicin, 1 (3.7%) was resistant to chloramphenicol, 1 (3.7%) was resistant to ofloxacin, 1 (3.7%) was resistant to ciprofloxacin, and 1 (3.7%) was resistant to norfloxacin. All 8 *S aureus* cultures (100%) were resistant to polymyxin, 5 (62.5%) were resistant to bacitracin, 1 (12.5%) was resistant to gentamicin, and 1 (12.5%) was resistant to tobramycin. All 3 *S pneumoniae* cultures (100%) were resistant to polymyxin.

Multi-drug resistance was detected for 16 of the 27 CNS cultures (59.2%) and 5 of the 8 *S aureus* cultures (62.5%). Multi-drug resistance was not detected for *S pneumoniae*. Overall, polymyxin resistance was the most common drug resistance, detected in 29 of the 42 culture-positive samples (69.0%), followed by resistance to bacitracin in 26 samples (61.9%), gentamicin and tobramycin each in 3 samples (7.1%), ofloxacin and norfloxacin each in 2 samples (4.8%), and ciprofloxacin and chloramphenicol each in 1 sample (2.4%).

Discussion

The estimated prevalence of ocular findings in patients with acne rosacea has been reported to be 6% to >50% in different populations.[8,9] The prevalence of ocular involvement in this study was 62.5%, compatible with the previous studies.

The most frequent ocular finding was lid disease–related manifestations, followed by marginal corneal infiltrates, corneal neovascularisation, thinning, and episcleritis. These findings are comparable with the ocular manifestations shown by previous studies.[3-5]

The ocular flora of healthy people is mostly composed of CNS followed by *S aureus*, *Corynebacterium* sp, and *Propionibacterium acne*.[10-12] The most commonly isolated bacteria from eyelid and conjunctival cultures of patients with acne rosacea, with or without

Table 2. Antibiotic resistance patterns of coagulase-negative *Staphylococcus*, *Staphylococcus aureus*, and *Streptococcus pneumoniae*.

Antibiotic	Coagulase-negative *Staphylococcus* resistance (n = 27) Number (%)	*Staphylococcus aureus* resistance (n = 8) Number (%)	*Streptococcus pneumoniae* resistance (n = 3) Number (%)
Bacitracin	21 (77.8)	5 (62.5)	—
Polymyxin	18 (66.7)	8 (100)	3/3 (100)
Tobramycin	2 (7.4)	1 (12.5)	—
Gentamicin	2 (7.4)	1 (12.5)	—
Chloramphenicol	1 (3.7)	—	—
Ofloxacin	1 (3.7)	—	—
Ciprofloxacin	1 (3.7)	—	—
Norfloxacin	1 (3.7)	—	—
Multi-drug resistance	16 (59.2)	5 (62.5)	—

ocular involvement, or patients with chronic blepharitis are reported to be the normal ocular flora but in greater quantities than in healthy people.[6,13-15]

The aerobic cultures from the eyelid and conjunctiva of patients with ocular rosacea patients in this study revealed CNS as the most commonly isolated bacteria followed by *S aureus,* similar to previous studies. The least frequent culture finding in this study was *S pneumoniae,* which has not been reported before in the normal ocular flora, among eyelid and conjunctiva cultures of patients with acne rosacea, or among patients with chronic blepharitis. *S pneumoniae* has been reported to cause soft tissue infections in patients with connective tissue disorders such as systemic lupus erythematosus and Sjögren syndrome.[16] Acne rosacea has been considered a chronic inflammatory disease of unknown aetiology and immunopathological studies have revealed anticollagen and antinuclear antibodies against nuclei of cells in the epidermis and dermis.[2,17] Isolation of *S pneumoniae* from eyelid and conjunctiva cultures of patients with ocular rosacea in this study might indicate a possible association of *S pneumoniae* and acne rosacea.

Previous studies have shown that ocular flora are susceptible to ciprofloxacin, ofloxacin, and newer generation fluoroquinolones, as well as chloramphenicol and aminoglycosides, except neomycin.[18-20] This study also revealed high susceptibility rates for ciprofloxacin, ofloxacin, chloramphenicol, gentamicin, and tobramycin. Neomycin and polymyxin have been reported to be ineffective for the reduction of ocular bacterial flora.[21] This study also revealed high rates of polymyxin resistance of CNS, *S aureus,* and *S pneumoniae*. High rates of bacitracin resistance of ocular flora have not been reported before. However, this study revealed that bacitracin resistance was the second most common drug resistance after polymyxin. Bacitracin has been widely used for the treatment of ocular rosacea.[5,22] These authors consider the high rate of bacitracin resistance in this study to be a significant factor that could affect treatment of ocular rosacea. Multi-drug resistance for CNS has been reported in chronically inflamed conjunctiva, and it has been proposed that the risk for multi-drug resistant CNS was increased in patients with chronic inflammatory conditions.[7] Multi-drug resistant *S aureus* in chronic inflammatory eye disease has not been reported before. This study revealed multi-drug resistance for both CNS and *S aureus* in patients with ocular rosacea.[1,2]

In summary, CNS was the most commonly isolated bacterium, followed by *S aureus*, from the eyelid and conjunctiva cultures of patients with acne rosacea with ocular involvement. The high rates of bacitracin resistance and multi-drug resistance of CNS and *S aureus* revealed in this study might affect treatment of ocular rosacea.

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Effect of Patch Therapy on Visual Acuity of Patients with Anisometropic Amblyopia

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Aim: *To evaluate the effect of patch therapy on visual acuity of patients with anisometropic amblyopia.*
Methods: *Sixty six patients with anisometropic amblyopia were randomised to receive patch therapy or no therapy. Visual acuity of both eyes was tested for all patients. Based on the visual acuity in the amblyopic eye, patients were prescribed daily patching of the better eye with an ophthalmic shield for 3 to 6 hours. Visual acuity of both eyes was tested 3 and 6 months after starting patch therapy.*
Results: *There was a significant difference in the mean visual acuity of the treatment group at the start of patch therapy, and at 3 and 6 months after therapy. There was no significant difference in the mean visual acuity in the control group. There was a significant difference in the mean visual acuity between the treatment group and the control group 3 and 6 months after patch therapy. There was no significant difference in the mean visual acuity between the prescribed times of 2, 3 to 4, and 5 to 6 hours.*
Conclusions: *Patch therapy to the better eye can increase visual acuity for patients with amblyopia.*

Key words: *Amblyopia, Visual acuity*

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Introduction

Amblyopia is a reduced corrected visual acuity without evidence of organic eye disease. Amblyopia affects millions of people throughout the world, but is usually recognisable and treatable. The condition is the most common cause of uniocular visual impairment in children, adolescents, and adults. Amblyopia is typically associated with strabismus, and less commonly with strabismus, anisometropia, and/or both.[1-3]

Although the cause of amblyogenesis is not completely understood, most ophthalmologists advise treatment as early as possible. Treatment includes occlusion therapy (patching of the sound eye), cycloplegic drugs such as atropine sulfate, optical correction glasses, contact lenses, or combination levodopa and carbidopa.[4-7]

The principle of therapy is that it can only be effective when the visual system is sufficiently plastic for cortical modification to occur. This stage of visual development is thought to end at the age of 7 years, although the theory of the plasticity of the visual system being confined to early childhood is increasingly being challenged.

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A study has found that central vision loss in the better eye improves visual acuity in the amblyopic eye.[8] Research has also shown that retinal detachment and age-related macular degeneration in the better eye can improve visual acuity of an amblyopic eye in adults.[9] The observation that trauma or disease affecting the better eye may result in spontaneous improvement of the eye with amblyopia suggests that residual neural plasticity continues well beyond the accepted critical period.[10] This study was performed to evaluate the effect of patch therapy on visual acuity in adults with anisometropic amblyopia referred to the Sadri Clinic, Shahroud Faculty of Medical Sciences, Shahroud, Iran.

Methods

Sixty six patients with anisometropic amblyopia were randomised to receive patch therapy or no treatment (control group). The cause of amblyopia in these patients was refractive error due to myopia or hyperopia. The criterion for amblyopia was visual acuity ≥0.2 logMAR (logarithm of the minimum angle of resolution).

Prior to enrolment in the study, refractive errors were corrected (best corrected vision; BCV). Patients with strabismus were excluded. Visual acuity of both eyes was measured and, based on the visual acuity in the amblyopic eye, daily patching of the better eye with an ophthalmic shield was prescribed for 2 to 6 hours. Each patient in the treatment group underwent monthly follow-up

to assess the condition of the retina, assess the number of hours required for treatment, and monitor possible complications of treatment such as irritation. Visual acuity of both eyes in both groups was measured at the first visit, and at 3 and 6 months after the start of therapy. Statistical analysis was performed using the Statistical Package for the Social Sciences. A p value of <0.05 was considered to be statistically significant.

Patients who defaulted follow-up were excluded from the study. All follow-up visits and examinations were free of charge to encourage compliance.

Results

Patients were aged 9 to 35 years (mean, 16.6 years; SD, 5.9 years). There was a female predominance (60.6% vs 39.4%). There was a significant difference in the mean visual acuity of the treatment group between the start of treatment and 3 months after treatment, and between 3 months and 6 months after treatment. The mean improvement in visual acuity in the amblyopic eyes from baseline at 3 months was 0.20 logMAR and at 6 months was 0.32 logMAR. There was no significant difference in visual acuity between baseline, 3 months, and 6 months for the control group (Figure 1).

There was a significant difference in the mean visual acuity between the treatment and control groups 3 months and 6 months after the start of therapy. The visual acuity in the amblyopic eyes of the treatment group showed improvement of 0.11 logMAR after 3 months and 0.19 logMAR after 6 months. There were no significant differences in the mean visual acuity between the older and younger age groups (9 to 16 years and 17 to 35 years) in the treatment and control groups at all time points (Table 1).

Figure 1. Mean visual acuity at baseline, and 3 and 6 months after start of patch therapy.

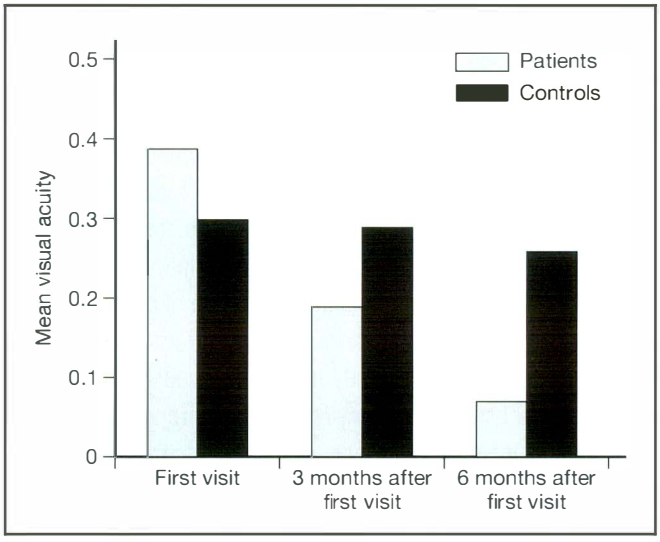
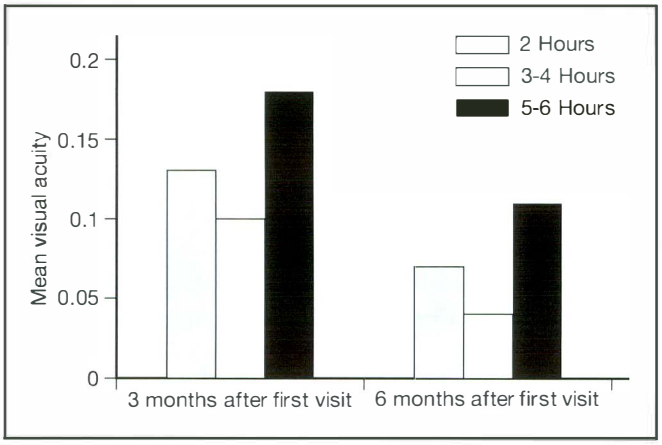


Table 1. Comparison of visual acuity at baseline, and 3 and 6 months after patch therapy by age group.

	Age group (years)			
	17-35		9-16	
	Control	Treatment	Control	Treatment
Baseline	0.28	0.34	0.32	0.43
3 months	0.28	0.15	0.32	0.22
6 months	0.27	0.05	0.27	0.09

Figure 2. Mean visual acuity after different treatment times.



There were no significant differences in the mean visual acuity between the different prescription times (2 hours, 3 to 4 hours, and 5 to 6 hours) [Figure 2].

Discussion

Although there are many studies of treatment of amblyopia in childhood by occlusion therapy, there are few studies of occlusion therapy for amblyopia in adults. The results of this study showed that occlusion therapy for 2 to 6 hours daily can improve visual acuity in the amblyopic eye by 0.20 logMAR after 3 months and by 0.32 logMAR after 6 months. Studies have shown that visual function can improve beyond the traditional critical periods for development in amblyopia and, with good patient compliance, age should not be a critical factor in the initiation of treatment for amblyopia.[11]

Scheiman et al studied the effectiveness of treatment of amblyopia in children aged 7 to 17 years at 49 clinical sites.[12] 507 patients with visual acuity ranging from 20/40 to 20/400 in the amblyopic eye were provided with optimal optical correction and then randomised to a treatment group (2 to 6 hours per day of patch therapy combined with near visual activities for all patients plus atropine sulfate for children aged 7 to 12 years) or optical correction alone. Patients whose amblyopic eye acuity improved by ≥10 letters (≥0.2 logMAR) by 24 weeks were considered responders. Among patients in the 7 to 12 years age group (n = 404),

53% of the treatment group were responders compared with 25% of the optical correction group ($p < 0.001$). In the 13 to 17 years age group ($n = 103$), the responder rates were 25% and 23% for the treatment and optical correction groups, respectively, but were 47% and 20%, respectively, among patients not previously treated for amblyopia.

Occlusive contact lenses can be used for treating amblyopia.[13] In the study by Eustis and Chamberlain of 25 patients aged 2.5 to 9.5 years, who were treated with an opaque hydrogel contact lens for amblyopia, 92% of patients improved by at least 1 line of visual acuity.[13] Eight patients improved ≥2 octaves and 12 patients improved ≥1 octave. Gianoli and Klainguti obtained similar results.[14] Mallah et al evaluated 465 patients with an established diagnosis of age-related macular degeneration to ascertain whether recovery of visual function in amblyopic eyes can occur when the sight in the fellow eye is lost.[15] These authors concluded that the mean improvement in distance and near acuity in amblyopic eyes was 3.3 and 1.9 lines, respectively, by 12 months. The improvement in acuity generally occurred between 1 and 12 months from baseline and remained stable over the follow-up period.

Beck et al compared patch therapy for 6 to 8 hours daily with atropine for moderate amblyopia in 419 children younger than 7 years.[16] Visual acuity in the amblyopic eye improved in both groups; improvement from baseline at 6 months was 0.32 logMAR in the patch therapy group and 0.28 logMAR in the atropine group. Patients in the atropine group had reduced acuity in the better eye at 6 months. Repka et al[17] and Kushner[18] found similar results in their randomised multicentre trials of the effect of daily patch therapy on the visual acuity of children younger than 7 years with moderate amblyopia.

It is well documented that non-compliance with occlusion therapy is a major factor leading to treatment failure. At the start of patch therapy, all patients were well informed about the treatment and it was well tolerated by most patients. Newsham reported that understanding of the treatment was significantly greater among parents given written educational material compared with parents who did not receive written information; compliance was significantly greater among the group given written instructions.[19] A large proportion of patients would benefit by increasing parental knowledge in key areas such as the critical development period, importance of occlusion, and potential negative consequences of not treating amblyopia.

The results of this study did not reveal a significant difference in the mean visual acuity between different treatment times (2 hours, 3 to 4 hours, and 5 to 6 hours). Repka et al, in a study of 189 children younger than 7 years with amblyopia, showed that the improvement in visual acuity of the amblyopic eye from baseline to 4 months averaged 0.24 in the treatment group, who received patch therapy for 2 hours daily, and in the control group, who received 6 hours of daily patch therapy.[20] Visual acuity improved from baseline by 0.3 or more for 62% of patients in each group. Therefore, patch therapy for 2 hours daily produces an improvement in visual acuity similar to that produced by patch therapy for 6 hours daily. There is no significant difference in compliance between patch therapy for 3 and 6 hours.[21] Although increasing the time beyond 2 hours hastened recovery of visual acuity, the outcome is not improved.[22,23]

The results obtained from this study show that occlusion therapy can produce substantial improvements in visual function in older patients with amblyopia, and age should not be a critical factor in the initiation of treatment. Prescribing 3 to 6 hours daily patch therapy can improve visual acuity in older patients, but it is necessary to evaluate whether visual acuity improvement in adults with amblyopia is sustained once treatment is discontinued.

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Occult Scleral Necrosis with Filtering Bleb as a Presenting Feature of Marfan's Syndrome

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Scleral thinning and scleral perforation have been reported in Marfan's syndrome, but they have essentially been frank perforations necessitating surgical repair. This report describes a patient presenting with paralimbic scleromalacia in which a bleb was seen without a frank perforation. The surgical treatment is described.

