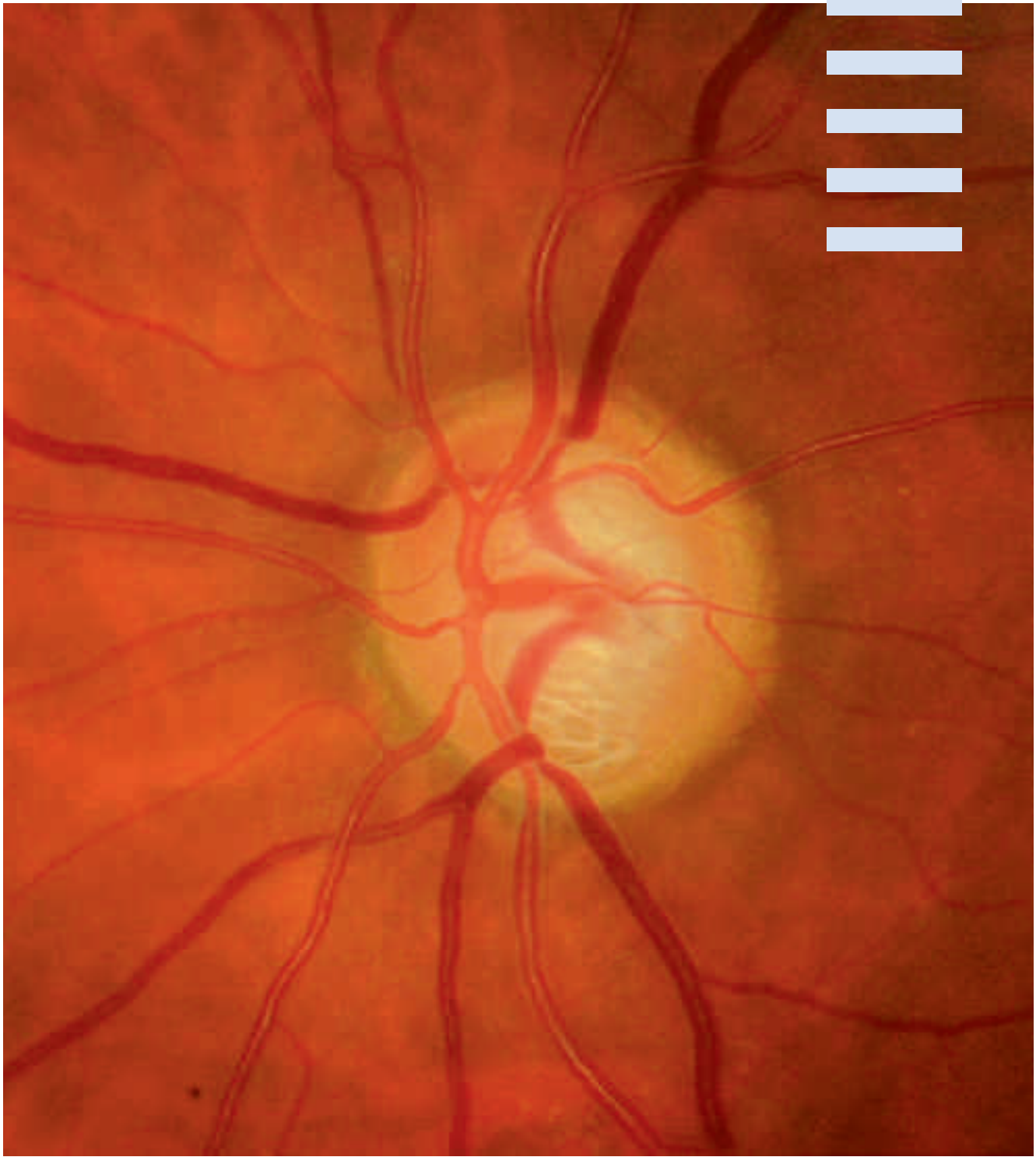
Supplement to
AUSTRALIAN OPTOMETRY

Special issue GLAUCOMA

pharma

MARCH 2013



- Structure-function relationship of glaucoma
- IOP and the 24-hour diurnal cycle
- Treatment of ocular hypertension
- Glaucoma diagnosis and management
- Drug delivery contact lenses to treat IOP
- Digital imaging and screening

XALACOM: It's a logical UPGRADE[1-4]

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Xalacom® latanoprost/timolol maleate

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Before prescribing, please review Product Information available from Pfizer Australia Pty Ltd. (www.pfizer.com.au) **MINIMUM PRODUCT INFORMATION: XALACOM® (latanoprost 50 µg/mL and timolol 5 mg/mL)** Eye Drops. **Indications:** Reduction of IOP in open-angle glaucoma and ocular hypertension, if insufficient response to other medications. Not for initial therapy. **Contraindications:** Reactive airway disease including bronchial asthma (and history), or severe chronic obstructive pulmonary disease (COPD). Sinus bradycardia, sick sinus syndrome*, sino-atrial block*, second or third degree atrioventricular block, overt cardiac failure, or cardiogenic shock. Hypersensitivity to ingredients. **Precautions:** Beta-blocker systemic effects: cardiovascular/respiratory reactions; first degree heart block*; severe peripheral circulatory disturbance/disorders*; mild/moderate COPD*; consider gradual withdrawal prior to major surgery; beta-blocking ophthalmological preparations may block systemic beta-agonist effects (inform anaesthesiologist)*; anaphylactic reactions; caution in hypoglycaemia, diabetes, hyperthyroidism, myasthenia gravis; concomitant beta-blocker or prostaglandin not recommended. Ocular: change in eye colour due to increased iris pigmentation; heterochromia; eyelid skin darkening; changes in eyelashes and vellus hair; macular oedema; caution in other types of glaucoma; herpetic keratitis*; pseudophakia; aphakia; filtration procedures; corneal diseases*; blurring of vision; contact lenses. Do not use in pregnancy (Pregnancy category C), lactation and children. See PI for details. **Interactions with other Medicines:** Additive effects with other drugs; thiomersal; combined treatment with CYP2D6 inhibitors*. **Adverse Effects:** Ocular: eye irritation; hyperaemia; abnormal vision; visual field defect; increased iris pigmentation; eyelash and vellus hair changes; corneal oedema and erosions; blepharitis*; keratitis*; vision blurred*; dry eyes*; eye pain*; conjunctivitis*; macular oedema*; photophobia*; periorbital and lid changes resulting in deepening of the eyelid sulcus*. Systemic: serious respiratory and cardiovascular events (worsening of angina pectoris, cardiac failure*, pulmonary oedema); anaphylaxis; non-specific chest pain*; herpetic keratitis*; localised skin reaction on the eyelids*; skin rash*; pruritus*; headache*; dizziness*; depression*; dysgeusia*; vomiting*; abdominal pain*; muscle/joint pain*; sexual dysfunction*. See PI for details. **Dosage and Administration:** One eye drop in the affected eye(s) once daily. Other eye drops at least 5 minutes apart. See PI for details. V10712

*Please note change(s) to Product Information

 References: 1. Diestelhorst M et al. Ophthalmology 2006; 113: 70–76 **2.** Konstas AGP et al. Arch Ophthal 2005; 123: 898–902 **3.** Higginbotham EJ et al. Arch Ophthal 2002; 120: 915–922 **4.** Higginbotham EJ et al. Arch Ophthal 2010; 128: 165–172 McCann Healthcare XAL0298AustPharm P7101-Jan 2013

Pfizer Established Products

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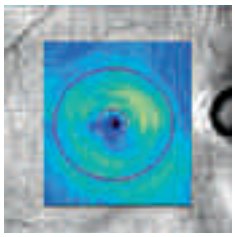