Key words: *Marfan syndrome, Sclera*

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Introduction

Up to 50% of patients with scleromalacia have evidence of an underlying systemic disease.[1] Scleromalacia is a rare disease, often seen in connective tissue disorders such as rheumatoid arthritis, Wegener's granulomatosis, polyarteritis nodosa, systemic lupus erythematosus, and relapsing polychondritis.[2] Although necrotising scleritis with or without inflammation can be a manifestation of a systemic vasculitic disease, scleral perforation in Marfan's syndrome can occur when the sclera is friable.

Scleral thinning and scleral perforation have been reported in Marfan's syndrome, but they have essentially been frank perforations necessitating surgical repair.[3-5] This report describes a patient presenting with paralimbic scleromalacia in which a bleb was seen without a frank perforation. The surgical treatment is described.

Case Report

A 14-year-old girl reported with a history of a small swelling in the left eye associated with congestion of the eye, lacrimation and diminution of vision for 1 month. She had a history of redness and mild pain in her right eye for 3 months 3 years previously, and was diagnosed with advanced glaucoma with band-shaped keratopathy in the right eye. She had had no prior surgical intervention in either eye. At systemic examination, she was found to have frontal bossing, a high arched palate, contractural arachnodactyly, dental anomalies, and a cardiac murmur (ejection systolic murmur with an aortic click). Echocardiography revealed a dilation of the root of the aortic trunk.

At ophthalmic evaluation, her best-corrected visual acuity was finger counting close to the face (-8.0 D) in the right eye and 6/18 (-12 D) in the left eye. The right eye had a shallow anterior chamber, band-shaped keratopathy, and a right divergent squint. The lens and fundus details could not be determined. The left eye had mild conjunctival congestion at presentation, which increased by the fourth day. Anterior segment evaluation of her left eye showed a clear cornea with a shallow anterior chamber. Pupillary reaction in both eyes was sluggish. A cystic swelling was noted at the 9 o'clock position near the limbus in the left eye, which increased in size by the fourth day (Figure 1). Uveal tissue could be seen through the overlying conjunctiva. The anterior chamber was shallow and there was gross hypotony in the left eye (2 mm Hg with applanation tonometry). On pupillary dilation, superonasal subluxation of the clear spherophakic lens was noted. Fundus evaluation showed a cup-disc ratio of 0.6 with a healthy neuroretinal rim. There was no evidence of retinal or choroidal detachment. Her axial lengths were 22.3 mm in the right eye and 21.8 mm in the left eye.

Laboratory investigations of total leukocyte count, differential leukocyte count, peripheral blood smear, serum electrolytes, and renal biochemical parameters were normal. Urinary sodium nitroprusside test was negative. Paediatric consultation confirmed the diagnosis of Marfan's Syndrome. The patient was given topical ciprofloxacin 4 times a day for 7 days and ibuprofen twice a day for 5 days. By the fourth day, the size of the bleb had increased and there was further shallowing of the anterior chamber and peripheral iridocorneal touch.

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Figure 1. Anterior segment photograph showing a cystic bleb at the nasal limbus.

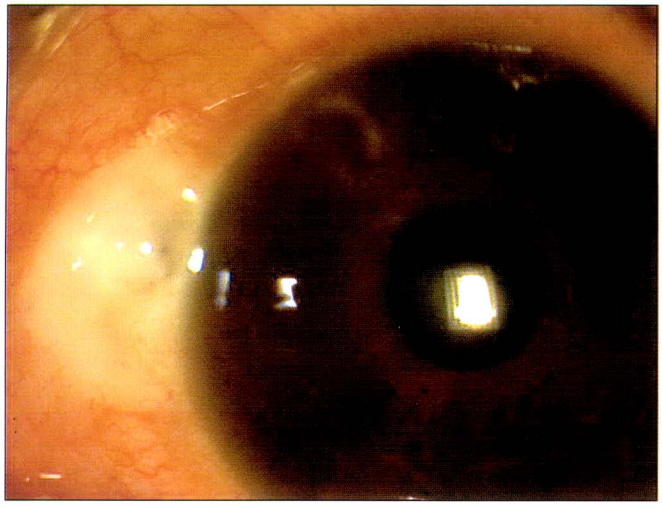
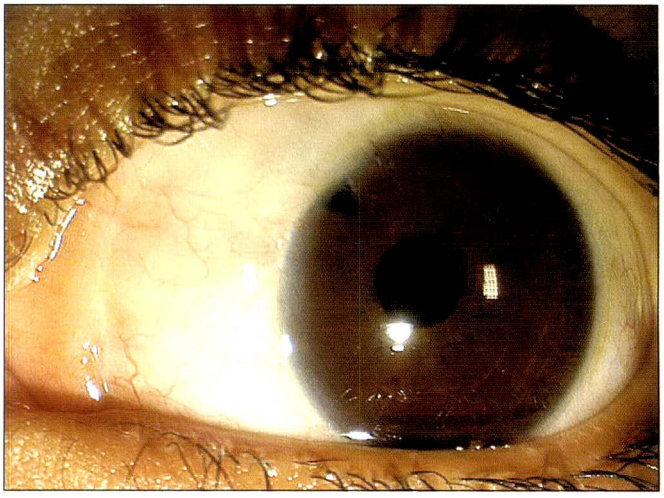


Figure 2. Postoperative (month 2) anterior segment photograph.



The patient was given topical steroids and underwent a superior site anterior route lensectomy with vitrectomy in her left eye. Her postoperative visual acuity was 6/18 with + 9 D. Her cornea was clear and the anterior chamber depth was 3 mm (Figure 2). After 2 months, the visual acuity was maintained at 6/18 and the intraocular pressure in her left eye was 18 mm Hg. The cystic bleb was flattened and there was no conjunctival congestion.

Discussion

This was a rare case of Marfan's syndrome presenting with a shallow anterior chamber due to possible microleaks from the necrosed corneolimbal junction secondary to scleromalacia. The microleaks resulted in a cystic bleb formation at the limbus in the patient's left eye resulting in hypotony. This patient had a rare form of systemic Marfan's syndrome, characterised by contractural arachnodactyly, ectopia lentis, and dilation of the base of the aorta. Besides Marfan's syndrome, the diagnoses of Loeys-Dietz syndrome and Shprintzen-Goldberg syndrome were also considered. However, typical clinical features of exophthalmos, hypertelorism, bifid uvula, cleft palate, mental retardation, and maxillary and mandibular hypoplasia were not seen in this patient. Since she had all 3 features of a severe Marfan's triad comprising long thin extremities with arachnodactyly, ectopia lentis, and aortic root dilation, a clinical diagnosis of Marfan's syndrome was made.

The decreased vision in her left eye was due to myopia caused by the anteriorly subluxated spherophakic lens. Surgical intervention was needed to extract the subluxated lens and to form the anterior chamber, which was done under cover of anti-inflammatory and antibiotic therapy. The microleaks also closed and hypotony subsided after treatment. This patient presented with paralimbic scleromalacia, which is characterised by a slowly progressive, non-inflammatory, painless scleral thinning at the limbus that can lead to spontaneous small perforations. Connective tissue disorders in Marfan's syndrome have been attributed to increased activity of matrix metalloproteinases, which also leads to functional insufficiency of zonules.[6] It is possible that the scleral necrosis in this patient was also a manifestation of the same pathogenesis.

To the best of the authors' knowledge, few patients with scleral perforation in Marfan's syndrome have been reported in the literature.[3-5] Rodriguez Ares et al described a patient who had undergone multiple surgeries, including trabeculectomy with mitomycin.[3] The scleral perforation occurred within 30 days of glaucoma surgery. Kontridze and Kvantaliani have described 3 patients with scleral perforation in Marfan's syndrome, which they repaired surgically.[4]

This report highlights that spontaneous occult scleral necrosis should be considered when evaluating a young patient with Marfan's syndrome. Eyes of patients with Marfan's syndrome should be examined for scleral necrosis. Given the rapidity of progression of the destructive process, early initiation of therapy is warranted.

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Refractory Grave's Ophthalmopathy — Is there a Role for Radiotherapy?

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Thyroid orbitopathy is a chronic sequela of systemic thyroid disease. Management is usually conservative, but symptoms may be refractory and radiotherapy may be useful. This report describes a patient with thyroid orbitopathy treated with radiotherapy.

Key words: *Graves ophthalmopathy, Hyperthyroidism, Radiotherapy*

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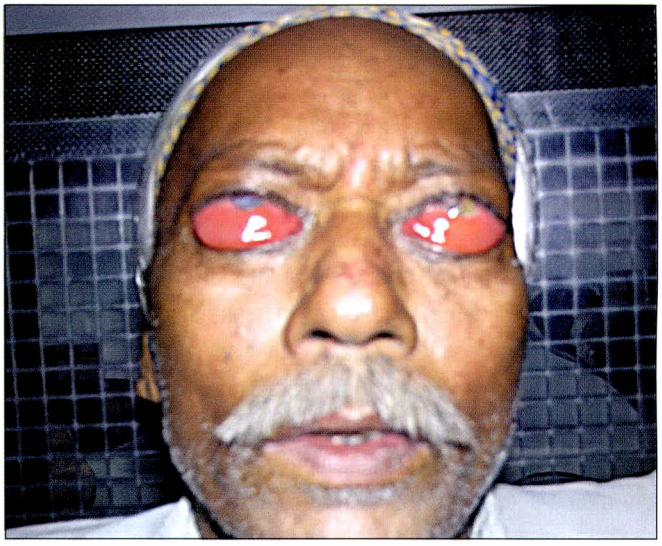
Introduction

Thyroid orbitopathy is a chronic sequela of systemic thyroid disease, where each patient experiences a unique combination of symptoms and signs for an unpredictable duration and with varying severity.[1] Conservative management with steroids can relieve this condition in nearly 50% of patients with moderately severe disease.[2] However, in a subset of patients the symptoms are refractory to conservative management. These patients can be managed with radiation but the exact role of radiotherapy in the curative management of thyroid orbitopathy is still not well defined with divergent results from various studies. This report describes a patient with thyroid orbitopathy treated with radiotherapy.

Case History

A 65-year-old man with hyperthyroidism presented to the outpatient department of a tertiary care hospital with a history of progressive bilateral proptosis, photophobia, excessive watering, and visual blurring for 1 year (Figure 1). He was taking regular antithyroid drugs and had been treated with long-acting steroids (methyl prednisolone) for 9 months, but had experienced no improvement in his symptoms despite regular medication. At ocular examination, both eyes were inflamed and proptosed with conjunctival chemosis. The corneas were hazy and blurred. Vision was reduced to light perception only. Computed tomography showed bilateral orbital proptosis with thickening of the extra orbital muscles (0.8 to 10 mm). The left optic nerve thickness was 13 mm and the right optic nerve thickness was 6 mm (Figure 2). In view of his painful and refractory symptoms, which were affecting his quality of life, external beam radiation to a dose of 20 Gy/5 fractions with 9 MeV electron beams was given (Figure 3). Following radiation therapy, the patient was referred for surgical decompression for progressive optic neuropathy. However, the patient refused to consent to the procedure. Three months post-radiotherapy, he was free of painful symptoms, although the proptosis persisted. There was objective diminution of conjunctival chemosis.

Figure 1. Bilateral orbital proptosis, corneal opacity, and diffuse conjunctival chemosis.



Discussion

Knowledge of the association between systemic thyroid disease and orbitopathy has evolved during the past few years, although the precise pathogenesis remains uncertain. It is hypothesised that

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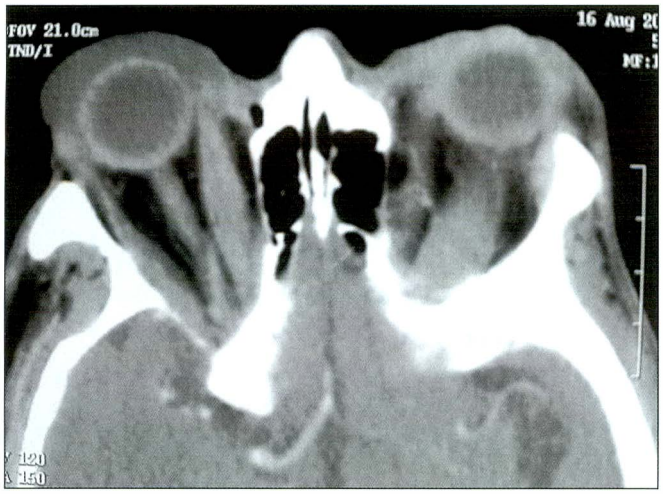
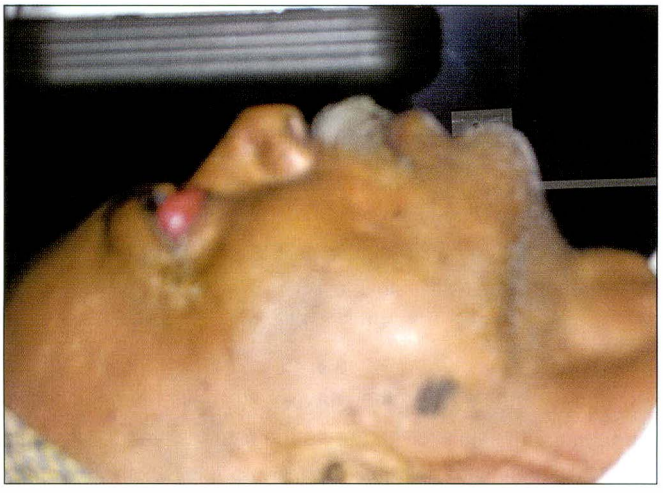
Figure 2. Axial section of the computed tomography scan showing bilateral orbital proptosis.



an unknown mechanism allows thyroid antigen to stimulate the immune system and produce antibodies to the thyroid stimulating hormone (TSH) receptor and other antigens that alter the release of thyroid hormones.[1] Orbital connective tissue shares some of the thyroid antigens that result in the production of activated T lymphocytes, which migrate and invade the orbital connective tissue.[3,4] This leads to proliferation of orbital fibroblasts, resulting in increased synthesis and release of glycosaminoglycans. Locally produced cytokines amplify the inflammatory response.[1] The combined cell-mediated and humoral response results in inflammatory cell migration and oedema in the orbit. The continuous deposition of these inflammatory exudates leads to thickening of the extraocular muscle and an increase in orbital fat volume.[1] The limited bony confines of the orbit allow minimal expansion of the orbital contents and are pushed forward resulting in proptosis.[3] However, irreversible alterations occur as a result of activation of orbital fibroblasts

Figure 3. Patient positioned for electron beam treatment with the electron applicator attached to the treatment head.



with formation of fibrotic tissues within the fibromuscular framework of the orbit.

The rationale for radiotherapy in thyroid eye disease stems from the fact that the lymphocytes and the fibroblasts are highly radiosensitive.[2,5] Radiation arrests the process of lymphocyte chemotaxis and fibroblast proliferation thereby relieving orbital inflammation permanently.[1] Prummel et al were the first to deliver evidence-based data on the efficacy of radiotherapy in thyroid orbitopathy.[2] In a prospective randomised study with stringent inclusion criteria, 56 patients were randomised to receive either radiotherapy and a placebo or sham irradiation plus prednisone. The response rates in both groups were similar, at 50% for radiotherapy and placebo and 47% for prednisone and radiotherapy. Improvement occurred in soft tissue inflammation and ocular motility, but not in proptosis. A number of published series were in agreement with Prummel et al's study, showing improvement rates ranging from 23% to 51%,[6-8] while other studies did not show any significant improvement in proptosis.[2,5,9] External beam irradiation was used effectively for this patient to suppress the active inflammation leading to subjective improvement in pain, although the morphological changes remained irreversible.

Glucocorticoid therapy has been the established therapy for Grave's ophthalmopathy, but the treatment seems to be more effective in association with low-dose orbital radiotherapy (20 Gy) to counteract inflammation.[6] Prednisone should be continued during radiation therapy as radiation causes temporary ocular irritation and exacerbates soft tissue inflammation.[10,11] Various clinical studies have demonstrated that radiation, especially in combination with oral prednisone, is effective in decreasing soft tissue signs and symptoms due to inflammation. There are conflicting results about the outcome of radiation with glucocorticoid therapy.[12,13] These studies did not show any temporal relationship between the radiation and the corticosteroid therapy. Hence, judicious patient selection and timing of radiation therapy is essential for obtaining optimal results as radiation therapy may lead to debilitating morbidities such as radiation-induced retinopathy, especially in patients with diabetes. Thus, radiotherapy is useful for a subset of patients with moderately severe thyroid orbitopathy. The role of radiotherapy in orbital proptosis is still controversial and not yet well defined as clinical studies have shown inconsistent results.

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Presumed Retinal Infiltration of Atypical Periocular and Orbital Xanthogranuloma

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Histiocytic disorders are rare and often unsuspected. There is biological and histopathological overlap that is often confounding. The presentations and natural history are often varied and ill defined. Periorbital xanthogranuloma in adults is rare and may be part of systemic involvement that might include paraproteinaemias, leukaemias, and Erdheim-Chester disease. Diagnosis is usually confirmed by histopathology. Intraocular involvement is rare. This report is of a patient whose clinical presentation included atypical periorbital and intraorbital lesions with presumed retinal infiltration.

Key words: *Histiocytic disorders, malignant, Orbit, Retina*

Asian J Ophthalmol. 2007;9:134-7

Introduction

Xanthogranuloma is a lipogranulomatous form of systemic histiocytosis affecting various tissues of the body, predominantly the skin, orbit, and bone. Xanthogranuloma affecting the eye has varied presentations, ranging from benign as in periorbital xanthogranuloma[1,2] to incurable as in Erdheim-Chester disease.[2-4] Systemic association of periocular xanthogranuloma suggests either Erdheim-Chester disease or necrobiotic xanthogranuloma, which are potentially fatal.[3,4] This report describes a patient with periocular and orbital xanthogranuloma with atypical morphology with presumed retinal infiltration.

Case Report

A 53-year-old woman presented to the Dr Rajendra Prasad Centre for Ophthalmic Sciences, All India Institute of Medical Sciences, New Delhi, India, in December 2005 with gradual progressive decrease in vision in both eyes for the past 8 months and eruption of multiple nodular skin lesions around the orbital margin for the past 5 years. The patient did not have any complaints of similar lesions anywhere else on her body or any history of asthma, diabetes mellitus, hypertension, or bone pain.

At ophthalmic examination, her best-corrected visual acuity was no perception of light in the right eye and 3/60 in the left eye. She had multiple confluent, non-tender firm to hard large papulo-nodular skin lesions along the entire orbital margin sparing the lids (Figure 1). Ocular motility was normal. Slit-lamp biomicroscopy of the right eye revealed florid iris neovascularisation and signs of healed keratouveitis with a secondary cataract (Figure 2). In the left eye, there was a senile cataract and no other anterior segment pathology. Fundus details were not visible in the right eye. Posterior segment evaluation of the left eye revealed mild to moderate vitritis associated with a hyperaemic disc, perivascular infiltration, and diffuse retinal pigment epithelial (RPE) changes throughout the posterior pole. Fluorescein angiography showed staining of the disc and vessels with no active leak. Diffuse transmitted fluorescence was noted throughout the posterior pole because of RPE changes. Choroidal folds were also observed (Figure 3). Intraocular pressure in the right eye was 8 mm Hg and in the left eye was 14 mm Hg. Posterior segment ultrasonography of the right eye revealed choroidal detachment, chorioretinal thickening, partial posterior vitreous detachment, and calcification of the ocular coats (Figure 4).

Haemogram, renal function tests, liver function tests, X-rays of the chest and long bones, lipid profile, serum electrophoresis, and ultrasound of the abdomen were within normal limits, suggesting the absence of any systemic association. Magnetic resonance imaging of the head and orbit revealed periocular and intraconal mass lesions with kinking of the optic nerves bilaterally (Figure 5) and enlarged Virchow Robin spaces. There was no evidence of any intracranial granuloma.

Skin biopsy of the periocular lesions showed a focal collection of sheets of histiocytes and lymphocytes within the dermis. The

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Figure 1. Multiple yellowish papulo-nodular lesions involving the periorbital areas (a) sparing the eyelids; and (b) with satellite lesions posteriorly (arrow).

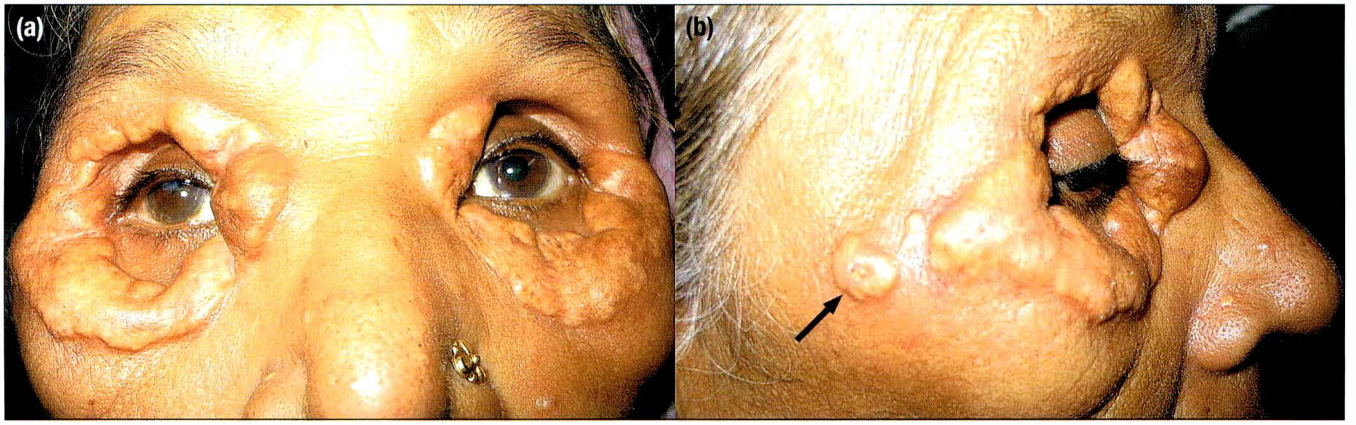


Figure 2. Slit-lamp micrograph of the right eye showing (a) nebulomacular corneal opacity (arrow) with filliform synechiae (arrowheads) showing signs of healed uveitis (original magnification, x 16); and (b) new vessels coursing along the iris (original magnification, x 25).

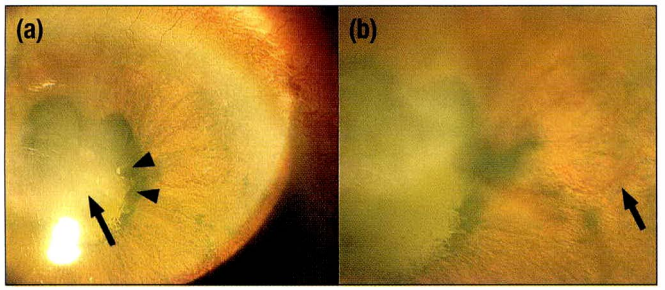
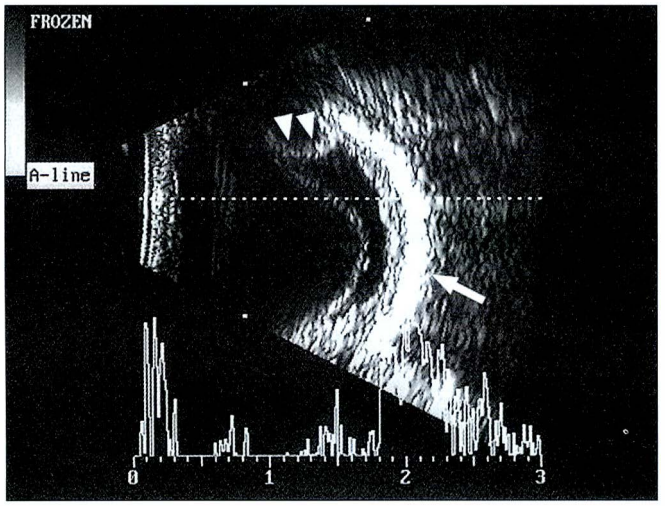


Figure 3. Combined A- and B-scan of the right eye showing partial posterior vitreous detachment with vitreous debris and choroidal detachment (arrowheads) and calcification of the coats (arrow) with shadowing.



histiocytes had abundant pale vacuolated cytoplasm with small round nuclei. Multinucleated foreign body-type and occasional Touton-type giant cells were also present (Figure 6a). Immunohistochemical staining of the paraffin-embedded tissues showed strong positivity for CD-68 (Figure 6b) and focal cytoplasmic immunoreactivity of the foam cells to S-100 antibody (Figure 6c).

A diagnosis of bilateral periocular and orbital xanthogranuloma with right eye pre-phthisis and left eye presumed retinal infiltration was made. A trial of oral corticosteroids 1 mg/kg body weight did not result in any improvement in her condition.

Discussion

The orbit may be affected by a spectrum of reactive and neoplastic disorders involving macrophages or histiocytes. Orbital xanthogranuloma is a rare condition with a chronic course, in which ocular involvement occurs infrequently. Although orbital xanthogranuloma is a clinical diagnosis, histological evaluation is confirmatory. The typical histologic picture of a granulomatous infiltrate with foreign body and Touton giant cells intermingled with few lymphocytes and eosinophils is unmistakable. CD-68 is the most useful and important antibody for identifying these macrophages. S-100-positivity in these cells is not uncommon.[5]

The appearance of eyelid lesions producing diffuse, yellow plaques is considered diagnostic for periocular xanthogranuloma.[1] However, none of the patients previously reported had the same pattern of extensive papulo-nodular periocular xanthogranuloma sparing the lids and with associated retinal and perivascular infiltrative lesions as this patient. Intraconal involvement with optic nerve kinking is another unusual association seen in this patient. Miszkiel et al have earlier described optic nerve encasement in only 1 of 9 patients.[6]

Exclusion of other xanthogranulomatous conditions is of prime importance in the management.[4] Uveitis and optic disc oedema have been associated with necrobiotic xanthogranuloma but the absence of paraproteinaemia and necrobiosis on histopathology in this patient clearly ruled out necrobiotic xanthogranuloma.[7] The periocular lesions in necrobiotic xanthogranuloma are usually non-pruritic plaques, waxy, violaceous or flesh-coloured nodules, which may ulcerate or scar and involve the eyelid skin;[8] these lesions were absent in this patient. The other condition that needs to be

Figure 4. Fluorescein angiography of the left eye showing (a) diffuse retinal pigment epithelial changes with disc staining (arrow) and choroidal folds (arrowheads) in the posterior pole; (b) perivascular cuffing with no leakage on fluorescein angiography; and (c) diffuse pre-retinal infiltrates (arrowheads) with retinal pigment epithelial changes (arrow).

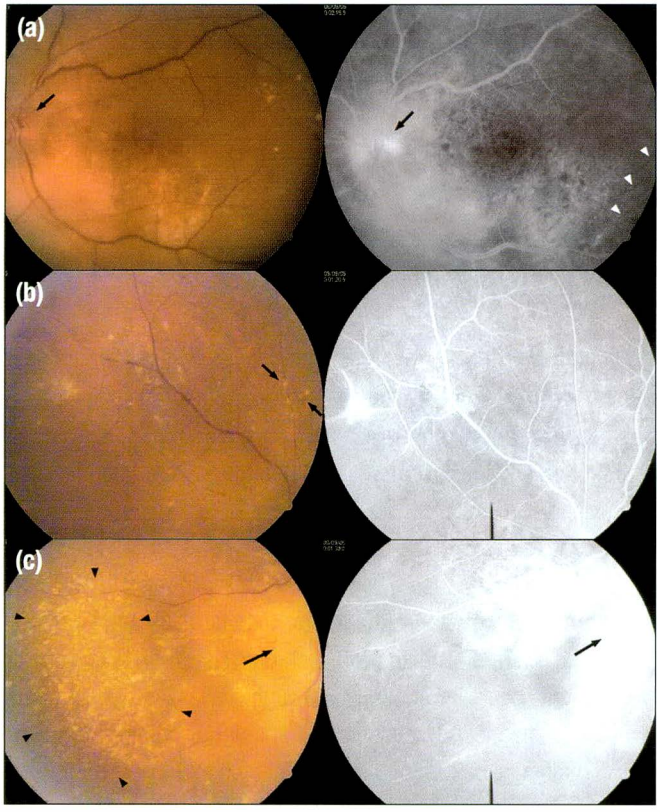
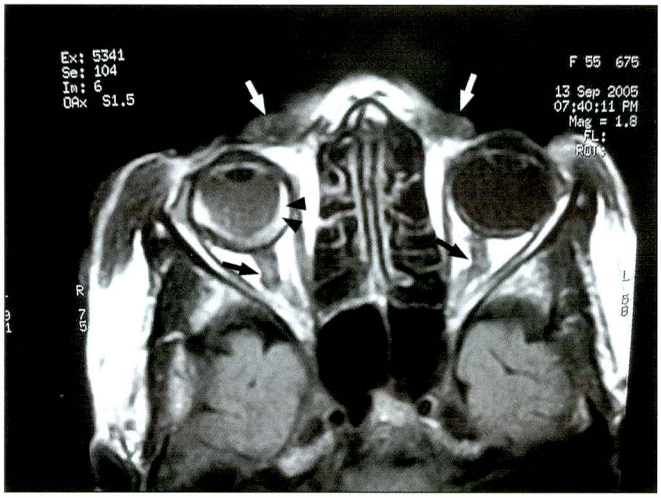
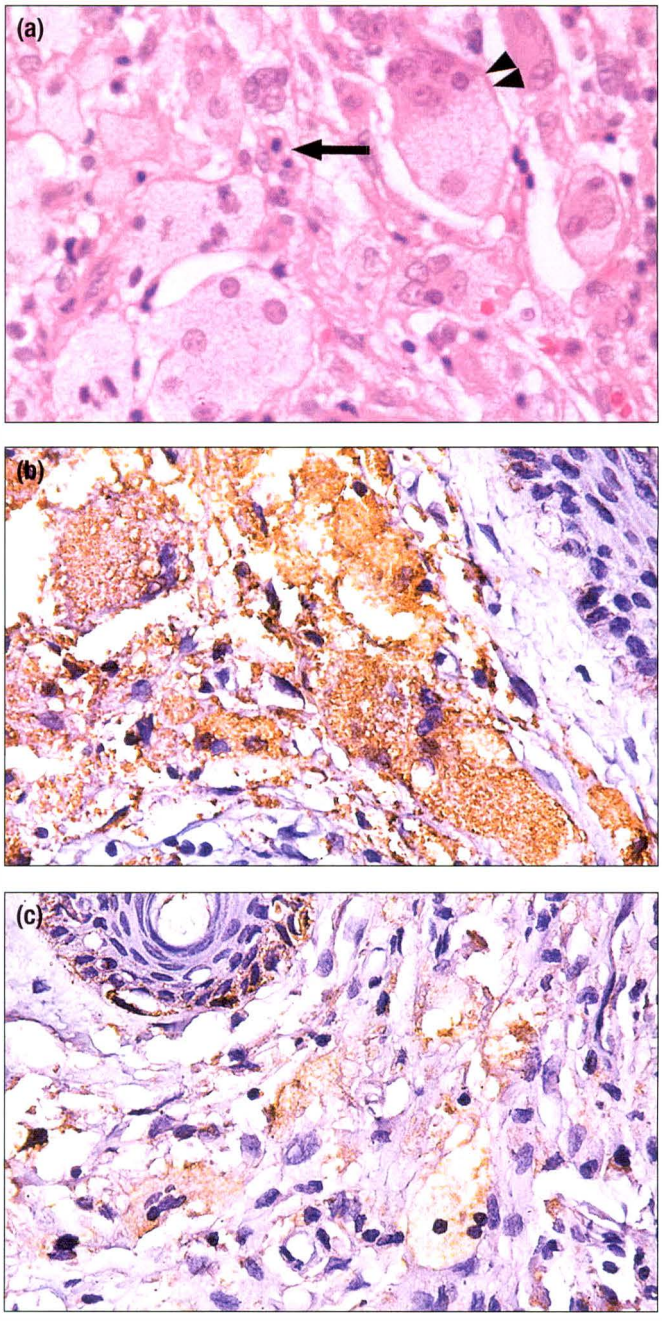


Figure 5. Axial T1-weighted magnetic resonance image of the orbit demonstrating bilateral low-signal intensity lesions in the intraconal space (black arrow) and anterior to the orbital septum (white arrow). High-signal intensity of ocular coats (arrowheads) suggestive of calcification is also seen.



ruled out because of its potential risk to life is Erdheim-Chester disease. This disease is characterised by infiltration of bone, retroperitoneum, heart, lungs, and other tissues with xanthoma cells.[3,4] Most patients do not have orbital involvement, but some

Figure 6. (a) Histopathology showing histiolymphocytic infiltrate (arrow) and foreign body giant cell (arrowhead) [haematoxylin and eosin stain; original magnification, x 400]; (b) immunohistochemical stain showing diffuse cytoplasmic positivity for CD-68 (original magnification, x 400); and (c) immunohistochemical stain showing focal cytoplasmic positivity for S-100 (original magnification, x 400).



may have bilateral xanthelasma and bilateral proptosis.[4] Although the histopathology of Erdheim-Chester disease resembles that of orbital xanthogranuloma, the absence of systemic involvement ruled out this condition in this patient.

Whether the retinal infiltration represents a point in the natural history of the systemic haematological disorder cannot be commented on. Although perivascular infiltrates have been described

in leukaemias,[9] none have been described in xanthogranulomatosis. Patients with orbital histiocytosis who developed chronic lymphatic leukaemia or non-Hodgkin's lymphoma during the natural course of histiocytosis have been reported.[1,6,7]

This report described a patient with periocular and orbital xanthogranuloma with ocular manifestations suggestive of infiltrative vasculopathy. To the best of the authors' knowledge, this has not been reported in the literature.

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In the Aftermath of Fungal Keratitis: What Have We Learnt?

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Contact lens wear is a major cause of microbial keratitis in Singapore. A survey performed in 1998 showed that 9% of the population used contact lenses, and the current estimate is for 225,000 contact lens wearers in Singapore. The national incidence of contact lens–related microbial keratitis is 5.4 per 10,000 contact lens wearers per year. In a 2-year survey conducted from 1999 to 2001, microbial keratitis was found to account for 25% of 721 complications of contact lens wear. Of these, 75% were due to *Pseudomonas* sp, with only 1 fungal ulcer. However, in 2006, there was an outbreak of *Fusarium* keratitis in Singapore, which spread to other parts of Asia, and eventually to the USA.

In early 2006, 68 cases of contact lens–associated fungal keratitis were found in 66 patients in Singapore. After an association was made with Bausch & Lomb ReNu contact lens solution, a national and international alert was raised and Bausch & Lomb suspended sales of ReNu in the area, after which the incidence of *Fusarium* keratitis rapidly declined (Figure 1).