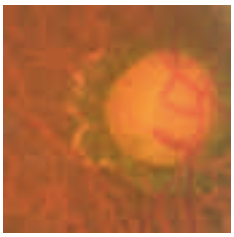

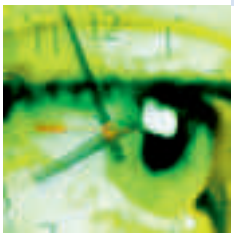

Published by
OPTOMETRISTS
ASSOCIATION AUSTRALIA

Editor: **JEFF MEGAHAN**

National Publications Manager:
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Associate Professor **MARK ROTH**
Department of Optometry and Vision Sciences, The University of Melbourne

Optometrists Association Australia
ABN 17 004 622 431
204 Drummond Street
Carlton VIC 3053
Tel (03) 9668 8500
Fax (03) 9663 7478
j.megahan@optometrists.asn.au
www.optometrists.asn.au

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Glaucomatous optic disc inferior notch Photo: Centre for Eye Health

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Moving forward in 2013

Shared care between eye-care practitioners is the next, vital step towards achieving Glaucoma Australia's mission statement: 'Working to minimise sight disability from glaucoma.'

Geoff Pollard
National executive officer
Glaucoma Australia

The prevalence of glaucoma, consistent with an ageing population, is increasing in Australia. There is a corresponding need for all eye-health providers, with Glaucoma Australia included, to work together in the best interests of those at risk of, or whom have glaucoma.

A recent Newspoll survey reported by the RANZCO Eye Foundation found that 40 per cent of Australians do not have their eyes tested on a regular basis. While non-attendance negatively affects detection rates, two studies–the Blue Mountains Eye Study and the Melbourne Visual Impairment Project–independently showed that about 50 per cent of glaucoma cases were previously undiagnosed. This was despite the fact that almost 60 per cent of the subjects had visited an eye-care provider during the prior year. Though both studies were conducted more than 15 years ago and there is a critical need for more up-to-date data, they mirror other, more recent, First World detection rates.

Awareness campaigns highlighting the need for regular eye checks can help, especially when they discuss family history as a clear determinant for the development of glaucoma. What may be needed though, is to work on getting the testing messages out at a 'pinch point', where the vast majority of the population visits on a regular basis. General practices and pharmacies are such places and a concerted effort by local eye-health providers to educate and inform local GPs and pharmacists may well pay dividends in higher eye examination attendance rates and in substantially higher glaucoma and other eye disease-detection rates.

Glaucoma Australia can likewise play a role in educating and supporting patients with glaucoma, especially when first diagnosed and treated. Glaucoma Australia helps to educate patients and provide eye-drop technique training, services which are especially important, given that statistics show that over half the patients started on glaucoma medication will lapse into non-compliance within one year.

Ultimately, the key to a positive health outcome for patients with suspected or confirmed glaucoma is a synergistic partnership between eye-care providers. On first presentation, a thorough patient history and a comprehensive examination are vital to making an accurate diagnosis that supports an informed referral and provides increased confidence when organising shared care for the benefit of that patient.

Glaucoma Australia believes optometrists should be well placed to review patients on an ongoing basis, seeking the advice of an ophthalmologist in the event of circumstances that may indicate disease progression or a change in therapy is required. To increase the ability of both groups of eye-care providers to focus on the needs of the patient, and to organise for initial and ongoing patient care for the betterment of those patients, are seen as laudable goals. ■

Genetics and the family in glaucoma awareness

Dr Alex Hewitt PhD
Adjunct Research Fellow,
Centre for Ophthalmology and Visual Science, University of Western Australia

As environmental risk factors for glaucoma remain elusive, genes and family history continue to be the strongest determinants of the disease.

Over the past two years there have been dramatic increases in our understanding of the molecular mechanisms of primary open angle glaucoma, with at least three novel genetic loci being identified. Despite our improved understanding of glaucoma genetic risk factors, family history remains one of the strongest known determinants for the development of this disease.

It had been almost a decade since the last major genetic discovery for glaucoma had been made when in 2010, researchers from deCODE Genetics in Iceland identified common variants near the CAV1 and CAV2 genes as being associated with disease development.[1] This novel finding was replicated in samples from across Australia and the United Kingdom. Previous work has suggested that the CAV1 and CAV2 are regulators of adult neural stem cell proliferation, and CAV1 activation can lead to nitric oxide production and neurodegeneration.[1] Nonetheless, genetic variants at this locus confer only a modest increase in disease susceptibility.

The following year, an Australian study reported the identification of two additional genetic loci, which are unequivocally associated with glaucoma. DNA samples from people with severe glaucoma were recruited through the Australian and New Zealand Registry of Advanced Glaucoma (www.anzrag.com) led by Professor Jamie Craig at Flinders University of South Australia, along with the recruitment of many population controls through the Blue Mountains Eye Study, led by Professor Paul Mitchell.

Genome-wide significant associations were identified on chromosome 1 (TMCO1) and chromosome 9 (CDKN2BAS1). The study-wide odds ratios for the most associated variants at each locus were 1.51 (95% CI: 1.35-1.68) and 1.39 (95% CI: 1.28-1.51), respectively.[2] Interestingly, the implicated region on chromosome 9 also harbors the tumour suppressor genes CDKN2A and CDKN2B. The association between the CDKN2BAS locus and POAG has now also been independently identified by other groups and found to be a major determinant for cup to disc ratio size in the general population. Interestingly, the TMCO1 locus was recently found to be associated with intraocular pressure in the general population.[3]

In our population, grouping individuals with one or two risk alleles together at both the TMCO1 and CDKN2BAS2 loci, conferred a 3.03 (95% CI: 1.52-6.07) fold increased risk for disease development.[2] However, it is important to note that about 18 per cent of the general population falls into this risk category. In an animal glaucoma model it was revealed that the retinal expression of CDKN2A and CDKN2B, but not TMCO1, occurred one week after induction of ocular hypertension, a time-point corresponding to ongoing retinal ganglion cell death.[2]

Identifying genes predisposing to glaucoma development ensures a greater understanding of the disease and in time will lead to new therapeutic avenues. It also allows for the direct identification of people at highest risk for developing glaucoma, an important issue given that about half the people in our community with glaucoma are unaware that they have the disease.

Questioning each glaucoma patient or suspect about their knowledge of a family history for this disease remains one of the most important facets of clinical risk profiling. No strong environmental risk factors have been identified, despite many large epidemiological studies.

The Glaucoma Inheritance Study in Tasmania (GIST), led by Professor David Mackey, revealed that a positive family history is present in about 60 per cent of people with primary open angle glaucoma when family members are examined.[4] Wolfs and colleagues found that first-degree relatives of glaucoma patients had a 22 per cent lifetime risk of developing glaucoma, in comparison to 2.3 per cent in the relatives of controls, implying a 10-fold increased relative risk of the disease in first-degree relatives of affected patients compared with the general population.[5]

Further work from the GIST demonstrated that disease severity scores, a phenotypic scale that provides a combined weighting of glaucoma severity based on findings from visual loss and optic disc analysis, were significantly skewed towards worse disease in people who have a known family history of glaucoma compared to patients who have 'sporadic' glaucoma.[6]

There have been dramatic inroads into furthering our understanding of the pathophysiology of glaucoma. Unfortunately, a genetic diagnosis of glaucoma is not ready for 'prime time'. It is, however, predicted that within the next decade, this will change.

In time, the most important question a clinician could ask their glaucoma suspect will change from 'Does anyone else in your family have glaucoma?' to 'Have you had your glaucoma genetic risk profile performed yet?' ■

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Can digital imaging be used to screen for glaucoma?