A study of the patients involved in the outbreak found that most patients used soft disposable contact lenses (98.5%) from 8 different manufacturers. Most patients (93.9%) used ReNu solutions, although many of these patients did not follow appropriate contact lens hygiene procedures.

The Centers for Disease Control (CDC) in the USA became involved when an outbreak became evident in the USA. At this stage, Bausch & Lomb recalled ReNu worldwide and the number of reported cases decreased dramatically. An epidemiological study found 160 cases in 33 states, 55 of which required transplant. ReNu MoistureLoc was clearly implicated (odds ratio, 13.3).

Bausch & Lomb conducted an investigation into *Fusarium* keratitis in contact lens wearers, and concluded that, under states of solution evaporation, MoistureLoc fails to kill *Fusarium* sp, but MultiPlus remained effective. It was felt that contamination occurred in the consumers' environment as the isolates were varied and common to sinks and drains, and that the unopened product was effective. Compliance with the instructions was thought to be a problem. In an independent report, it was found that *Fusarium solani-Fusarium oxysporum* complex grew and survived in stressed multipurpose contact lens care solution films in situ and in vitro.

Figure 1. Four months of *Fusarium* fever.
Abbreviations: SNEC = Singapore National Eye Institute; SERI = Singapore Eye Research Institute; B&L = Bausch & Lomb.

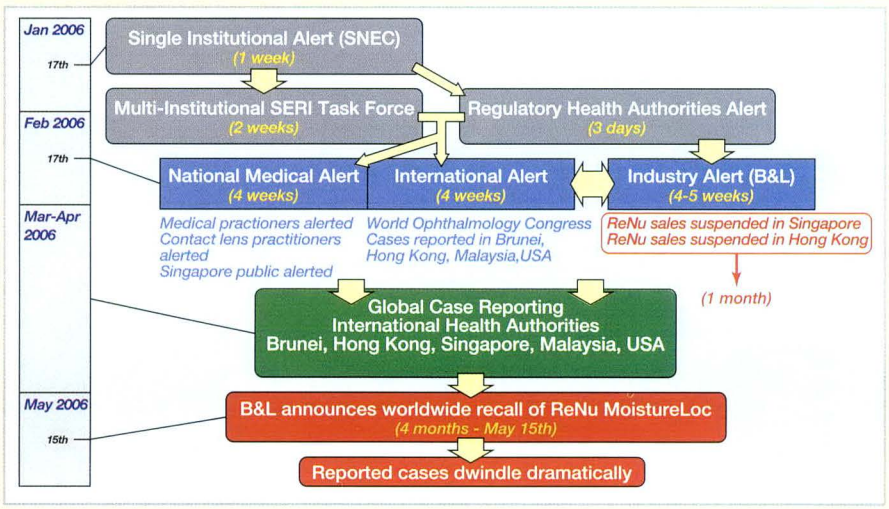

Table 1. Comparison of the Singapore and Centers for Disease Control (CDC) case control studies of Fusarium keratitis.

	CDC study	Singapore study
Number of cases	55	61
Number of controls	78	367
Odds ratio for ReNu MoistureLoc	13.3	99.3
Odds ratio for ReNu MultiPlus	0.7	21.5

Case Control Study

Since the original outbreak of *Fusarium* keratitis, a case control study has been performed in Singapore involving 61 patients, 188 population-based controls, and 179 hospital-based controls.[1] The results showed that more patients (95.1%) used ReNu solutions than the population-based controls (34.3%) or hospital-based controls (30.1%). Multivariate analysis showed that the association between *Fusarium* keratitis and ReNu solutions was still present.

Both this study and the CDC study implicated ReNu MoistureLoc. The CDC study suggested that ReNu MultiPlus was not associated with infection. However, the Singapore study suggested that although association with MoistureLoc was 5 times greater than MultiPlus, the odds ratio for MultiPlus (21.5) was still much higher than the odds ratio for MoistureLoc (13.3) in the USA trial (Table 1), implicating MultiPlus in the Singapore outbreak.

Conclusion

There is now an increasing prevalence of all forms of infectious keratitis. Emerging studies suggest a multifactorial aetiology to contact lens–related infections. Rapid global networking between physicians, governmental health care regulators, and industry are essential for noting and connecting isolated outbreaks of infectious keratitis.

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Designing and Optimising Contact Lens Solutions

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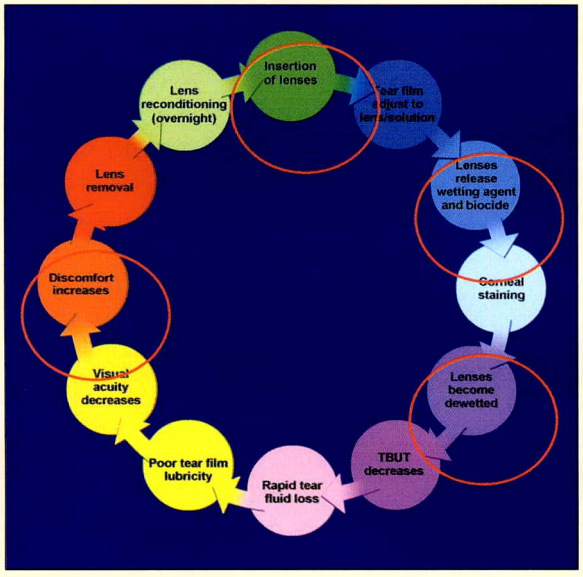
The development of contact lens care (CLC) products takes several years from the research stage, through non-clinical and clinical testing, to regulatory review and clearance to market. CLC solutions must be compatible with the ocular tissues. However, these products must also be tested with contact lenses, contact lens cases, and the solution containers, as interactions with these materials can occur.

CLC solutions should perform varying functions throughout a contact lens wearer's day (Figure 1). When the lens is first inserted, the solution should perform a cushioning action so that the lenses are immediately comfortable. The solution must not irritate the eye. During the day, the lenses release wetting agents and biocides that have been absorbed by the lenses during the overnight soaking period. Lenses can become dewetted (hydrophobic) during the day, which can cause discomfort, so wetting is important later in the day. The ingredients in the CLC solutions need to be carefully assessed during the development process. The components in CLC solutions include disinfectants/preservatives; polymers to maintain/enhance comfort; wetting agents to promote good tear film stability; cleaning/chelating agents; ions and buffer agents; and osmotic agents. Manufacturers have a multitude of ingredients with which to work when formulating CLC solutions, and it is important that these work together.

Figure 1. Daily contact lens wear cycle.
Abbreviations: TBUT - Tesr break-up time.



Clinical Evaluation

The Food and Drug Administration's (FDA) 510(k) guidance document for CLC solution testing requires that 60 patients be tested in a 3-month study, with an active and control solution. The objective is to show substantial equivalence to a similar currently marketed product. The guidelines for obtaining CE marking in Europe require clinical studies, but there are few specifications. Typically, the same data as those submitted to the FDA are used for Europe. Several factors regarding CLC solution testing should be noted. For example, it is often not difficult to demonstrate substantial equivalence, particularly if a study is not specifically designed to detect differences. However, there are measurable differences in CLC product performance that can have clinically significant effects.

Study design factors such as lens brand, study population, time of day of study visits, and corneal staining and comfort scales can mask or minimise differences between products. The desired study goals are to demonstrate safety and efficacy, demonstrate statistical and clinically relevant differences between the test solution and competitor products, evaluate the test solution in different populations, and evaluate the test solution with multiple lens types, including silicone hydrogel lenses. CLC solution manufacturers optimise their chances of success by using well-developed non-clinical models, performing well-controlled clinical studies, listening to doctors, and having an active post-marketing surveillance system.

A series of double-blind randomised clinical studies for a new multi-purpose disinfecting solution enrolled more than 900 patients at more than 40 sites in the USA and used a variety of lens brands and materials and 2 different competitor (control) products. The safety information assessed included corneal staining, slit-lamp parameters, and ocular adverse events. Efficacy information included lens cleanliness, average wear time, rewetting drop use, comfort, and wettability.

The studies showed significant differences between the test and control solutions. Corneal staining was significantly lower for the test solution compared with one of the controls with silicone hydrogel lenses (day 7, $p = 0.0236$; day 14, $p = 0.0034$; day 30, $p = 0.0223$). Mean residual lysozyme on group IV lenses was significantly different between products ($p < 0.0001$) in favour of the test solution. Testing for crystal-line deposits showed similar results (day 60, $p < 0.02$; day 90, $p < 0.03$). There were many significant differences between the test solution and the control solutions for comfort, specifi-cally with one brand of silicone hydrogel lenses and symptomatic patients wearing group IV lenses ($p \leq 0.05$). Rewetting drop use was significantly lower for silicone hydrogel lens wearers using the test solution compared with one of the control products ($p < 0.004$). Lens wettability was significantly better with the test solution than one of the control products following 1 and 30 days of wear ($p < 0.0001$).

Conclusion

Clinical studies follow years of formulation screening and development with extensive preclinical evaluation. There are methods to differentiate CLC systems that clearly demonstrate the differences. CLC makes a difference to successful lens wear.

Asia ARVO

Alcon®

Contact Lens Solution Testing: Beyond the Standard Requirements

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There is a high incidence of contamination of contact lens cases and solutions, despite good compliance with hygiene techniques. Disinfection efficacy depends on a number of factors, including the nature and number of micro-organisms present, disinfectant exposure time, presence of organic material, and biofilm formation. There are several micro-organisms that contact lens care (CLC) systems need to be effective against, including *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Serratia marcescens*, *Candida albicans*, and *Fusarium solani*. The 2 main tests required by regulatory bodies are the stand-alone test and the regimen test (Figure 1).

Clinical Studies

A study was performed to determine whether clinical strains vary in their susceptibility to 2 chemical disinfectants. Fifteen strains of *P aeruginosa* isolated from 1994 onwards were tested and 20 standard laboratory strains and ocular strains isolated prior to 1988 were used as controls. The relationship between cytotoxicity and resistance was assessed. Inorganic ions were added to the disinfectants and they were stored at room temperature to mimic normal use.

P aeruginosa strains varied significantly in their susceptibility to both disinfectants ($p < 0.05$), with variation of up to 4.0 log units. Cytotoxic strains showed greater resistance than invasive strains ($p < 0.01$). Susceptibility was not related to the date of isolation ($p > 0.05$). Interestingly, susceptible strains could not be made resistant with repeated disinfectant exposure. Resistance appears to be inherent and linked to acute cytotoxicity. Chemical disinfection solutions may select for contamination with cytotoxic strains. Resistance and adaptation to contact lens disinfection are likely to contribute to contamination of CLC systems and increased exposure of the eye to microorganisms during lens wear. Clinical isolates should be included in disinfectant testing and alterations to disinfectant formulations should be made to influence susceptibility.

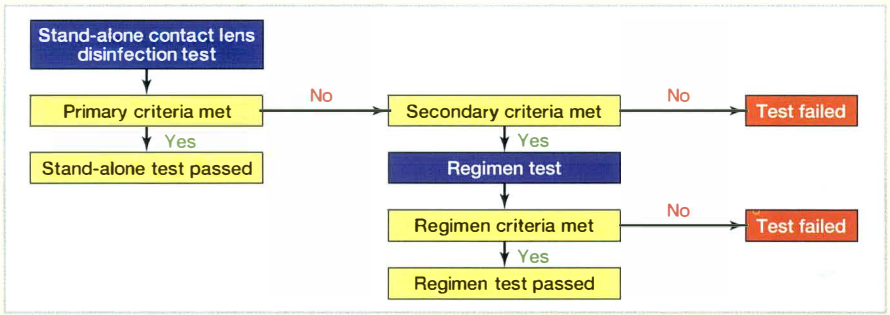
A study to investigate the effect of CLC solutions on soiled contact lenses was performed. Organically soiled contact lenses, unsoiled contact lenses, and disinfectant only controls were included. All *P aeruginosa* strains were found to be susceptible to the disinfectants alone when organic soiling was not included (>3.0 log reduction). Susceptibility to solution A did not vary between soiled and unsoiled contact lenses ($p > 0.05$), but there was some variation in resistance to solutions B, C, and D between strains, with poorer efficacy with soiled contact lenses compared with unsoiled contact lenses for at least 1 isolate ($p < 0.05$). Invasive strains were more resistant than cytotoxic strains in the presence of organically soiled contact lenses for solutions B and D ($p < 0.05$). There were no significant differences for solutions A and C when tested with soiled contact lenses ($p > 0.05$).

Organic material affects the antimicrobial activity of polyhexamethylene biguanide (PHMB)–preserved disinfectants, although susceptibility varied between strains. Invasive strains appeared to be more resistant than cytotoxic strains for 2 of the PHMB solutions. This is the opposite effect to that seen with testing with inorganic ions.

Further study investigated the susceptibility of *S marcescens* clinical isolates to 3 hydrogel disinfectants. Resistance to disinfection varied significantly between the strains for solutions A and B, with poorer efficacy observed with the addition of organic soil for at least one of the isolates ($p < 0.05$). There were no significant differences between strains for solution C with or without organic soil ($p > 0.05$). Overall, resistance to solution B was significantly greater with the addition of organic soil ($p < 0.05$). The efficacy of solution A improved significantly over time for both soiled and unsoiled samples ($p < 0.05$).

S marcescens isolates varied in susceptibility to 2 of 3 disinfectants in the presence of organic soil. The majority of isolates showed greater resistance with organic soil. The presence of organic material, such as tear film components, during contact lens disinfection may increase bacterial resistance to disinfection and result in subsequent contamination of contact lenses and CLC systems.

Figure 1. Contact lens care system testing.



Conclusion

There seem to be limitations to the current standards of testing and these need to be addressed. Additional information regarding disinfection efficacy can be obtained by testing a variety of clinical isolates in contact lens cases and on worn contact lenses, with the addition of organic or inorganic material. Other tests to consider include mixed micro-organism challenges and investigating the effects of elevated temperature, different contact lens types, and non-compliance with hygiene procedures on disinfection efficacy. Understanding the mechanisms and factors responsible for resistance will help reduce contamination and adverse events.

Compatibility, Comfort, and Cleaning: the 3Cs of Safe Contact Lens Wear

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Despite the availability of high-quality products, studies indicate that 20% to 30% of contact lens wearers cease lens wear within 5 years. Approximately 50% cite discomfort as the primary reason, with inconvenience, cost, and clinical complications being contributory factors. However, the development of silicone hydrogel lenses that are highly permeable to oxygen have revolutionised the practice of contact lens wear. As new technologies are developed for contact lenses, new compatible cleaning solutions are required.

Solution Components

There are 3 major components of contact lens solutions: antibacterial agents/preservatives, surfactants, and chelating agents. Hydrogen peroxide 3% is a commonly used biocidal agent, which has been used since the early 1970s and is not associated with preservative hypersensitivity. A disadvantage of hydrogen peroxide contact lens care (CLC) systems is that the lenses need to be neutralised before insertion into the eye. Neutralisation can be done with a platinum disc or enzymes, but requires an extra step in care, which can be inconvenient to contact lens wearers. 'Designer' preservatives were developed to overcome the problem of preservative hypersensitivity, while remaining easy to use. The most widely used of these 'designer' preservatives are polyquaternium-1 and polyhexamethylene biguanide (PHMB). The major advantage of these newer generation preservatives is that they are large molecules that do not enter the lens pores and thus only small amounts are released onto the eye following insertion. Surfactants are surface active agents, with 2 components that are water soluble (hydrophilic) and water insoluble (hydrophobic). The 2 primary functions of surfactants are to remove loose debris and micro-organisms, and to aid with wetting contact lens surfaces.

Chelating agents work synergistically with the biocide to help kill bacteria. Ethylenediamine tetra-acetic acid is the most commonly used chelating agent, and acts to bind-up metal ions, which are needed by bacteria to metabolise. Other chelating agents include citrate and hydranate, which aid passive protein removal during overnight soaking.

Clinical Performance

There are 4 important factors for evaluation of clinical performance: efficacy, cleaning, wetting, and toxicity/sensitivity. As all solutions are Food and Drug Administration–approved, efficacy tends to be assumed, but the recent MoistureLoc episode shows that efficacy in the laboratory may not translate to efficacy in clinical use. The biocidal agent used in MoisturLoc was alexidine, which has high fungicidal activity in the laboratory, but it's efficacy was compromised in clinical practice in situations where patients were non-compliant.

Compatibility has historically been an issue with certain preservatives. A study of different concentrations of PHMB 0005%, 0.0001%, 0.00005% found clinically high rates of corneal staining in the solution with the highest concentration of PHMB. Sixty percent of patients using a group 2 lens combined with the highest concentration of PHMB had unacceptable levels of corneal staining, compared with only 10% of patients using a group 4 lens. This result suggests an interaction between certain lens materials and the contents of the contact lens care (CLC) system.

Although silicone hydrogel lenses were originally designed for continuous wear, most practitioners prescribe them for daily wear. These lenses became available after the development of most of the currently available CLC systems. A study of the compatibility of these new lenses with the CLC systems found clinically significant staining associated with one PHMB-preserved product in more than one-third of the participants. Interestingly, this association is not due to the concentration of PHMB, but rather to the way in which it is formulated. Further study found a significant amount of corneal staining correlated with a silicone hydrogel lens and 1 of 2 PHMB-preserved products (Table 1).[1] A study of the kinetics of corneal staining found significantly increased corneal staining after 2 hours with some, but not all, products tested. After 6 hours, the corneal staining had decreased almost to baseline levels, suggesting a time effect. In addition, the standard deviation was extremely wide, suggesting this result is patient-driven. Interestingly, this degree of corneal staining did not affect comfort, with most patients being relatively asymptomatic. Importantly, it is the combination of lens material and CLC regimen that results in corneal staining issues, rather than a specific lens or solution.