Dr Ridia Lim
MB BS MPH FRANZCO
Sydney Eye Hospital

Glaucoma is universally underdiagnosed and finding people with glaucoma who are undiagnosed is one of the main challenges we need to meet as eye-care professionals. Glaucoma imaging systems have had an exponential rise in use in the past decade so it is increasingly important to reflect on whether imaging could be used to screen for glaucoma.

Structural testing for glaucoma is appealing: it is objective, fast, painless, reliable and less dependent on the patient and operator. It may offer earlier glaucoma diagnosis than standard automated perimetry (SAP). The diagnosing clinician needs a clear understanding of the role of imaging and its use, benefits and limitations.

What are the modalities for optic disc imaging?

There are three imaging modalities used in glaucoma diagnosis: the Heidelberg retina tomograph (HRT), GDx and optical coherence tomograph (OCT). The hardware and software of all have advanced over time. The three technologies are different and their findings, such as CD ratio and RNFL thickness, are not interchangeable between the technologies.

HRT is a confocal scanning laser ophthalmoscope. A diode laser (670 nm) scans the retina in sequential sections of increasing depth. GDx is a scanning laser polarimeter (SLP). It uses a 785 nm polarised light to measure the thickness of the retinal nerve fibre layer by measuring retardation of the light by birefringent tissues. OCT uses an infrared light source (840 nm for Stratus and Cirrus) and a Michelson type interferometer to measure either time of flight of light (time domain) or wavelengths (spectral domain) of back scattered light and thereby acquire spatial information.

How do we measure the strength of a test?

With any test for glaucoma, we need to know its precision: the validity (does it measure what it is supposed to measure?), reliability/reproducibility, sensitivity and specificity. All three imaging modalities have been shown to have very good reproducibility. SD-OCT has improved on TD-OCT in reproducibility. Older studies have shown that HRT2, GDX-VCC and Stratus OCT have similar sensitivities and specificities.

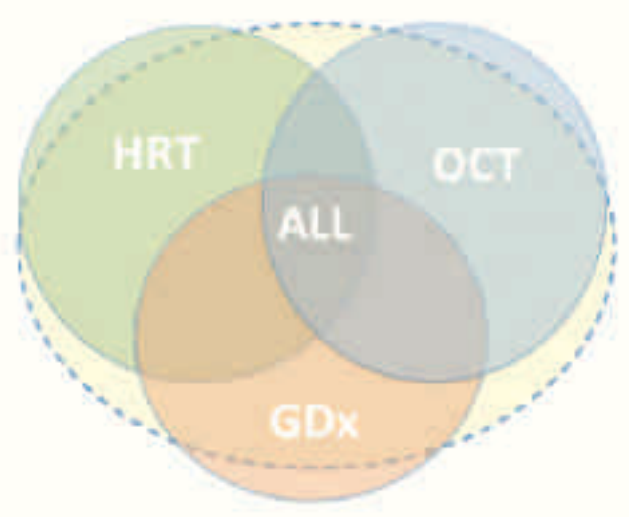

Figure 1. Glaucoma diagnosis by different modalities; they overlap but are not necessarily diagnosing the same people

As seen in Figure 1, each technology will diagnose a subset of the true positives. Each imaging device might have similar sensitivities and specificities but not necessarily diagnose the same eyes having disease or not having disease. As they measure different aspects of structure, they are likely to be complementary to one another, rather than 'one technology fits all'.

The sensitivity and specificity results differ, depending on the cases tested: mild, moderate and severe cases chosen with reproducible SAP defects give rise to variable sensitivity and specificity (Table 1). Generally, studies are flawed due to our lack of a gold standard for glaucoma diagnosis. If the SAP is already reproducible, why do we need another diagnostic test?

What we really want to do is apply the test to glaucoma suspect cases and thereby reduce the uncertainty of the diagnosis following the test. What we are looking for is increased post-test probability of diagnosis (Table 1). This relies on the prevalence of the disease in the tested population. Another interpretation would be that there is little value in screening a general population but much more value in using imaging for case finding among glaucoma suspects.

What are some of the errors seen in the imaging?

The imaging tests are all colour-coded and give some indication of whether the patient tested falls within the 'normal' category. To interpret the tests results, we need to understand who is in the normative database, so that we can differentiate between the 'real' disease from the 'red' disease of false positives.[1]

Artefacts and errors in acquisition can occur with media opacity, blinking, nystagmus, scan decentration or misalignment, and disc outline error. Older age, high myopia and lightly-coloured fundus may have higher birefringence and thus higher signal-to-noise ratio for SLP. Macular scans used for GCA in OCT are affected by macular disease such as epiretinal membranes.

To differentiate the 'red' disease from the 'real' disease can be challenging. Once artefacts have been excluded, the baseline may still be red but not necessarily abnormal

Terms	Definition
Sensitivity	Number of diseased people who test positive/number of people with the disease
Specificity	Number of healthy people who test negative/number of people without disease
Positive likelihood ratio	Probability of a person with disease testing positive/probability of a healthy person testing positive = sensitivity/(1-specificity)
Pre-test odds	Occurrence/non-occurrence = prevalence/(1-prevalence)
Post-test odds	Pre-test odds x likelihood ratio
Pre-test probability	Pre-test odds/(1+pre-test odds)
Post-test probability	Post-test odds/(1+post-test odds)

Table 1. Useful statistical definitions

because of the limitations of the normative database. In addition, statistically, the greater the number of parameters measured, the higher likelihood that one parameter will fall within the 'abnormal' group, purely by chance alone.

Each imaging system has a different normative database (Table 2). The people in this database have been chosen as the reference against which patients are tested. If the patient falls outside the normative database, for example, in age, race, refraction or disc size, then the results should be interpreted with greater caution. The normative database is not definitive and is a reference only. This is important to keep in mind. Some databases have recently been updated, for example, the new Asian database for the Cirrus OCT.

We must keep in mind the costs of both false positive and false negative diagnoses. Over-diagnosis and false positives can cause stress of diagnosis, immediate loss of quality of life and fear of blindness. It may lead to unnecessary treatment and side-effects. There is also a cost to society with the cost of treatment. There can be a false sense of security from false negatives, possible loss to follow-up and missed diagnosis until a later date. Late presentations are associated with worse visual outcomes.

What is the future?

If you apply imaging tests with their multiple output parameters and screen the general population—that is, a population with low prevalence—the false positive rate would be very high and unacceptable. In practice what is done is 'case finding' by clinically assessing the patient and assessing their overall risk status, particularly looking at their optic disc appearance by indirect, stereoscopic slitlamp examination and having a reasonable pre-test probability of disease.

We then look to the imaging and perimetry to reduce our uncertainty of diagnosis. In fact, what we are doing is an intuitive Bayesian analysis. In the future, we will see more of this formally between our tests, for example, the OCT and visual field combination. Given the excellent reproducibility with imaging and the limitations of the normative database, the true value of imaging may be in following people over time for progression.

We must not forget assessment and case-finding for angle closure. If glaucoma screening were based purely on structural disc and RNFL assessment, then many cases of angle closure would be missed. Angle assessment is important, even in the absence of glaucomatous optic neuropathy. Imaging of the angle with anterior segment OCT (Visante, SL OCT) and UBM does not replace dark room gonioscopy.

Conclusion

A thorough clinical assessment is required to ascertain glaucoma diagnosis. As yet, no imaging system can take the place of full clinical assessment to find cases of glaucoma. General population glaucoma screening with imaging is not advised. Technological advances are occurring faster than we can critically evaluate them. Over-reliance on technology, particularly if it takes the place of a thorough clinical examination and without understanding the tools' limitations, could lead to more harm.

We must not lose sight of our aims. We must balance the potential benefit of technology's use in diagnosis against the possible risks of harm from misdiagnosis and missed diagnosis, not just for the patient but for society as a whole. ■

Further reading

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Imaging	Normative database	Limitations
HRT 2	349 normals for stereoscopic parameters 112 normals for the MRA	All Europeans Poor sensitivity with small discs
HRT 3	733 Europeans, 215 Africans, 100 Asian Indians	No Eastern Oriental Asians
GDx VCC	540 normal (18-82 years) 271 glaucomatous (25-89 years) 70% Caucasians or Latino, 18% African American, 12% Asian	
Stratus OCT	350 USA volunteers 63% Caucasians, 24% Hispanic, 8% Black, 3% Asian Mean age 47 (20-80 years)	No data for paediatric population
Cirrus OCT	284 healthy, age 18-24 Mean age 46.5 years 43% Caucasian, 24% Asian, 18% African American, 12% Hispanic, 1% Indian, 6% Mixed ethnicity Stratified into 6 age groups: 18-29, 30-39, 40-49, 50-59, 60-69, 70+ New Asian normative database: 315, age 19-84, 44% Chinese, 44% Japanese, 12% Indian (Zeiss)	No data from < 18 years Only 3 normals in the > 80 years group Only 28 people in 70-79 group Both OCT databases have no normals with refractive error outside -12 D and +8 D Disc area 1.33-2.5 mm^2

Table 2. Normative databases of glaucoma imaging (Chong and Lee, Zeiss)

Monitoring and management of steroid-induced glaucoma

Identify susceptible patients before ocular hypertension develops into steroid-induced glaucoma.

Dr Simon Chen
MBBS BSc FRCOphth FRANZCO
Retinal specialist
Vision Eye Institute, Sydney

Steroids are commonly used for a wide variety of ophthalmic disorders and generally have a very high safety profile when used in the short term. The potential for ocular steroids to cause ocular hypertension or glaucoma is widely known by eye-care professionals and cases of visual loss due to steroid-induced glaucoma continue to occur, particularly in patients who are not monitored or who self-medicate. Because this vision loss is preventable, it is important that all ophthalmic practitioners consider when steroid use is appropriate, which patients are at risk of developing steroid-induced glaucoma, and how to monitor, manage or refer patients with possible steroid-induced glaucoma.

Steroids are an important and commonly prescribed treatment for a diverse range of inflammatory eye disorders including dry eye, allergic eye disease, inflammation following eye surgery, uveitis, diabetic macular oedema and many others.

Steroids can cause a rise in intraocular pressure (IOP) in susceptible individuals. Topical steroid use for six weeks causes an increase in IOP of >5 mmHg in approximately 20 per cent of the population and >15 mmHg in five per cent.[1] Following an intravitreal steroid injection, about 40 per cent of patients develop a significant IOP elevation.[2] Individuals who develop ocular hypertension in response to steroid use are termed 'steroid responders'. The rise in IOP is believed to be due to increased aqueous outflow resistance associated with steroid-induced structural and biochemical changes in the trabecular meshwork.

Who is at risk of steroid-induced glaucoma?

A steroid-induced rise in IOP may not be associated with optic nerve damage or vision loss, in which case it is termed steroid-induced ocular hypertension. Patients with healthy optic nerves can tolerate higher IOPs and longer periods of ocular hypertension before their nerves develop sufficient damage to cause vision loss.[3]

If the IOP rise is high enough or sustained for long enough, then optic nerve damage may occur, leading to steroid-induced glaucoma. Patients who have pre-existing glaucomatous optic nerve damage are at an elevated risk of vision loss from steroid-induced glaucoma.[4]

Most steroid-induced glaucoma is caused by steroids administered via eye-drops, periocular or intravitreal injections. It can also occur when steroids are given orally, in topical skin cream,[5] and even following the use of nasal or oral inhaled steroids for the treatment of hay fever or asthma.[6] The likelihood of an IOP rise occurring with a particular route of administration, starting from most likely to least likely is intravitreal > periocular > topical > systemic.

Steroids with more potent anti-inflammatory effects are more likely to cause an elevated IOP, occurring more rapidly and to a greater level of IOP than weaker steroids. The likelihood of an IOP rise occurring with a particular steroid, from most likely to least likely is dexamethasone 0.1% > prednisolone 1.0% > fluorometholone 0.1% > hydrocortisone 0.5%.

Recognised risk factors for developing steroid-induced ocular hypertension or glaucoma include patients with open angle glaucoma and their first-degree relatives, high myopes, old age or age younger than six years, patients with traumatic angle recession, and patients with a high baseline IOP.

How to monitor patients for potential steroid-induced glaucoma

All patients being treated with ocular steroids should have a baseline IOP and optic disc assessment, especially those with specific risk factors for steroid-induced glaucoma, for example, patients with open angle glaucoma, high myopes, children et cetera.

Patients should be warned about the risk of elevated IOPs that may lead to steroid-induced glaucoma if left unmonitored. The importance of complying with follow-up arrangements should be continually emphasised to the patient.

Common clinical scenarios in which a steroid-induced IOP rise occurs are when topical steroids are used to treat post-operative inflammation following cataract or other eye surgery; when topical steroids are used to treat anterior uveitis; and when periocular or intravitreal steroids are used to treat macular oedema associated with diabetic retinopathy, retinal vein occlusions or cataract surgery.

The timing of the IOP rise varies with the potency, dose and route of steroid administration as well as individual patient factors. A rise in IOP usually occurs within the first few days or weeks after starting steroid treatment, thus all patients on steroids should have their IOP and optic nerves monitored typically within two weeks, or sooner if the patient is at high risk, after starting treatment. Occasionally, the IOP rise can occur only after several months so it is important to monitor IOP regularly as long as steroid treatment is continued.

Steroid-induced glaucoma causes the same optic disc and visual field changes as those associated with primary open angle glaucoma. Patients with suspected steroid-induced glaucoma should have visual field testing possibly combined with objective assessment of the optic disc and retinal nerve fibre layer, for example, using optical coherence tomography. Visual field assessment can be difficult because many patients on steroids have impaired visual function due to their underlying eye disease.

Treating steroid-induced ocular hypertension and glaucoma

The decision regarding when and how to treat steroid-induced ocular hypertension or glaucoma requires sound clinical judgement, taking into account the condition being treated, individual patient factors, the severity of pre-existing optic nerve damage and the level of IOP rise. A rise in IOP from 14 mmHg to 19 mmHg in a patient with no risk factors for glaucoma and healthy optic nerves may be monitored conservatively, whereas a patient with pre-existing open angle glaucoma, documented visual field loss and a rise in IOP from 15 mmHg to 29 mmHg should be managed aggressively to reduce the IOP and prevent progressive optic nerve damage. If the IOP is very elevated, for example >30 mmHg, in the absence of glaucomatous damage, treatment is still needed because the eye may be at risk of developing a central retinal vein occlusion.[7]

Stopping the steroids usually causes the IOP to fall back to baseline levels but the IOP can remain elevated in some patients, particularly those who have received steroid treatment for several months. If continued steroid use is deemed to be clinically necessary or the IOP remains elevated despite stopping the steroids, then the treatment options are essentially the same as for primary open angle glaucoma. Drug treatment is often initiated with topical beta-blockers or prostaglandin analogues. Contraindications to beta-blockers such as cardiovascular or bronchial disease should be excluded. Prostaglandin analogs are effective in patients with diabetic macular oedema and uveitis but may be associated with a risk of macular oedema and increased inflammation. Other topical hypotensive drops include alpha-agonists and carbonic anhydrase inhibitors. If topical treatment is inadequate, oral acetazolamide, laser trabeculoplasty or surgery may uncommonly be required.