Table 1. Interaction of silicone hydrogel lenses and contact lens care solutions.*[1]

Contact lens	Peroxide-based	Polyquad-based	Polyhexamethylene biguanide-based	
	AOSept	OFX	ReNu MultiPlus	Focus Aqua (AQuify MPS)
PureVision	0%	2%	37%	
			47%	
Focus Night & Day	0%	8%	21%	0%
	0%		24%	

* Percent of patients with unacceptably high staining.

Conclusion

Solution choice plays a highly relevant role in contact lens success. There is growing evidence that certain combinations of solutions and materials may show incompatibility. It is important to check all patients for corneal staining after 2 to 3 hours of contact lens wear, regardless of whether they have symptoms.

Reference

1. Jones L. Understanding incompatibilities. Contact Lens Spectrum. 2004;19;7 (Suppl):4-7.

The Staining Grid: Importance of Prescribing the Best Care System for the Patients

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Silicone hydrogel contact lenses were introduced worldwide at the beginning of this decade. These lenses have many advantages over traditional contact lenses, including better oxygen transmission and reduced protein deposits.

However, a major disadvantage is that many multipurpose contact lens care (CLC) solutions are incompatible and may cause corneal staining when used with these lenses. In addition, some lens/solution combinations can cause toxic keratitis.

There have been several reports of corneal staining or ocular stress due to solution properties or interactions with lens materials. However, each study investigated only a small selection of the available lenses and/or solutions. In a recent series of 24 randomised studies involving nearly 2000 participants, 10 solutions and 7 lens materials have been investigated for comfort and corneal staining. Corneal staining was checked after 2 and 4 hours of contact lens wear and participants rated their comfort and symptoms on a 100-point scale. Staining was graded by type and area.

Depending on the lens/solution combination, staining tended to increase from baseline to 2 hours, peak around 2 hours, and then slightly decrease from the 2-hour high at the 4-hour time. When the Oasys lens was used, the amount of staining of the 4 solutions tested ranged from 4% to 12% at 2 hours. However, when tested with the PureVision lens, the amount of staining of 5 solutions ranged from <10% to nearly 80%.

By plotting the results on the grid (Figure 1),[1] it was possible to see certain trends:

Figure 1. Corneal staining grid.
Green = minimal staining (<10%); yellow = marginal staining (10% to 20%); red = excessive staining (>20%).

	Unisol 4 Saline	Clear Care	Optifree Express	Optifree Replenish	Renu MLoc	Reni MPlus	Walmart MPS	Target MPS	Complete MoistPlus	Aquify
Acuvue 2	1%	1%	2%	5%	25%	1%	1%	1%	2%	1%
ProClear	1%	Testing ongoing	1%	2%	No further testing	57%	Testing ongoing	Testing ongoing	16%	Testing ongoing
Advance	1%	1%	1%	1%	No further testing	13%	16%	13%	20%	2%
Oasys	2%	1%	3%	5%	10%	9%	12%	8%	5%	3%
Pure Vision	2%	1%	4%	7%	6%	73%	71%	76%	48%	21%
O_2 Optix	2%	1%	2%	5%	7%	24%	41%	28%	18%	3%
Focus ND	2%	1%	2%	3%	No further testing	24%	36%	24%	16%	3%
		H_2O_2	POLYQUAD		BIGUANIDES					

Withdrawn

- all the solutions causing >20% staining contained biguanide
- PureVision is the lens material that stains the most
- all the solutions causing 10% to 20% staining contained biguanide
- saline used as a control and hydrogen peroxide showed minimal staining
- solutions containing polyquad showed minimal staining.

Although the biguanide-containing solutions resulted in greater corneal staining, this was not consistent across the solutions. This result suggests that the staining is not caused by biguanide but is associated with an interaction between the formulation and the lens material.

The mechanism of staining depends on the uptake of preservative absorbed into the lens during the overnight soak, the release of the preservative from the lens to the eye, and the toxicity of a specific preservative to corneal epithelial cells. These factors determine whether a lens/solution combination is compatible.

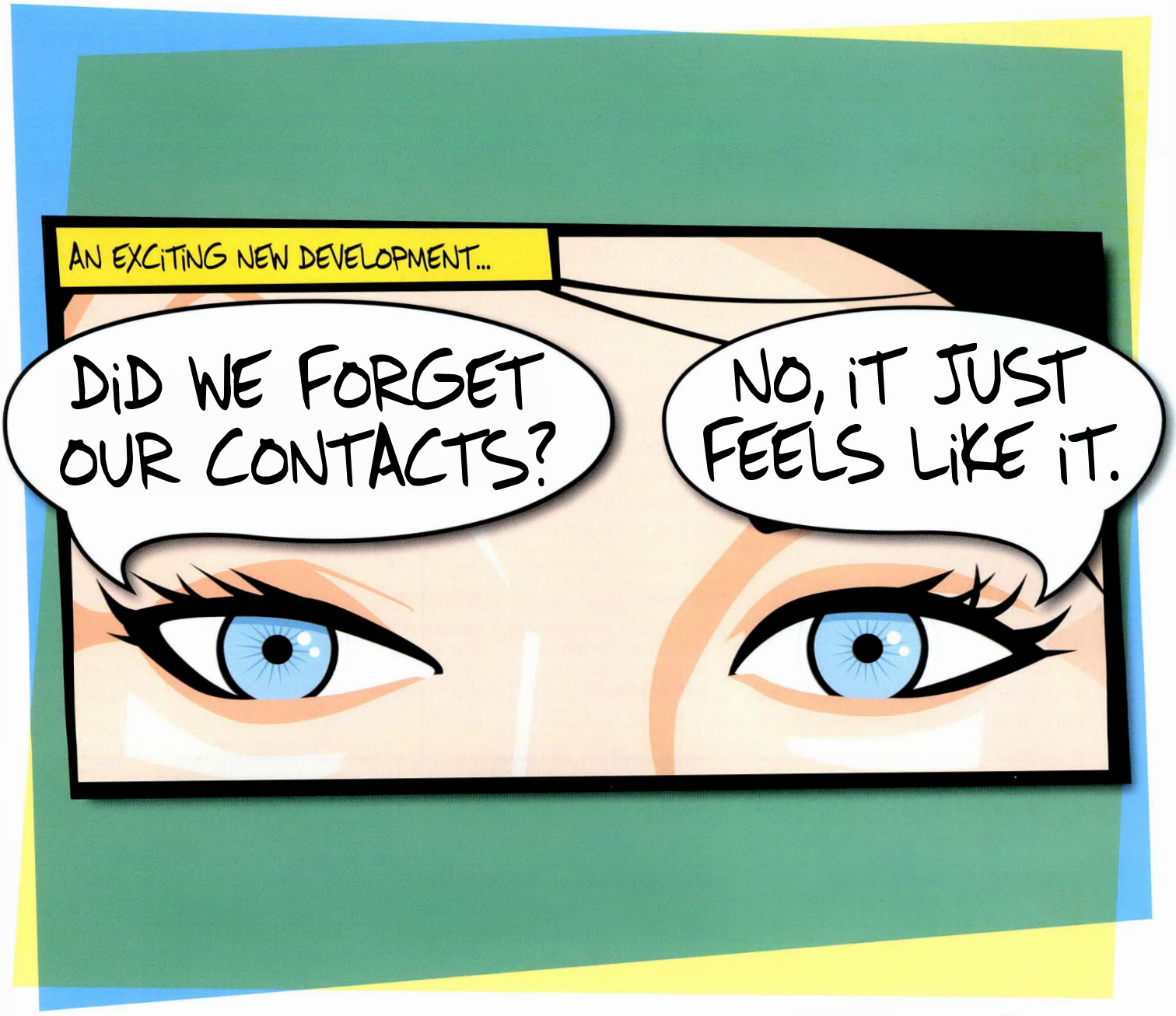
Conclusion

Corneal staining due to contact lens wear is chronic in nature. Disruption of the epithelial barrier layer is a risk factor for corneal health. A group of researchers in Australia found that when staining from solutions is present, there is an increased risk of infiltrates and infiltrative keratitis, and increased discomfort. Some lens/solution combinations, especially when used with silicone hydrogel lenses, may cause chemical keratitis. The days when patients could safely switch from a practitioner prescribed-solution to a different solution are over, so patient education is imperative. The staining grid will help to guide compatibility of a solution with the prescribed lenses. The solution is as important as the contact lens.

Reference

1. Andrasko G. Andrasko corneal staining grid. www.staininggrid.com/

From the Alcon, Inc satellite symposium Catching Current Trends in the Compatibility, Safety and Care of Contact Lenses *held at the Asia-ARVO Meeting, Singapore, 2 March 2007.*



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Implications of Dry Eye

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Dry eye is a common condition worldwide. The prevalence of dry eye in Asia ranges from 14% to 36%, compared with that in western countries of 2% to 28%. The prevalence rate increases with age, and dry eye occurs more commonly among women than men; menopause and age-related hormonal changes are thought to be associated with dry eye.

The SERI Dry Eye Study found that 27.5% of 1058 participants reported at least one dry eye symptom often or all of the time. There was a significant increase in symptoms with age and the male to female ratio was 1.4:1. The risk factors in this population were age, pterygium, male sex, and smoking.

Environmental factors such as wind and sun exposure, smoking, and air pollution have a role to play in dry eye. Farmers and housewives are more likely to have dry eye than factory and office workers. East Asians are more susceptible to dry eye after laser in situ keratomileusis than Caucasians (28% versus 5%; $p < 0.001$). In a cross-cultural study of tear volume, Japanese participants had significantly less tear volume than western participants (18.8 versus 23.9; $p < 0.05$).

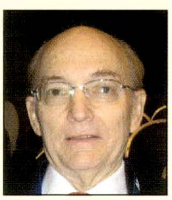
The Shihpei Eye Study from Taiwan found that dry eye is under-diagnosed. Of 50% of participants who visited a doctor for their symptoms, only 5% received a diagnosis. Dry eye treatments are also under-utilised, with only 2% of participants being prescribed artificial tears.

The economic implications of dry eye are shown in Table 1. The cost of lost productivity due to dry eye in the US is estimated to be US$5000 per employee per year due to lost work time. Cost benefit analysis for the use of artificial tears shows that use of other ophthalmological medications is reduced.

Table 1. Economic implications of dry eye.

Direct costs	Indirect costs	Intangible costs
Visits to health care professionals	Days of work lost	Days of leisure lost
Pharmacological therapies	Change in work	Decreased leisure time
Non-pharmacological therapies	Decreased work time	Reduced physical and social functioning
Surgical procedures	Days off work with symptoms	Mental and physical health effects
		Pain

Dry Eye Research in Asia



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Dry eye is a greater concern in Asia than in western countries. Dry eye occurs at an earlier age in Asia (approximately 40 years). In the US Women's Health Study, the incidence of dry eye among women older than 75 years was 10%. A study from Thailand found an incidence of one or more symptoms of 34% among patients aged 40 years or older and the Shihpei Eye Study from Taiwan revealed an incidence of 33%. There is agreement that the prevalence of dry eye in Asia ranges from 27% to 35%, although one study from Japan found a rate of approximately 17%.

Most Asian dry eye studies report involvement of the meibomian glands and have minimal mention of ocular surface discomfort, in contrast to studies from the USA. Dry eye in Asia also tends to involve pterygium. However, Asian studies have some variation in the methods of data collection which can make comparisons between countries difficult, and some countries such as India and China need further studies.

Dry eye is a clinical problem, in that accurate diagnosis and therapeutic progression is time-consuming and relies on tests lacking objectivity. Peptide analysis of tear proteins using mass spectrometry may help in the diagnosis. Research into this is ongoing and shows promise when patient comparisons are made with their clinical classification. A biomarker panel is promising for reducing false-positive results and for classification into mild, moderate, and severe disease based on peptide composition. As research progresses, it is likely that a tear-based test will help in the diagnosis and treatment of dry eye.

Inflammation in Dry Eye

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Dry eye is a disease of the lacrimal functional unit. Stimulation of nerves in the ocular surface results in innervation of the tear-secreting organs of the ocular surface resulting in secretion of the tear film. Tears function as a homeostatic and anti-infective environment for the ocular surface epithelium. It is the composition of tears that changes in dry eye, leading to the term 'dysfunctional tear syndrome' to describe the condition.

The tear film reflex is maintained by circulating androgens; androgens are reduced in older women who tend to be at high risk

for dry eye. The other important factor is the presence of the immune system, as dry eye is an autoimmune phenomenon. When patients with low androgens or protective factors are in hostile environments — low humidity, high allergen content — inflammatory changes and immune activation of the ocular surface develops, releasing CD4+ T helper (T_H) cells.

Presentation of an antigen or change in environment to a CD4+ T cell precursor results in a T_H1 or T_H2 cell. Allergy results in production of T_H2 cells, while dry eye is a T_H1 disease of inflammatory changes. A mouse model of dry eye resulted in decreased tear production, tear turnover, and goblet cell density, apoptosis on the ocular surface, and increased cytokines. The hypothesis of the study was that T cells are the main immune effector cells mediating the inflammatory pathogenesis of dry eye. Further research showed that T cells alone cause the inflammatory response that leads to dry eye. T-regulatory cells are anti-inflammatory and inhibit upregulation of T cells. Studies in mice have shown that these cells eliminate the disease process.

Adoptive transfer of CD4+ lymph node cells from animals exposed to dessicating stress results in inflammation. T cells are directly responsible for mediating dry eye, and under normal circumstances this can be regulated by T-regulatory cells. Therapeutic regulation of T-regulatory cells is a potential treatment for immune-mediated ocular surface diseases.

Treatment of Dry Eye

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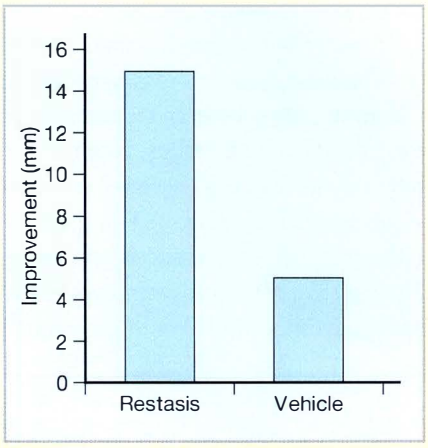
Optical clarity and refractive power are the most important functions of the tear film. Other functions include lubrication, protection from insult, and provision of a trophic environment for the corneal epithelium. It is an imbalance in lipid, aqueous, and mucin secretion in the tear film that creates the signs and symptoms of dry eye. There are inflammatory components such as interleukin-1 in the tear film, which are only released in the presence of damage or death of the superficial epithelial cells. These components are kept in balance by anti-inflammatory modulators in the healthy tear film. In patients with dry eye, these components become imbalanced, resulting in inflammation.

Artificial tears contain electrolytes, but lack the complex factors found in healthy tears. Cyclosporine ophthalmic emulsion 0.05% (Restasis) inhibits T cell activation, restoring the natural composition of tear production.

Approval of Restasis was based on 4 studies of 1200 patients with moderate to severe dry eye. These studies demonstrated that Restasis administered twice daily was highly effective for improving tear production. The phase III study investigated objective and subjective variables. The pivotal finding was that 15% of patients had a >10 mm increase in the Schirmer's test at 6 months (Figure 1), and 59% had some increase. Blurred vision, itching, and light sensitivity improved versus baseline and patient reliance on artificial tears decreased. Improved corneal staining was also noted for cyclosporine compared with the vehicle alone.

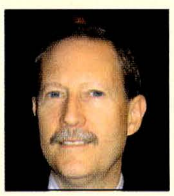
Figure 1. Improvement from baseline of >10 mm for the Schirmer test.



Importantly, conjunctival biopsies were performed and there was a 191% increase in goblet cell density in eyes treated with 0.05% cyclosporine. It may be that improving the tear film leads to more normal differentiation of goblet cells in patients treated with cyclosporine.

Adverse events were minimal, with the main side effect being stinging. Contra-indications include active infection of the eye. Although initially recommended for patients with moderate to severe disease, Restasis induces marked improvement in patients with mild disease in terms of restoration of the ocular surface. Some patients will experience complete resolution of all signs and symptoms after a 6- to 12-month course and even obtain a permanent cure. Restasis is the first and only treatment that restores natural tear production.

Advances in Artificial Tears



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One of the most common characteristics of dysfunctional tear syndrome (DTS; dry eye) is the development of a hyperosmotic tear film. When the ocular surface is exposed to a hyperosmotic tear film, compensatory mechanisms and apoptosis activate, pro-inflammatory pathways upregulate, and signs and symptoms of dry eye appear.

At the cellular level, hypertonicity initially causes water loss, followed by a rapid regulatory volume increase usually requiring sodium uptake. However, sodium and other electrolytes tend to destabilise the function of

intracellular protein metabolism. This process results in stress activation leading to damage and cell death. An alternative regulatory volume increase mechanism is osmoprotection, whereby cells take up solutes that are compatible with normal cellular metabolism (unlike sodium), at no detriment to normal cellular function.