> **Topical steroid use for six weeks causes an increase in IOP of more than 5 mmHg in about 20 per cent of the population and more than 15 mmHg in five per cent of people.**

Conclusion

All patients treated with steroids for eye disease are at risk of transient ocular hypertension or possibly steroid-induced glaucoma. Part of any management and treatment plan should include taking into consideration the risk factors for each individual patient, particularly if there is a history of glaucoma. Thereafter, patients require careful monitoring for signs of steroid induced ocular hypertension. Monitoring and intervention, if required, are the key factors to prevent steroid-induced ocular hypertension from developing into steroid-induced glaucoma. ■

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Correction

The article 'Lessons to learn about pterygium' published on pages 10 to 12 of the December 2012 issue of *Optometry Pharma* carries the subheading 'Chemo agents necessary but risky'. The subheading was incorrect. The author, Professor Lawrie Hirst notes that 'use of chemo drops for pterygium surgery is not only unnecessary but potentially sight-threatening'.

Rigid definitions of glaucoma critiqued

In a notable speech given at the 2012 European Glaucoma Society Congress in Copenhagen, Dr George Spaeth, a recipient of the Lifetime Achievement Award from the American Academy of Ophthalmology, listed a range of factors that often lead to misdiagnoses and incorrect treatment of glaucoma. The provocative speech encourages practitioners to reassess their approach to glaucoma detection.

- **Over-reliance on tonometry**

Dr Spaeth described tonometry as an example of an indirect measurement that could lead to false positive and false negative diagnoses of glaucoma. 'Some ophthalmologists continue to regard IOP in excess of 20.0 mmHg and 24 mmHg as diagnostic of the disease,' Dr Spaeth said. 'Conversely, some will fail to make the diagnosis of glaucoma in patients with loss of vision because their IOP is in the lower regions.'

- **Overlooking the optic disc**

Citing a study conducted in the US that showed that optic discs were mentioned in only half of the surveyed glaucoma patients' charts, Dr Spaeth pointed out that failure to look at the optic disc or evaluate it properly had given rise to a high proportion of misdiagnoses.

- **Misleading cup/disc ratios**

Another common mistake discussed is the use large cup/disc ratios as a predictor of glaucoma. 'It is only when cup/disc ratios are about 0.8 or 0.9 at initial presentation that they have any diagnostic value at all,' he said. 'Otherwise, it is only when the ratio increases over time that it becomes indicative of glaucomatous optic neuropathy.'

Spaeth described the case of a 63-year-old engineer with no symptoms of glaucoma who expressed doubt over his ophthalmologist's recommendation for surgery. When Dr Spaeth examined him, he noted that the optic discs were large but symmetrical and lacking in pathology. 'He had no visual field loss,' Dr Spaeth explained. 'He does not have glaucoma, he just has huge optic discs.'

- **Unconscious bias**

Studies have shown that trained observers are three times more likely to say a disc has changed for the worse if they believe that the second photograph was taken after the first. 'That biases you because you know that glaucoma tends to get worse,' Dr Spaeth said. 'If you want to compare photographs without bias, don't tell the person making the judgment which one is first and which one is second. You have to look at them masked. Knowing ancillary information leads to biased interpretations.'

- **Over-reliance on technology**

Dr Spaeth asserted that while digital information provided by technology such as OCT allowed for a deconstructive approach to diagnosis, it did not provide qualitative information. 'We can deconstruct the glaucomatous optic nerve into its individual components or we can look at a nerve and ask, "What does that nerve look like?" We have marginalised that information, we have forgotten that it can be valid,' he said.

TheraVu: the contact treat IOP and

TheraVu is a medical device drug delivery system that can control elevated intraocular pressure and correct vision. The device enables polymers and drugs that have been approved and are on the market and can be used as a combination product, to be administered with good clinical effect. This drug delivery system uses lower doses of drug than are ordinarily prescribed for patients. Patients who may have been contact lenses wearers may have the option of returning to lens wear for both vision correction and IOP treatment.

Introduction

Glaucoma is a progressive optic neuropathy characterised by a specific pattern of damage to the head of the optic nerve. The visual system is damaged by the death of nerve cells, which carry the visual impulse from the eye to the brain. When a sufficient number of nerve cells are destroyed, blind spots develop, usually beginning in the peripheral field of vision.

Numerous ocular drugs and some delivery systems have been developed to manage elevated IOP but over time, the complex anatomy of the eye limits their effectiveness. Medications introduced into the eye are quickly washed out of the pre-corneal area by the rapid production of lacrimal fluid. In addition, medication in the eye is poorly absorbed because of the low permeability of corneal tissue. Ointments, gels and high viscosity eye-drops have been used to provide a longer-acting formulation for anti-glaucoma medication.[1]

Compliance is also an issue with many individuals with glaucoma or elevated IOP. Patients will often forget to take their medications, compromising their care. These delivery systems have caused blurring of vision and ocular discomfort in many of the patients who have tried them. Ocular insertions have produced discomfort and are often blinked out of the eye of their users.[2]

The work described below features polymeric hydrogel contact lenses containing timolol maleate, or brimonidine tartrate. The name of this medical device/drug delivery system is TheraVu. TheraVu was used to treat several patients with a history of glaucoma or elevated IOP. Analytical chemistry techniques were used to monitor uptake and release of these drugs with different materials.

Materials and methods

Method of fabrication

The two glaucoma drugs used in these studies were timolol maleate and brimonidine. The drugs were diluted 1/10 (0.2 mg/mL brimonidine tartrate and 0.65 mg/mL for timolol maleate) in sterile saline for injection. In addition, timolol maleate was diluted 1/100 or 0.065 mg/mL.

Contact lenses (etafilcon A) were washed three times in cold sterile

lens drug delivery system to correct vision

An investigation into the efficacy of extended-wear polymeric hydrogel contact lenses yields encouraging results.

Dr Clyde Schultz PhD
University of Calgary, Calgary, Alberta, Canada
Dr Janet Mint OD
Southside Eye Associates, Jacksonville FL

physiological saline and then dried for about 10 seconds. They were then placed (aseptically) into one of the solutions listed above for 18 hours at 4o C until use.

Clinical

Three patients underwent a two-week wash-out period, during which their intraocular pressures became elevated. The patients were then put on TheraVu treatment for two weeks. Patients wore the lenses for a maximum of 30 minutes per day. They were routinely monitored every three days for IOP and toxicity. Two of the patients wore lenses treated with timolol maleate. The other patient wore lenses treated with brimonidine tartrate.

The IOP for all three patients remained below 20 mmHg for this period. No toxicity was seen on slitlamp examination.

One of the volunteers wore TheraVu prepared with 0.065 mg (1/100 dilution) of timolol maleate over a two month period. This individual wore the product only every other day. IOP remained stable over this period. No toxicity was observed on slitlamp examination.

Analytical

The purpose of these experiments was to determine the kinetics of release of these drugs from the lens. These experiments have been described previously.[3] Contact lenses were removed to a solution of timolol maleate or brimonidine tartrate that had been diluted in phosphate buffered saline (PBS). There was a seven-hour passive transfer period in which no more of the drug was taken into the lens.

Release from the lens was monitored by placing the lenses into fresh PBS and then withdrawing aliquots for analytical analysis at 0, 1, 2, 4 and 7 hours. High-pressure liquid chromatography (HPLC) was used to evaluate the solution for drug. The release of drug from the lens is shown in Figure 1. Drug is passively released into solution for about six hours. Figure 1 shows this data for lenses pretreated with brimonidine tartrate. The profile for timolol maleate is similar. If lenses are placed in fresh solution, more drug is released from the lens.

Discussion

The data presented on this limited number of patients indicate that contact lenses manufactured with anti-glaucoma medications can treat patients who are on simple treatment regimens for the condition. The medical device drug delivery system described could treat the disease and correct vision, while no toxicity was observed in the volunteer patients. Preliminary data in one patient indicate that long-term wear of the product may allow for every other day administration of treatment.

The analytical data show a steady uptake and release of both drugs evaluated. Since the concentrations used are below normal levels given to patients, no toxicity was observed. Changing solutions could prolong the release of the drug. This indicates that as a local build-up of drug occurs in the ocular environment, passive release is halted from the lens. Therefore, the release of drug on the eye is step-wise and does not follow an inverse curve, but is influenced by blink rate and by tear flow on the ocular surface. These parameters are particular to a given individual.

Conclusion

The product can be worn on an extended wear schedule with no toxicity observed. In addition, vision is corrected. This product provides treatment for two conditions, elevated IOP or glaucoma and vision correction, with greater compliance and no toxicity. ■

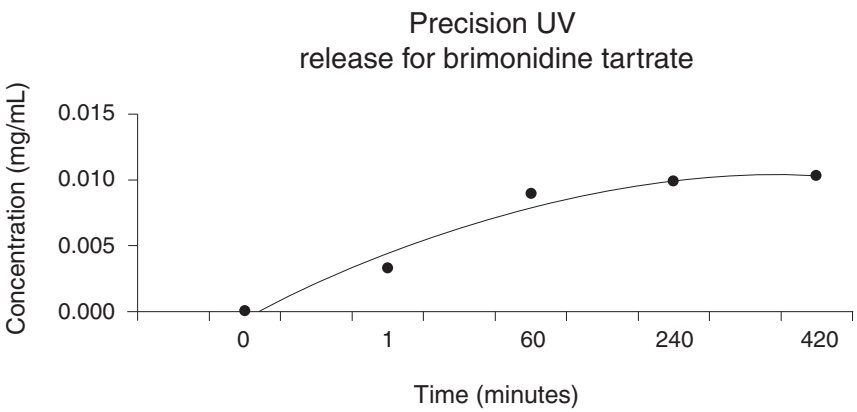

Figure 1. Release of brimonidine tartrate from a Precision UV lens. A plateau is reached at about two hours. If a lens is removed to fresh solution, more drug is released into solution.

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2. Lewis T. Glaucoma. *Review of Optometry* 2003; 11: 51-56.
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Diagnosis and management of glaucoma

A patient with advanced optic nerve loss achieves target IOP level through vigilance and persistence.

Dr Murray Fingeret OD
Chief, Optometry Section, Department of Veterans Affairs, New York Harbor Health Care System, Brooklyn, NY USA
Clinical Professor, State University of New York, College of Optometry, New York, NY USA

Case report

Glaucoma may present in different ways, with the most common being in an asymmetric manner with one eye showing greater loss than the other. It is unusual for both eyes to present with similar amounts of damage, but this may occur if the loss is moderate to advanced in nature. In other words, the condition has been present and undiagnosed for a period of time. Bilateral symmetric loss indicates that while the disease started in one eye, damage has progressed so that both eyes are involved.

In this case, an 82-year-old African American male presented for a comprehensive eye examination. He had not had an eye examination in more than 10 years and had been using store-bought reading glasses, which had broken recently. His eye and family eye history were negative, and his medical history was significant for hypertension with the individual using hydrochlorothiazide and amlodipine.

The patient's visual acuity was corrected to 6/6 in each eye with a low myopic prescription. The Frequency Doubling Perimetry Screening N 30-5 examination showed two points flagged in the right eye and one in the left on first examination (Figure 1A). When the test was repeated to confirm the loss, each eye was full (Figure 1B). There was a high number of false positive responses (100 per cent) in each eye which influenced the test results. When a high number of false positive responses are present, field loss may be masked or reduced.

The pupils were sluggish with no Marcus Gunn pupil noted. Intraocular pressure (IOP) using Goldmann tonometry was 33 mmHg OD and 30 mmHg OS at 3pm. Due to the IOP being elevated, corneal thickness was measured and found to be 522 microns OD and 520 microns OS, indicating thinner than average readings. Because the IOP was elevated, 24-2 SITA Standard visual fields were performed using a Humphrey Field Analyzer. Superior arcuate scotomas were present in each eye. The high false negative rate was associated with the dense scotoma present. The mean deviation was approximately -13 dB in each eye, indicating moderate to

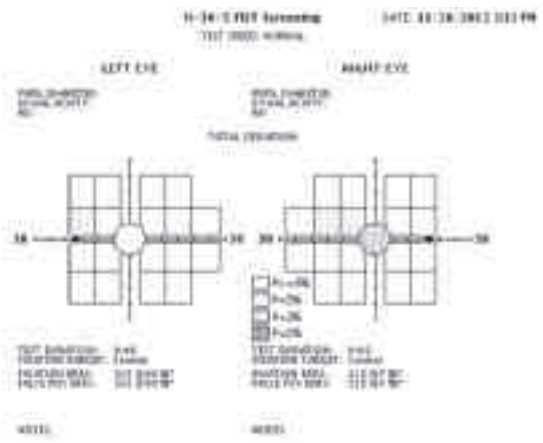

Figure 1A. Initial examination (Frequency Doubling Perimetry Screening) showed two points flagged in the right eye and one in the left