As corneal cells are exposed to hyperosmolarity in dry eye, a study was performed to ascertain whether corneal cells undergo osmoprotection and whether this process can be stimulated by adding compatible solutes to an artificial tear formula. In a model system comprised of rabbit corneal epithelial cells grown in a multi-layer culture, the transepithelial electrical resistance (TEER, a measure of epithelial health) response changes over time when exposed to hyperosmotic conditions in a tonicity-dependent manner. Compared with an isotonic medium, hypertonic media cause an early increase and a later decrease in TEER. However, compatible solutes were found to normalise the TEER response, with combinations being more effective than single compounds.

In another study, human corneal cells were exposed to a salt solution that was isotonic, hypertonic, or hypertonic plus compatible solutes. MAP kinase activation (a marker for pro-inflammatory changes) was found to be reduced in the presence of compatible solutes. Radiolabel uptake experiments in rabbit corneal cells found that compatible solutes were taken up at a significantly greater rate than a control, indicating that they can enter corneal cells via specific transport mechanisms.

These tests have shown that compatible solutes added to a hyperosmotic medium protect corneal cells from hyperosmotic stress as may be experienced in DTS. These results suggest that use of compatible solutes in artificial tear formulations for DTS may be beneficial.

Optive™ has been developed as an osmoprotective artificial tear preparation. Optive contains glycerine and other specific compatible solutes in addition to lubricants, electrolytes, and a preservative. The formula is isotonic with no additional sodium chloride. Clinically, Optive has shown significant improvement in signs and symptoms, including Schirmer's test and tear film break-up time, in comparison with the prior product used. By incorporating state-of-the-art lubrication with osmoprotection, Optive is the next generation of artificial tears.

Clinical Efficacy of Refresh® Tears

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Refresh® Tears is a carboxymethylcellulose-based artificial tear formulation with Purite® preservative. A prospective randomised study to compare the efficacy and tolerability of Refresh Tears with Tears Naturale Free® was performed among 68 patients with dry eye in both eyes. Assessment was performed at baseline, 1 week, and 1 and 3 months. The dry eye parameters evaluated were conjunctival hyperaemia, Oxford staining scheme, Schirmer's test, and tear film break-up time (TFBUT). All dry eye parameters were comparable between the groups at baseline.

After 3 months, there was improvement from baseline in conjunctival hyperaemia, Oxford staining scheme, and Schirmer's test for patients in both groups, although the difference in TFBUT did not reach statistical significance (Table 1). There were no significant differences in dry eye parameters between the 2 groups at 3 months. Assessment of subjective symptoms showed that both groups had comparable baseline symptom scores. After 3 months of treatment, there were significant differences from baseline for all of the symptom score subscales in both groups.

This study demonstrated that both Refresh Tears and Tears Naturale Free demonstrate an improvement in dry eye after 3 months of treatment. Both artificial tears are comparable in terms of efficacy and tolerability. However, Refresh Tears may be a cheaper alternative treatment.

Table 1. Comparison of groups 3 months post-treatment.

	Refresh Tears	Tears Naturale Free
Shirmer's test	8.0 ± 7.3	8.1 ± 6.2
Tear film break-up time	3.4 ± 1.3	3.8 ± 2.0

Restasis for Dry Eye

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Australia

Restasis represents a paradigm shift in the treatment of dry eye in recent years. The following case histories highlight the benefits of this treatment.

Patient 1 was a 31-year-old woman who worked in an air-conditioned office. She had a 3-year history of dry eye symptoms. She had become contact lens-intolerant and was considering photorefractive keratectomy. She had increased punctate staining, reduced Schirmer's test, and blepharitis. She had tried a variety of treatments, including collagen plugs, punctum silicone, autologous serum, and flaxseed oil. Following recurrent punctal inflammation, the punctal plugs were removed. She was then given Restasis, which resulted in resolution of nocturnal symptoms. However, she experienced increased epiphora and surgery for occluded puncta was performed. As of February 2005, she has continued to improve. This case history raises questions

about the use of punctal plugs with the advent of Restasis in terms of destructive versus reconstructive procedures.

Patient 2 was a 53-year-old man who worked in an air-conditioned office and used computers. He had a 7-year history of corneal erosions and nocturnal symptoms, for which he had undergone photorefractive keratectomy, which was unsuccessful. He had a rapid tear film break-up time and blepharitis. He had previously tried punctal plugs, autologous serum, doxycycline, and flaxseed oil, all of which had failed. In February 2004, he tried Restasis and his symptoms improved within 2 months. He remained well until he ran out of Restasis, and his symptoms returned within 2 months. He restarted Restasis and remains asymptomatic as of February 2006. This patient raises the question of when, if ever, to stop Restasis. Some patients have remained free of symptoms for at least 12 months after stopping Restasis, representing possible cure of dry eye through elimination of the underlying chronic inflammation.

Patient 3 was a 49-year-old menopausal woman who worked in an air-conditioned office and used computers. She had tried topical treatments, punctal plugs, autologous serum and doxycycline with no effect. In August 2005, she commenced Restasis and had improvement within 2 months. There was minimal change in signs, but maximum change in symptoms. Signs do not always correlate with symptoms, and both may fluctuate.

Patient 4 was a 53-year-old woman who had progressive problems with contact lens wear. She had tried punctal plugs and autologous serum to no effect. In September 2006, she started Restasis and quickly improved. In addition, her vision improved to 6/9 and 6/12. Improvement in visual acuity can occur after treatment with Restasis.

Even moderate dry eye is a problem for many patients, but symptom improvement can improve quality of life.

Efficacy of Topical Cyclosporine for Pterygia

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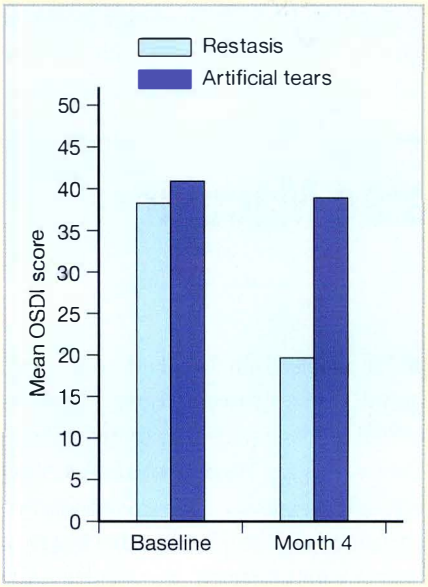
Pterygium is an elevated superficial ocular mass that usually forms over the perilimbal conjunctiva and extends onto the corneal surface within the interpalpabral area. The condition is prevalent throughout Asia, but there are a variety of treatments available, including surgery. Artificial tears can be effective for patients with small pterygia, but steroids or surgery may be required for patients with chronic inflammation.

Topical cyclosporine 0.05% (Restasis) has been shown to increase tear production and improve the quality of naturally produced tears in patients with dry eye. Restasis has also been shown to significantly reduce the number of activated T lymphocytes within the conjunctiva. Our study of the efficacy of Restasis for alleviating symptoms in 41 eyes of 26 patients with symptomatic pterygia was undertaken with a control group using the vehicle for Restasis. Ocular surface disease index (OSDI) scores improved significantly with Restasis as compared with vehicle during the 4-month study (Figure 1); there was also significantly less corneal and conjunctival staining and less perceived pain. Schirmer's testing and tear film break-up time (TFBUT) improved significantly. There was no increase in pterygium growth during the follow-up period. Only 1 patient in the Restasis group elected to undergo surgical excision of their pterygium compared with 7 of 8 patients who decided to have pterygium surgery in the control group.

Figure 1. Mean ocular surface disease index (OSDI) scores at baseline and after 4 months of treatment.



A 48-year-old man who had undergone pterygium surgery in his left eye 7 years previously complained of both eyes being red and irritated, and of smoke and wind sensitivity. He was trying artificial tears to alleviate the symptoms. He had developed a primary pterygium in his right eye and a recurrent pterygium in the left eye. He started Restasis, and after 1 month, Schirmer's test improved, TFBUT improved from 1 second to 4 to 5 seconds, and the redness and sensitivity improved. After 3 months, further increases were noted in the Schirmer's test and TFBUT, and the redness was alleviated.

Restasis significantly improved TFBUT, OSDI and Schirmer's scores, and reduced subjective pain and corneal staining in all 41 eyes. The ability of Restasis to improve the signs and symptoms of pterygia may be attributed to the immunomodulating properties of topical cyclosporine. The use of topical cyclosporine may reduce or delay the need for surgical excision of pterygia.

From the Allergan satellite symposium **Dry Eye Management for 2007 and Beyond** *held at the Asia-ARVO Meeting, Singapore, 2 March 2007.*

Epidemiology of Age-related Macular Degeneration

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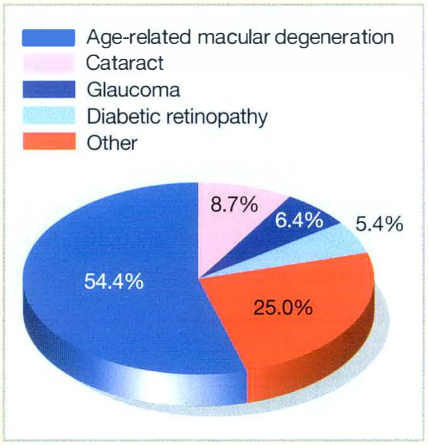
Age-related macular degeneration (AMD) is a chronic progressive disease of several stages, some of which are potentially amenable to intervention. Early AMD starts with drusen and lipofuscin-like deposits, and progresses to choroidal neovascularisation and, ultimately, subretinal fibrosis, destruction of photoreceptors, and limitation of vision.

The impact of neovascular AMD is far-reaching — more than 50% of irreversible visual loss in western countries arises from AMD.[1] Along with loss of visual acuity, patients lose independence — reading is affected, ambulation and driving become difficult, and decreasing face recognition affects social interaction. Up to one-third of patients experience clinical depression during the course of the disease.

AMD is a major public health issue in many countries, with 200,000 new patients diagnosed each year in the USA alone. More than 1.5 million people in the USA have late-stage AMD and AMD is the leading cause of blindness in adults in the USA (Figure 1).[2] It is estimated that nearly a million people will become blind with AMD during this decade. It is expected that there will be a 60% to 70% rise in the prevalence and incidence of AMD by 2020.

Figure 1. Leading causes of blindness in adults aged 40 years or older in the USA.



There are 2 stages of AMD. Dry or non-exudative AMD accounts for approximately 10% of visual loss. This stage is characterised by drusen and abnormalities of the retinal pigment epithelium. Wet or neovascular AMD is characterised by new vessel growth from the choroidal layer and usually has a severe impact on vision. The risk for developing AMD increases with age. The aetiology of AMD is poorly understood. There may be certain systemic factors in association with other risk factors that give rise to the disease. Free radicals and antioxidants may play a role in the prevention of the disease. Recent attention has been placed on the role of genetics, particularly complement hyperactivity — an AMD-type disease occurs in children with complement hyperactivity. There is growing concern that the inflammatory cascade may be responsible for initiation of neovascularisation in AMD. Approximately 50% of AMD in the West has been attributed to factor H and 25% to factor B. While there are many potential therapies, there is an unmet need for effective management of neovascular AMD. Anti-vascular endothelial growth factor therapy has shown promise in recent years, and heralds the onset of a golden age in ophthalmology.

In Conclusion

AMD impacts a significant and growing number of people worldwide. There is an unmet need for treatment of patients who lose vision from AMD. Rapid advances have been made in the management of exudative AMD, but strategies to prevent oxidative damage and activation of the complement pathway need to be established.

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Treatment of Age-related Macular Degeneration

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Age-related macular degeneration (AMD) has 2 recognised late forms: a neovascular form and an atrophic form. Two-thirds of late types of AMD are neovascular. Early precursors of these lesions include large drusen and pigmentary changes. The prognosis for late AMD is poor if left untreated. A meta-analysis that pooled the results of 53 trials found that most people with untreated neovascular AMD progressed to legal blindness within 3 years.[1]

Ocular risk factors for progression include large soft drusen and pigment clumping. Predictors of progression include the area involved by drusen and their proximity to the macular centre. The Age-Related Eye Disease Study Severity Scale is based on the presence of drusen or pigmentary changes in 1 or both eyes. Patients with 0 to 4 risk factors had a 5-year incidence of AMD of 0.5% to 50%, respectively.[2] This scale was validated using 10-year data from the Blue Mountains Eye Study.[3]

The common denominator in neovascular AMD is vascular endothelial growth factor

(VEGF). All types of neovascular AMD have demonstrated expression of both VEGF and VEGF receptors. Pegaptanib (Macugen®) is an anti-$VEGF_{165}$ aptamer that binds selectively to the pathological isoform of VEGF. The mechanism of action includes anti-angiogenicity, anti-permeability, and anti-inflammatory effects.

Pegaptanib in Clinical Practice

The VEGF Inhibition Study in Ocular Neovascularization (VISION) trial was a large randomised controlled multicentre study of pegaptanib.[4] 1190 patients were randomised to 4 groups to receive pegaptanib 0.3 mg, 1.0 mg, 3.0 mg, or usual care every 6 weeks. Photodynamic therapy (PDT) with verteporfin was allowed for classic lesions at the physician's discretion.

There were broad inclusion criteria to encompass all types of AMD. The baseline characteristics were similar between the groups in terms of lesion subtype and size. At 1 year, 70% of pegaptanib 0.3 mg-treated patients had maintained their vision (loss of <15 letters) compared with 55% of patients receiving usual care; this represented a 27% relative difference between pegaptanib 0.3 mg and usual care. The treatment benefit for pegaptanib was consistent across all subtypes (Table 1), which is comparable to the results for PDT. The pegaptanib treatment response was also independent of PDT use.

There was a continuous treatment benefit for pegaptanib over 2 years, representing a 45% relative benefit ($p < 0.01$). Approximately 30% of patients receiving pegaptanib progressed to legal blindness compared with nearly 60% for patients receiving usual care, representing a 36% relative benefit ($p < 0.01$). There was a 67% relative difference in time to develop vision loss of 3 lines in favour of the treatment group ($p < 0.05$).

Table 1. Treatment response for subtypes of age-related macular degeneration.

Subtype	Pegaptanib	Usual care
Predominantly classis	68%	57%
Minimally classic	75%	53%
Occult no classic	66%	56%

Table 2. Ocular safety profile of pegaptanib by year of study.

	Rate (% per injection)		
	Year 1 (n = 7545 injections)	Year 2 (n = 4091 injections)	Year 3 (n = 3227 injections)
Endophthalmitis	0.16	0.10	0.06
Traumatic cataract	0.07	0.02	—
Retinal detachment	0.08	0.17	0.03

Pegaptanib demonstrated a favourable safety profile over 2 years. Serious systemic adverse events were uncommon and were similar for the pegaptanib and usual care groups. Most ocular adverse events were attributed by the investigators to the injection procedure and did not increase in incidence over time.

The rate of endophthalmitis was low and was demonstrated to be a modifiable risk factor when an appropriate aseptic procedure was used. The endophthalmitis rate decreased as the trial progressed, possibly due to improved aseptic procedures, reinforced by study amendment, together with greater experience of intravitreal injections.

Early Treatment

Pegaptanib directly targets the underlying disease process in neovascular AMD. It is biologically plausible that less established neovascular lesions in eyes with healthier photoreceptors have the potential to be more responsive to the benefits of VEGF inhibition. Enhanced efficacy may be possible with earlier diagnosis and treatment of neovascular AMD with pegaptanib. It has been shown in animal models that new vessels have a better response to pegaptanib than mature or stable vessels.

Analysis of a subgroup of patients with early lesions found a 76% relevant benefit in favour of pegaptanib ($p < 0.006$). Eighty percent of patients with early lesions maintained their vision and 20% gained ≥3 lines.

Long-term Safety

161 patients were included in a 3-year ocular safety review. The ocular safety profile for each year is shown in Table 2. Intraocular pressure rose by 3 to 4 mm Hg during the first 30 minutes after injection, but there was no difference between baseline and 1 week, which was maintained throughout the study period.

There was no difference in deaths or discontinuations due to adverse effects between pegaptanib and usual care throughout the study period. Similarly, there were no differences between the groups for systemic hypertension, bleeding, ischaemic coronary artery disorders, or stroke. This is important, as AMD may be associated with an increased risk for stroke and coronary heart disease.

In Conclusion

There is a strong scientific rationale for selective anti-$VEGF_{165}$ therapy. The VISION trial 2-year clinical efficacy and safety data, extended now to 3 years for the safety data, indicate no long-term ocular or systemic safety concerns. Subgroup analysis indicates better outcomes for patients with earlier stage lesions.

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Targeted Pegaptanib: Experience from The Philippines

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Makati
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Patient 1 was a 61-year-old man with blurring of vision in the right eye. The vision in the right eye was 20/100. He had no history of diabetes or hypertension, but did have an early cataract and myopia in the right eye. He had had photodynamic therapy (PDT) 3 times in the right eye in 2004. Fluorescein angiography (FA) of the right eye showed significant swelling, oedema, and bleeding over the macula.

This patient had a series of 5 pegaptanib injections, resulting in a significant decrease in the amount of swelling after every injection, with resolution of the membrane (Figure 1). Pigment epithelial detachment also reduced. The patient's vision remained stable at 20/100.