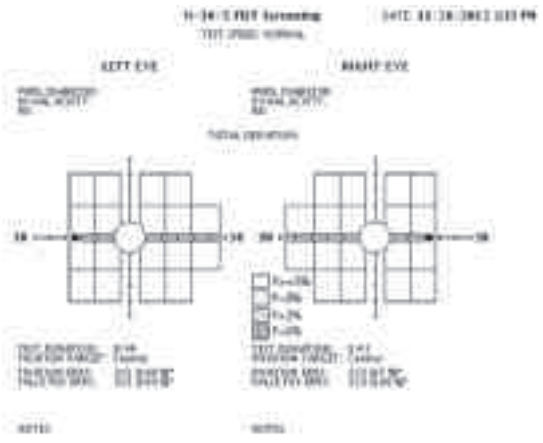

Figure 1B. When test was repeated to confirm the loss, each eye was full

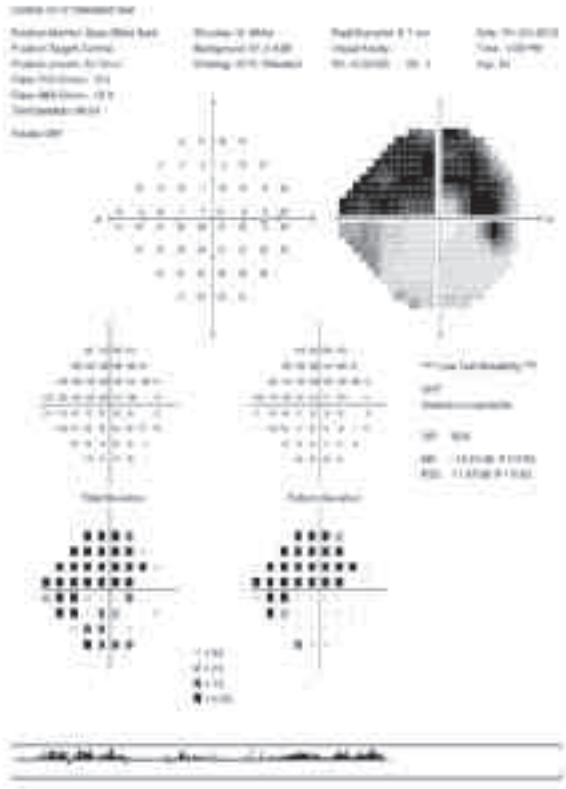

Figure 2A

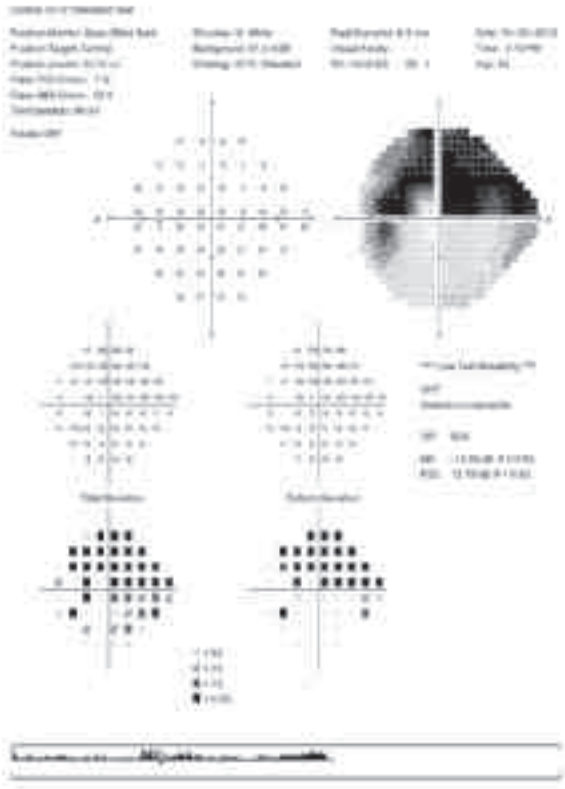

Figure 2B

Superior arcuate scotomas present in each eye; mean deviation approximately -13 dB in each eye, indicating moderate to advanced loss

advanced loss (Figures 2A, 2B).

The dilated optic nerve examination showed advanced cupping in a moderately large optic disc with the rim absent inferiorly OD and OS (Figures 3A, 3B). Examining the retinal nerve fiber layer (RNFL) thickness map of Cirrus Spectral Optical Coherence Tomographer (OCT) print-out showed an optic pit developing at 6 o'clock as seen by the dark spot just below the disc margin. There was significant parapapillary atrophy in each eye, and rim loss also present superiorly. It is interesting that the inferior field remained clean in each eye even though the rim was thin superiorly. RNFL loss was present as seen on the OCT print-out superior and inferiorly (Figure 4A). Note that the RNFL thickness measurements are similar in both the superior and inferior quadrants while the neuro-retinal rim thickness is thinner inferiorly in both eyes, indicating that for this patient the rim is a better indicator of functional status than RNFL thickness.

The OCT ganglion cell complex (GCC) analysis shows slightly greater loss in the OD than OS, with both showing significant damage (Figure 4B). The ganglion cell

Continued page 12

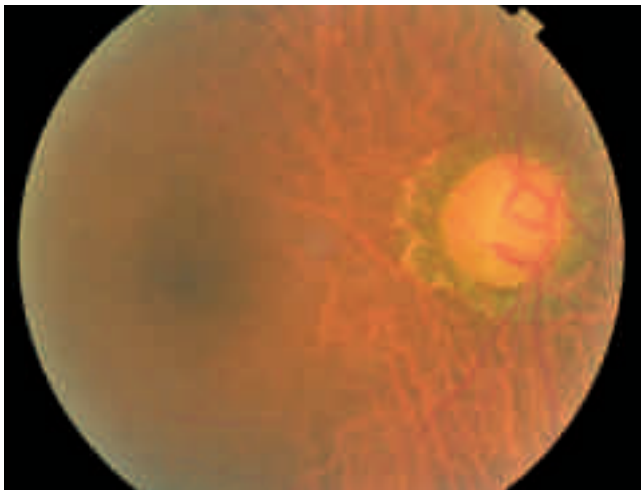

Figure 3A

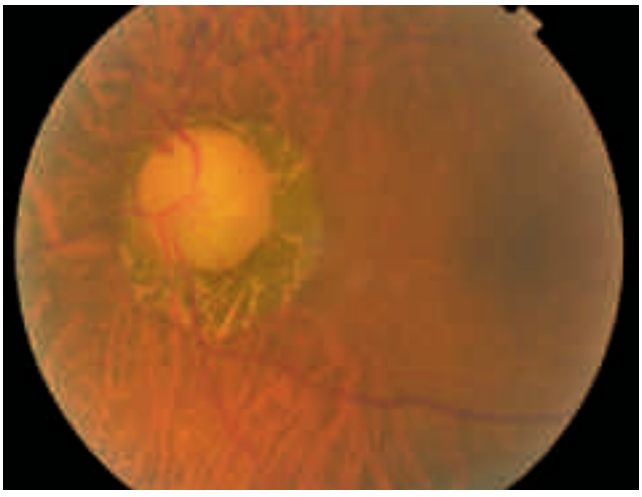

Figure 3B

Advanced cupping in a moderately large optic disc, with the rim absent inferiorly OD and OS

Cataract surgery affects IOP

Cataract surgery leads to an immediate and persistent reduction in IOP for patents with ocular hypertension.

Researchers from the Devers Eye Institute/Discoveries in Sight, Legacy Health System, Portland, Oregon studied 42 participants (63 eyes) who underwent cataract surgery in at least one eye during the study and a control group of 743 participants (743 eyes) who did not undergo cataract surgery.

Researchers found that IOP for patients with known hypertension decreased a mean 16.5 per cent after cataract surgery; the difference between pre- and post-operative IOP (23.9 ± 3.2 mmHg vs 19.8 ± 3.2 mmHg) was significant ($P < 0.001$) and was still measurable 36 months after the procedure. However, there was a trend toward increasing postoperative IOP over time of 0.05 mm/month (95 per cent confidence interval, 0.02 - 0.07; $P < 0.001$).

The effect of cataract surgery varied from eye to eye, but IOP fell more than 20 per cent for 39.7 per cent of eyes after cataract surgery, and the decrease ranged from 0 per cent to 20 per cent for half of the eyes (49.2 per cent).

Significantly, the study authors were unable to state whether cataract surgery reduces the risk for the development of glaucoma in patients with ocular hypertension, only that it decreases IOP.

Ophthalmology 2012; 119: 1826-1831

Glaucomatus visual fields and Macular thickness

Statistically significant structural relationships between each macular parameter and its anatomically-related visual field defect were noted in a study conducted at the Indiana University School of Medicine. The results of the study, published in the *Journal of Glaucoma*, highlight the important role of macular scan OCT in the diagnosis and management of glaucoma.

The retrospective study included 236 glaucoma patients seen over the period January 2004 to December 2009. From a total of 236 glaucoma patients, 127 patients were included for data analysis. Participating patients were diagnosed with primary open angle glaucoma (n = 114), pseudoexfoliative (n = 2) or pigmentary glaucoma (n = 11). Stratus OCT scans of the macula, in addition to Humphrey Visual Field Analyzer results performed within four months on the OCT macular scans were included in the data.

The study determined that a predictable and statistically significant structural relationship occurs between specific macular thickness parameters and anatomically related visual field defects, lending further support to the idea that macular functional and structural abnormalities are present in glaucoma.

The authors of the study concluded that physicians should take a closer look at macular data when diagnosing and managing patient with glaucoma. 'Improved macular visual field testing and macular OCT reproducibility will likely provide more parameters of predictive ability to aid the clinician in safeguarding the glaucomatous eye', they wrote.

Journal of Glaucoma 2012; 21: 8: 505-509

Superior hemifield defects

Superior hemifield defects may progress at a faster rate than other hemifield defects in normal-tension glaucoma patients, according to an American study.

The records of 142 normal-tension glaucoma patients who had more than five reliable standard visual field tests were examined in the retrospective, observational cohort study; 51 had superior hemifield defects, 44 had inferior hemifield defects and 47 had both hemifield defects.