Patient 2 was an 82-year-old woman with blurring of vision in the left eye. The vision in the left eye was 20/80. She had no history of diabetes or hypertension, but did have pseudophakia in the left eye. She had had PDT 5 times in the right eye in 2004. FA of the left eye at the time of PDT therapy showed some signs of dry degeneration, but no significant leakage. After a few months she complained of blurring of vision and FA showed signs of leakage. This patient had 3 injections of pegaptanib. There was a reduction in the amount of swelling after each injection, and her vision improved from 20/80 to 20/40 (Figure 2).

Patient 3 was a 68-year-old woman with distorted vision in her left eye. The vision in the right eye was 20/80. She had no history of diabetes or hypertension, but did have an early cataract in her left eye. FA showed bleeding around the foveal area and significant leakage in the left eye. She also had some leakage in the right eye. This patient had 2 injections of pegaptanib in the left eye. There was some resolution of the membrane and a decrease in the amount of leakage, and her vision improved from 20/80 to 20/60.

Patient 4 was a 76-year-old man with distorted vision in the right eye. His vision was 20/60 in the right eye and 20/100 in the left eye. He had diabetes and hypertension, and pseudophakia in both eyes. He had had cataract surgery to the right eye resulting in vision of 20/15. He had macular degeneration and scarring in the left eye and some leakage in the right eye. As his vision remained good at 20/15, the patient waited for treatment. After 6 months, he returned with scarring and

Figure 1. Patient 1 after 5 injections of pegaptanib.

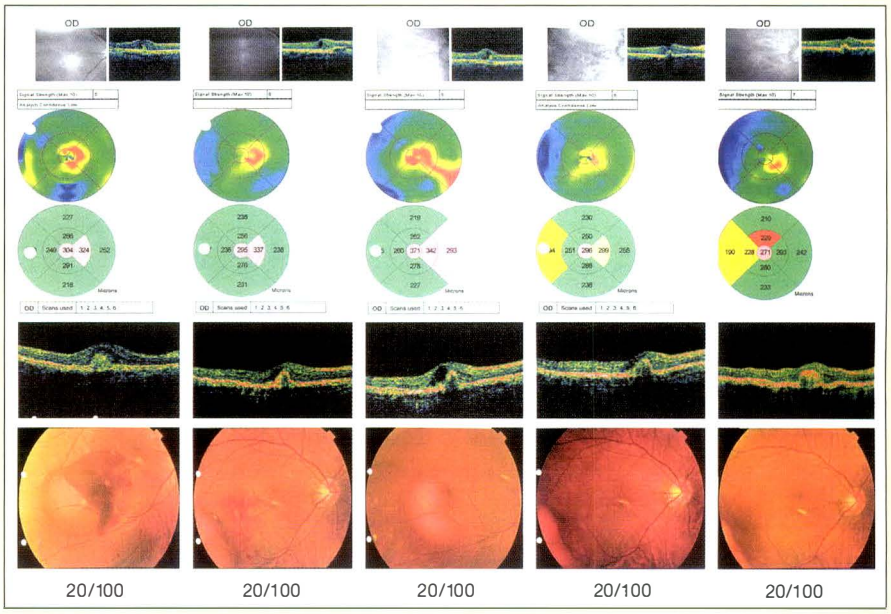
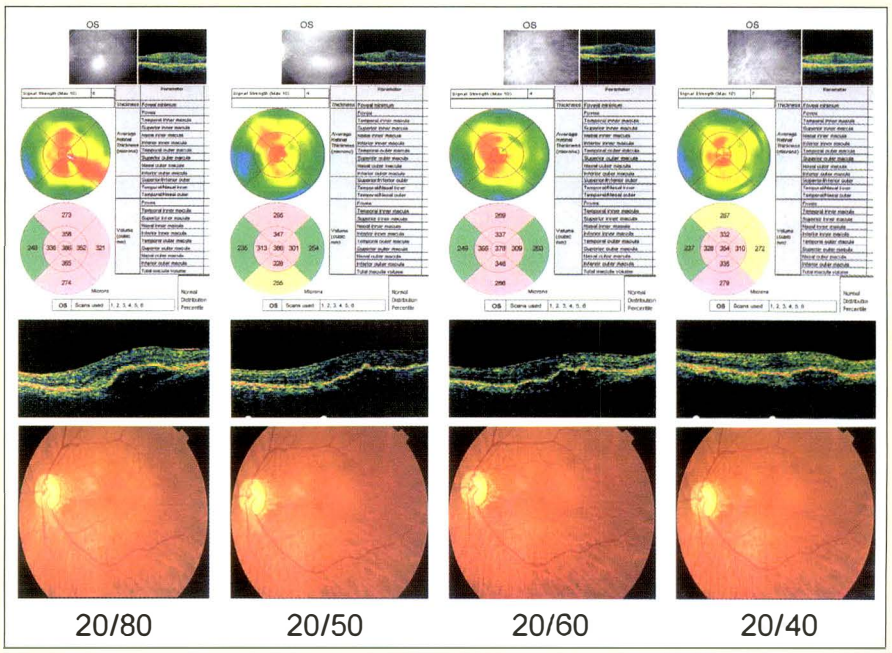


Figure 2. Patient 2 after 3 injections of pegaptanib.



bleeding in the left eye, with stable vision at 20/100, and his vision had decreased to 20/60 in the right eye. FA showed bleeding in the right eye. The patient had 3 injections of pegaptanib in the right eye, resulting in a reduction in the amount of swelling and leakage.

In Conclusion

Pegaptanib is the first anti-vascular endothelial growth factor drug for intravitreal injection. Clinical experience with pegaptanib is greater than for other drugs in this class. Long-term data show that this drug has a proven efficacy and safety profile. Pegaptanib has been studied in, and is approved for, all subtypes of wet age-related macular degeneration, including 'predominantly classic', the most aggressive form of the disease.

Targeted Pegaptanib: Experience from India

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Angiogenesis is a natural process, although it can lead to pathological problems such as tumour growth, arthritis, diabetes, and eye disorders. Vascular endothelial growth factor (VEGF) has a critical role to play in normal and pathological angiogenesis, particularly blood pressure control, pregnancy, wound healing, atherosclerosis, and protecting retinal neurones. $VEGF_{165}$ is the predominant isoform involved in choroidal neovascularisation (CNV). Selective blockade preferentially inhibits pathological retinal neovascularisation, but has no effect on normal retinovascularisation or retinal neurones. A patient with early CNV with subretinal fluid had visual acuity of finger counting at 1 metre (Figure 1). After pegaptanib treatment, subretinal fluid resolved and his vision improved to 6/12. A patient with occult CNV had visual acuity of 6/60 (Figure 2). After treatment with pegaptanib, his vision improved to 6/24.

Figure 1. A patient with early choroidal neovascularisation (a) before and (b) after pegaptanib treatment.

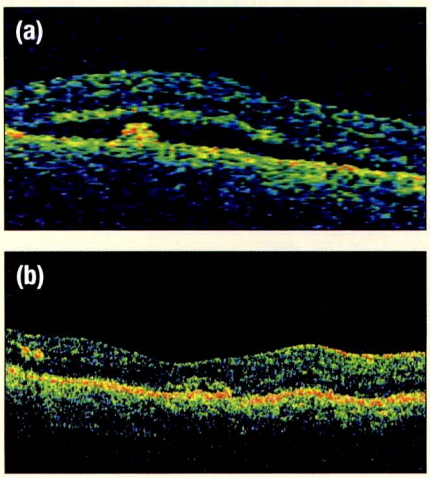
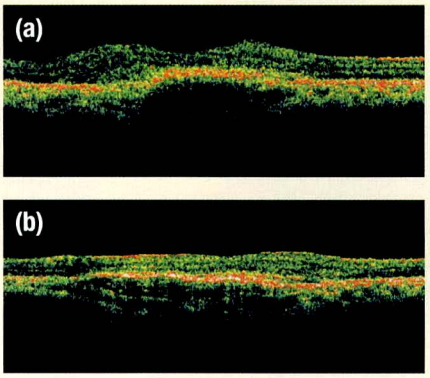


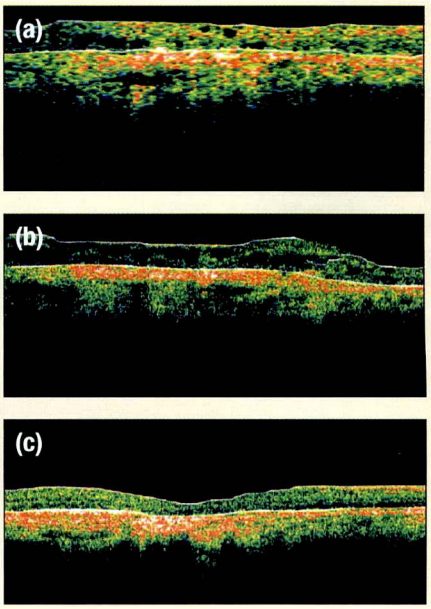
Figure 2. A patient with occult choroidal neovascularisation (a) before and (b) after pegaptanib treatment.



Pegaptanib exerts its maximum effect when used early in the course of the disease. Experience with pegaptanib shows that the visual acuity does not always correspond with the anatomic response, with visual acuity often improving despite the presence of residual fluid on fluorescein angiography images.

Anti-VEGF has shown promise as a treatment for diabetic macular oedema (DMO) and proliferative diabetic retinopathy, although pegaptanib is not yet approved for these indications. In a study of patients with retinal neovascularisation, most eyes showed regression after a series of pegaptanib injections, up to a maximum of 6. A phase 2 trial of patients with DMO found that eyes treated with pegaptanib had better visual outcomes, with reduced central macular thickness, and were less likely to need laser therapy.

Figure 3. A patient with diffuse macular oedema (a) before and (b,c) after pegaptanib treatment.

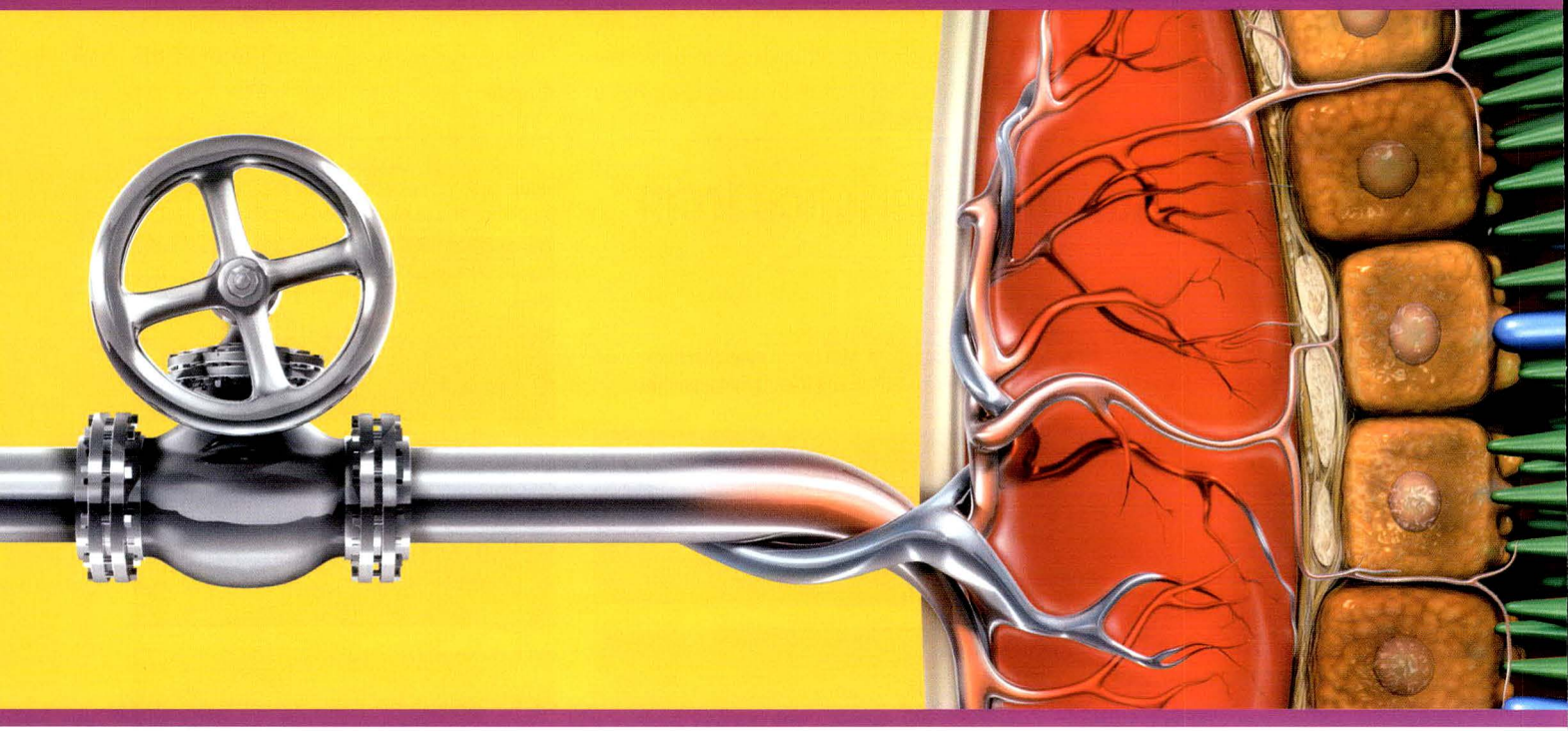


A patient with diffuse macular oedema and central macular thickness of 421 µ received 2 injections of pegaptanib 0.3 mg. After treatment, the macular had thinned to 215 µ (Figure 3).

Pegaptanib has been shown to regress neovascularisation before performing diabetic vitrectomy. Ideally, surgery should be performed 1 week post-injection. Side effects to consider when treating patients with anti-VEGF include hypertension, thromboembolic events, and proteinuria. However, adverse effects are rare and data have shown a good safety profile for pegaptanib.

From the Pfizer Ophthalmic satellite symposium **Optimizing the Targeted Treatment of Age-related Macular Degeneration: An Asian Perspective** *held at the Asia-ARVO Meeting, Singapore, 4 March 2007.*

NOW, ONE THERAPY CAN TREAT ALL NEOVASCULAR AMD*... AT ITS SOURCE



MACUGEN is the first selective VEGF$_{165}$† inhibitor with clinical efficacy to preserve‡ visual acuity in all neovascular AMD

- Overall, a reduced risk of visual-acuity loss was observed as early as 6 weeks after the treatment was started and was sustained through 2 years[1,2]

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* Age-related macular degeneration. † Vascular endothelial growth factor. ‡ Defined as <15 letters lost over 2 years.

References: 1. Data on file. Pfizer Inc, New York, NY. 2. Gragoudas ES, Adamis AP, Cunningham ET Jr, Feinsod M, Guyer DR, for the VEGF Inhibition Study in Ocular Neovascularization Clinical Trial Group. Pegaptanib for neovascular age-related macular degeneration. *N Engl J Med.* 2004;351:2805-2816.

MACUGEN ABBREVIATED PACKAGE INSERT TRADE NAME: Macugen **PRESENTATION:** Macugen injection is supplied in a single use 1 mL glass syringe containing pegaptanib sodium 0.3 mg in a 90 µL deliverable volume. **INDICATIONS:** Treatment of neovascular (wet) age-related macular degeneration. **DOSAGE:** 0.3 mg administered once every six weeks by intravitreous injection into the eye to be treated. Macugen should be inspected visually for particulate matter and discoloration prior to administration. The injection procedure should be carried out under controlled aseptic conditions. Adequate anesthesia and a broad-spectrum microbiocide should be given prior to the injection. **CONTRAINDICATIONS:** Patients with ocular or periocular infections. **WARNINGS & PRECAUTIONS:** FOR OPHTHALMIC INTRAVITREAL INJECTION ONLY. Intravitreous injections have been associated with endophthalmitis. Proper aseptic injection technique should always be utilized when administering Macugen. Patients should be monitored during the week following the injection to permit early treatment, should an infection occur. Intraocular pressure as well as the perfusion of the optic nerve head should be monitored and managed appropriately. **INTERACTIONS:** Pegaptanib is metabolized by nucleases and is generally not affected by the cytochrome P450 system. **PREGNANCY AND LACTATION:** Pregnancy Category B. Pegaptanib crosses the placenta in mice. There are no studies in pregnant women. The potential risk to humans is unknown. Macugen should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the fetus. It is not known whether pegaptanib is excreted in human milk; caution should be exercised when Macugen is administered to a nursing woman. **SIDE EFFECTS:** Anterior chamber inflammation, blurred vision, cataract, conjunctival hemorrhage, corneal edema, eye discharge, eye irritation, eye pain, hypertension, increased intraocular pressure (IOP), ocular discomfort, punctate keratitis, reduced visual acuity, visual disturbance, vitreous floaters, and vitreous opacities. Injection procedure related side effects include endophthalmitis, retinal detachment, iatrogenic traumatic cataract. **STORAGE:** Store in refrigerator at 2°C to 8°C. Do not freeze or shake vigorously. Reference: USPI (Dec 2004). **FULL PRESCRIBING INFORMATION IS AVAILABLE UPON REQUEST.**

MAC06003P

9th International Congress of the International Ocular Inflammation Society

17-20 September 2007, Paris, France

Contrary to what some predicted years ago, the field of ocular immunology has expanded with the inclusion of new diseases, immune-related diseases, and fascinating new theories that suggest an immunological role for classic 'degenerative' and 'pure metabolic' pathologies. Again, and this time with much more scientific support, this conference discusses the possibility that infectious agents in genetically predisposed patients living under specific environmental conditions cause a higher risk of development of severe immune-mediated ocular diseases. Age-related maculopathy and diabetic retinopathy are examples.

The discovery of new biologics and various orphan drugs have expanded the number of therapeutic agents. Equally importantly, there are now many new routes of administration. There is a whole new group of drugs available with specific indications, side effects, and complications. Never has the challenge of mastering this knowledge been so great.

More than 20,000 ocular specialists from around the globe have been invited to attend the 9th International Congress of the International Ocular Inflammation Society in Paris, France, from 17 to 20 September 2007 to join leading specialists in the field of ophthalmology and visual sciences. Classic immunology has evolved, and now includes many aspects of other fields that in the past were compartmentalised. Molecular biology, genetics, epidemiology and pharmacology applied to ocular diseases will be discussed in depth.

Today, congresses in medical sciences, and particularly in the field of ocular inflammation and immunology are more important than ever, and are vibrant events covering new ideas, concepts, paradigms and diagnostic and therapeutic challenges. New communication tools enable investigators and clinical ophthalmologists to exchange ideas, but congresses remain the ideal forum for intense scientific interaction. Where else could we experience all that is happening, discuss with colleagues and industry, explore new ideas, compare experiences, and discover new potential projects within just a few days?

For more information, visit the website at: **www.iois-paris-2007.com** or e-mail: **contact@iois-paris-2007.com.**

Participating Societies

The International Uveitis Study Group (IUSG)
The American Uveitis Society (AUS)
The Society for Ocular Immuno-Infectiology in Europe (SOIE)
The Sociedad Panamericana de Enfermedades Inflamatorias Oculares (SPEIO)
The Hellenic Society for the Study of Ocular Inflammations and Infections (HSSOII)
The Uvea-Behcet Division of the Turkish Ophthalmological Society (UBDTOS)
The Chinese Ocular Immunology Association (COIA)

30th Annual Congress of the Ophthalmological Society of Pakistan and 4th Khyber Eye Symposium

22-24 February 2008, Peshawar, Pakistan

The 30th Annual Congress of the Ophthalmological Society of Pakistan and 4th Khyber Eye Symposium — *Challenging Frontiers in Ophthalmology* — will be held in Peshawar, Pakistan, from 22 to 24 February 2008. Many eminent ophthalmologists from Pakistan and abroad will be presenting papers on various important aspects of ophthalmology. There will be state-of-the-art lectures on cataract, glaucoma, oculoplasty and orbit, paediatric ophthalmology, ocular surface, and vitreoretina.

For further information, contact e-mail: **osp_nwfp@hotmail.com**

pSivida and Pfizer Collaborative Research and Licensing Agreement

pSivida Limited has signed an exclusive worldwide Collaborative Research and License Agreement with Pfizer Inc for pSivida's controlled drug delivery technologies, including the Medidur™ technology, in ophthalmic applications. The 2 companies will work together on a joint research program aimed at developing ophthalmic products using pSivida's sustained drug delivery technology. "We believe that this collaboration is another significant validation of the drug delivery systems that pSivida has been developing since its founding," said Dr. Paul Ashton, Managing Director, pSivida Limited.

Injectable Medidur

Medidur is a tiny, injectable device designed for the sustained release of drugs and is currently being studied for the treatment of diabetic macular oedema, the leading cause of blindness for Americans younger than 65 years. Medidur, in combination with fluocinolone acetonide, is in phase III clinical trials for diabetic macular oedema, in collaboration with Alimera Sciences Inc, a specialty pharmaceutical company focused on the ophthalmic industry.

IMAGE Modules 5 and 6 Released

The South East Asia Glaucoma Interest Group (SEAGIG) is pleased to announce the release of the third 2 modules of the educational resource from the Initiative for Management, Awareness and Glaucoma Education (IMAGE) project. Intended for use by ophthalmologists for their own educational advancement, as well as to facilitate educational programmes, the slides have been prepared by SEAGIG/IMAGE members to be clinically relevant to glaucoma care in the region and to have educational value relevant to the region.

The *Setting IOP Targets* module covers the rationale for setting target intraocular pressure (IOP) and outlines data from important glaucoma clinical trials with their implications for patient management. The first part of this presentation discusses the rationale behind setting IOP targets and is designed to aid the practising ophthalmologist in establishing an IOP range for each patient that will help preserve vision and quality of life.

In-depth evidence from landmark trials in glaucoma, covering major findings that impact clinical care, is reviewed in the second portion of this module. This section may be discussed separately depending on time constraints and the educational objectives of the presentation. The final slide lists key take-home messages (Figure 1).

At the end of the presentation, participating clinicians should be able to: understand the importance of establishing and maintaining consistently low target IOP ranges; list the different treatment categories for glaucoma based on the SEAGIG guidelines; confidently set a target IOP range based on the treatment categories and individual patient factors; and describe the outcomes and implications of key clinical trials demonstrating the role of IOP lowering in preventing disease progression.

The *Medical Treatment* module provides an overview of the medical therapies available for the treatment of glaucoma. Clinical data on the efficacy and safety of these medicines is presented. Tips for optimising medical treatment, including how to maximise patient adherence, are covered in the first section of this module. A medical treatment algorithm is provided to guide clinicians in making treatment decisions, and the pros and cons of various drug classes are also discussed. The next portion of this module presents some of the clinical trial data available on the efficacy and safety of these medicines. Finally, the role of preservatives in ocular medications is explored. The key points are shown in Figure 2.

Acknowledgement

With gratitude to the members of the SEAGIG-IMAGE Project Working Group.

Reference

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

Figure 1.

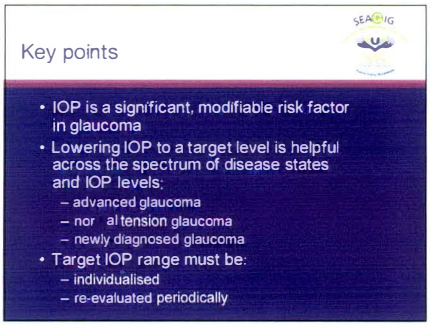
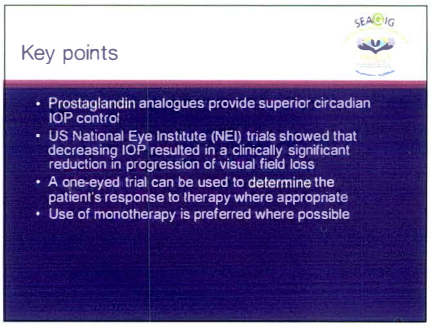


Figure 2.



Erratum

The name of Dr Neeraj Wadhwa was inadvertently missing from the list of presenting authors to Free Paper 1 on page 51 of the abstract book to the 2007 Asia-ARVO Meeting on Research and Vision and Ophthalmology held at Suntec Singapore International Convention and Exhibition Centre, Singapore, 2-5 March 2007.

The full reference to the abstract is as follows:

Wadhwa N, Venkatesh P, Garg S, Mehrotra A, Mandal S. Rhegmatogenous retinal detachments in children in India: clinical characteristics, risk factors and surgical outcomes. Asian J Ophthalmol. 2007;9 (Suppl 1):51.

The full abstract is printed below.

1

RHEGMATOGENOUS RETINAL DETACHMENTS IN CHILDREN IN INDIA: CLINICAL CHARACTERISTICS, RISK FACTORS AND SURGICAL OUTCOMES

N. WADHWA, P. VENKATESH, S. GARG, A. MEHROTRA, S. MANDAL
Dr. Rajendra Prasad Centre for Ophthalmic Sciences, New Delhi, INDIA

Purpose: To describe the spectrum of clinical features and surgical outcomes in a series of children with rhegmatogenous retinal detachments (RRD's) in a tertiary care hospital of north India.

Methods: 230 eyes of 216 children 18 years of age or younger who underwent surgery for RRD were studied. Detailed history, complete ophthalmic and systemic examination wherever essential was done. Characteristics of retinal detachment were noted with respect to macular status, and proliferative vitreretinopathy (PVR) graded. Risk factors for retinal detachment were noted and classified into following categories: (1) trauma - open globe or closed globe (2) Predisposing lesions in peripheral retina - with and without myopia (3) Iridofundal coloboma related RRD (4) Associated with structural ocular abnormalities, (5) previous surgery, and (6) preceding uveitis. Buckling alone or with pars plana vitrectomy was done.

Results: Mean age was 11.12 + 3.56 years, and 81.9% of patients were boys. Thirty-five (16.2%) patients had bilateral retinal detachment at presentation. Every eye had at least one risk factor for retinal detachment, if more than one risk factor was there, eye was grouped according to primary pathology causing RRD. Detachments tended to be complex, with 54.3% (125/230 eyes) having some form of PVR. Mean follow-up was 12.3 months. Complete retinal reattachment was achieved in 88.7% of eyes; however, visual recovery was modest. Mean preoperative and postoperative visual acuities were 0.032 + 0.119 and 0.096 + 0.168 respectively (p=0.000).

Conclusions: Most common causes predisposing to RRD were peripheral degenerations and posttraumatic. RRD's secondary to iridofundal coloboma may be more common than previously reported. Combination of buckling and vitreoretinal techniques can help achieve retinal reattachment in most cases. Presence of anterior PVR is a poor prognostic factor in terms of both anatomic success as well as visual gain.

Table Abstract 1.

Our results as compared to other studies

Study	No. of Eyes	Patient Age	Mean Follow-up (months)	Visual Acuity > 0.1 n (%age)	Success No. of Eyes (%age)	Comments
Ferrone et al, 1994	48	< 16	23	2 (4.2)	16 (35)	Vitrectomy with 1000 cs or 5000 cs oil
Moisseeiev et al, 1998	28	< 15	24	5 (18)	9 (32)	Vitrectomy with 1000 cs oil
Akabane et al, 2001	32	< 15	16.6	28 (87.5)	30 (93.8)	Buckling in 25 eyes while vitrectomy in 7 eyes out of which two failed
Scott et al, 1999	211	< 16	13.9	38 (18)	117 (56)	Vitrectomy for complex RRD with 1000 cs oil
Weinberg et al, 2003	39	< 18	24	NR	31 (79)	Scleral buckle (41%) as well as vitrectomy (67%)
Our study	230	< 18	12.3	69 (30)	204 (88.7)	Buckling (85 eyes) as well as vitrectomy (159 eyes) with 1000 cs oil

August 2007

25-29
2007 Annual Symposium of the International Society for Clinical Electrophysiology of Vision (ISCEV)
Hyderabad, India
Contact: Dr Subhadra Jalali, Secretariat
Tel: (091 040) 3061 2607
Fax: (91 040) 2354 8271
E-mail: Subhadra@Lvpei.Org
Website: www.Iscev2007.Org?Ophthalmology

September 2007

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

17-20
9th International Congress of the International Ocular Inflammation Society
Paris, France
Contact: Rubens Belfort
E-mail: contact@iois-paris-2007.com
Website: www.iois-paris-2007.com

28-30
Asia Pacific Association of Cataract and Refractive Surgeons Annual Meeting
Hanoi, Vietnam
Contact: Secretariat
E-mail: apacrs2007@snec.com.sg
Website: www.apacrs2007.org

November 2007

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

24-28
2007 National Congress Of The Royal Australian & New Zealand College Of Ophthalmologists
Perth, Australia
Contact: Congress West
Tel: (61 89) 389 6906
Fax: (61 89) 389 1234
E-mail: Conwes@Congresswest.Com.Au
Website: www.Congresswest.Com.Au/Ranzco2007?Ophthalmology

December 2007

2-4
Asian Oceanic Glaucoma Society 2007
Bangkok, Thailand
Contact: Secretariat
E-mail: tenkn@mahidol.ac.th

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

February 2008

22-24
30th Annual Congress of the Ophthalmological Society of Pakistan and 4th Khyber Eye Symposium
Peshawar, Pakistan
Contact: Tariq Farooq Babar
Tel: (92 91) 5825 087
E-mail: osp_nwfp@hotmail.com

28-2 March
7th International Symposium on Ocular Pharmacology and Therapeutics
Budapest, Hungary
Contact: Robert Nesbitt
Tel: (44 229) 080 488
Fax: (44 227) 322 850
E-mail: isopt@kenes.com

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

March 2008

30-3 April
7th International Diabetes Federation Western Pacific Region Congress, Diabetes Asia Pacific, Working for Solutions
Wellington, New Zealand
Contact: Russ Finnerty
Tel: (64 44) 738 442
E-mail: congress@diabetes.org.nz

May 2008

21-24
18th International Visual Field & Imaging Symposium (IPS2008)
Nara, Japan
Contact: Chota Matsumoto
Tel: (81 72) 366 0221
Fax: (81 72) 368 2559
E-mail: ips2008@med.kindai.ac.jp

June 2008

28-2 July
World Ophthalmology Congress
Hong Kong
Contact: Ms Angela Cho
Tel: (852) 2762 3128
Fax: (852) 2194 0695
E-mail: angelacho@woc2008hongkong.org
Website: www.woc2008hongkong.org/

July 2008

7-10
9th International Conference on Low Vision Rehabilitation - Vision 2008
Montreal, Canada
Contact: Beatrice Laham
Tel: (514) 906 1979
E-mail: blaham@opus3.com

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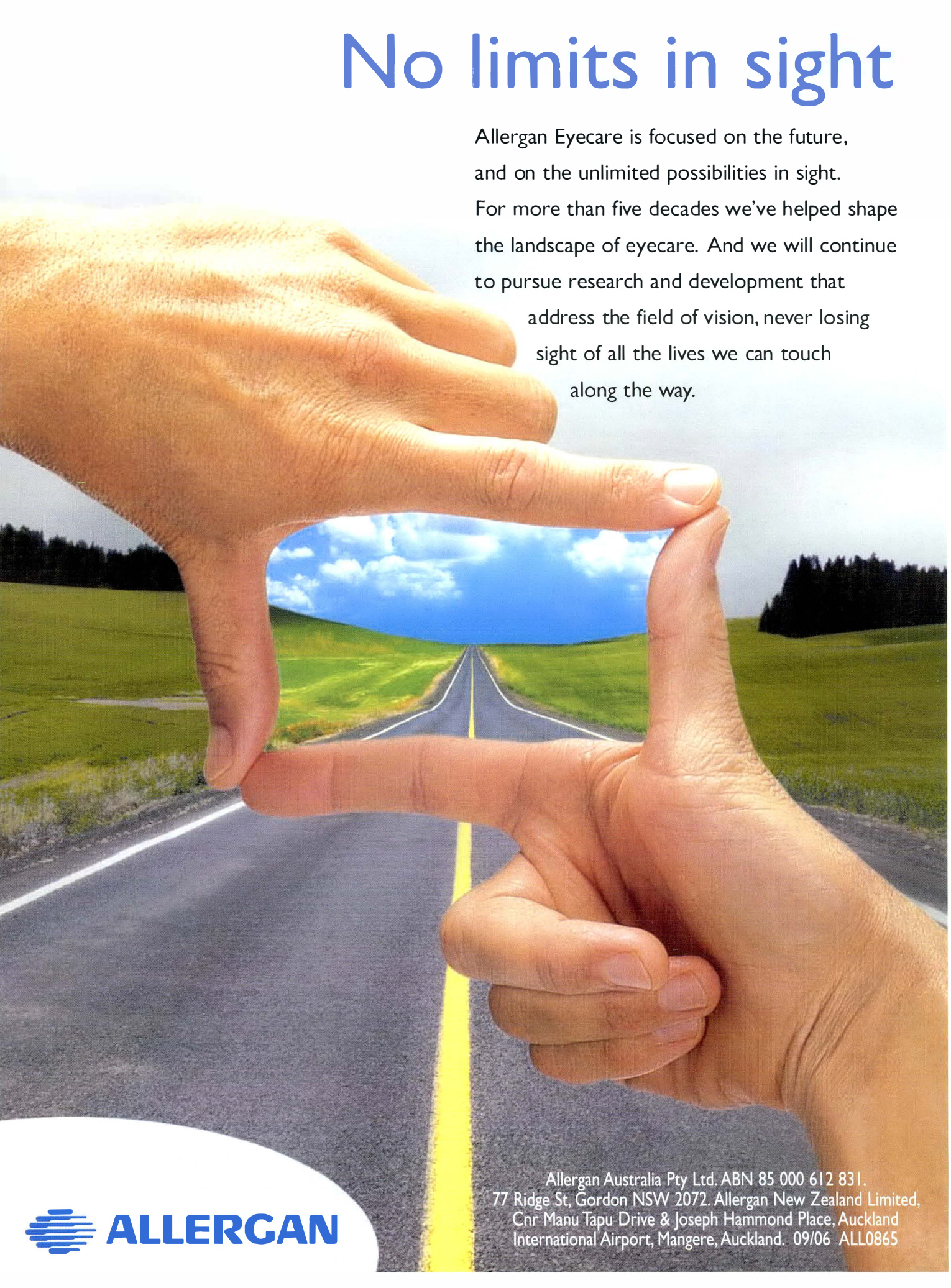

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References:
1. Higginbotham EJ, Feldman R, Stiles M, Dubiner H, for the Fixed Combination Investigative Group. Latanoprost and timolol combination therapy vs monotherapy: one-year randomized trial. *Arch Ophthalmol.* 2002;120:915-922. 2. Data on file.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

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