Subjects with superior hemifield defects had a significantly faster progression rate than those with inferior hemifield defects ($p = 0.19$), and the central and nasal zones had more pronounced progression.

Similarly, subjects with superior hemifield defects had a faster progression rate than patients with both hemifield defects ($p = 0.001$).

Am J Ophthalmol 2012; 154: 6: 958-968

Diagnosis and management

From page 11

analysis is a test in which loss in the macular region is assessed, compared to at or around the optic nerve. Most OCTs now have GCC tests as well as those measuring the RNFL and optic nerve, though it is still not clear if their performance is better or even equal to the traditional RNFL/optic nerve tests.

This person was diagnosed with primary open angle glaucoma (POAG) with treatment delayed for one day to allow additional IOP measurement as well as gonioscopy to be performed. Getting additional IOP measures allowed us to better understand if the IOP we found was at the high or low point. The FDT fields were not consistent with other structural or functional tests because of the high number of false positive responses, which masked the field loss. Due to bilateral damage, an afferent pupil defect was not observed.

Target IOP

The patient returned the next morning with the IOP being 31 mmHg OD and 30 mmHg OS at 8:00 am. Gonioscopy revealed the angles to be wide open, with the ciliary body band present 360 degrees in each eye. Due to the extent of damage, we wanted a 50-60 per cent IOP reduction in each eye and started the patient on latanoprost OU QHS, with the patient to return in two weeks. The target IOP was a goal that would take time to achieve. We needed to be patient as one medication was initiated at each visit. He was taught how to instill the medication using a bottle of artificial tears and we explained the nature of glaucoma and provided reading materials concerning the disease.

On the first follow-up examination, the IOP was 21 mmHg OD and 18 mmHg OS, and the patient stated that he had been using the medication faithfully and without problems. The eyes were white and quiet, and while the IOP reduction was substantial, it was not at the target level and dorzolamide was added. The dosage used was BID in both eyes with the patient to return

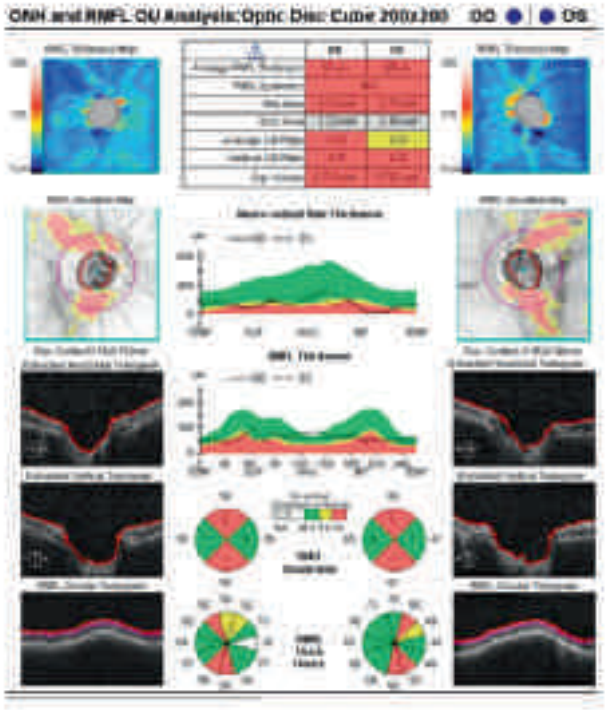

Figure 4A. RNFL loss is present, superiorly and inferiorly

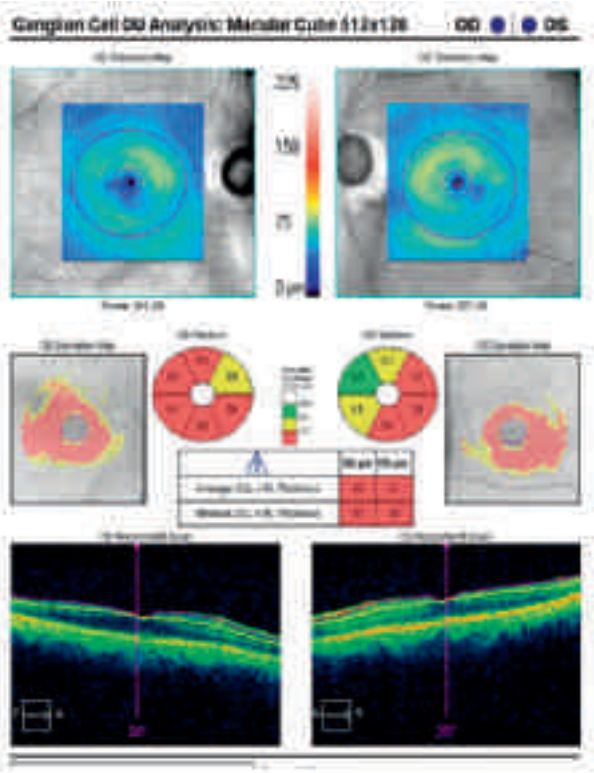

Figure 4B. Ganglion cell complex analysis showing greater loss in OD than in OS

in one week. We were aggressive in having the patient return relatively quickly because if the patient had not been able to tolerate the medication(s) or the IOP could not have been reduced sufficiently, we wanted to ascertain this quickly so that we could move on to other therapeutic options.

At the next visit, using dorzolamide and latanoprost OU, the IOP was reduced to 18 mmHg OD and 15 mmHg OS, again with no problems. The IOP was responding nicely and getting close to the target level. Dorzolamide was switched to CoSopt OU BID (which contains dorzolamide and timolol) with the patient again asked to return in one week. The patient had no systemic contraindications to the use of a beta blocker and we had him close his eyes for three minutes after instilling CoSopt.

At the next visit, the IOP was 16/15 mmHg, showing slight additional reduction. We were then faced with a challenge of what to do next. While the IOP was close to the target level, we would have liked to get it slightly lower and discussed with the patient the option of having selective laser trabeculoplasty performed or another medication added. We explained the risks and benefits of each approach. While my recommendation was for SLT to reduce the number of drug instillations, the patient was concerned when he heard the word 'laser' and asked that a medication be added instead. Brimonidine 0.2% solution was added in a BID dosage to each eye, with the patient told to return in two weeks.

At this visit, with the patient using three bottles (four medications) in each eye (latanoprost, timolol-dorzolamide, brimonidine) the IOP was reduced to 11 mmHg OD and 12 mmHg OS. We were then at the target IOP level and explained our plan to the patient. We gave him written instructions on how to use the medication as well as again having him demonstrate his ability to instill eye-drops using a bottle of artificial tears, which he did well.

He is to return in three months, at which time the patient will be dilated and imaging and visual field tests performed, allowing us to develop a baseline of tests to use to follow for progression.

Watch for change

While the target IOP is a concept used to initiate therapy and provide some structure for initial therapy, the only way to know if the patient is at the target IOP appropriate for him or her is to periodically perform perimetry and imaging, watching for change. Due to the advanced nature of the optic nerve loss, it will be difficult to recognise change using retinal photography. If the fields and imaging are stable, this is the best indication that the patient is properly controlled. If change is noted, the therapeutic regimen needs to be re-evaluated.

Due to the advanced nature of the condition, the patient understands he needs to be evaluated at least every three months, with imaging and fields done twice a year. If change is noted or the IOP elevates over time, the next therapeutic option is for SLT to be performed. While the diagnosis was made late due to the patient not having had an eye examination for many years, with prompt and careful management there is an excellent chance that he may remain symptom free throughout his lifetime, which is the goal of glaucoma management. ■

Treatment of ocular hypertension

Distinguish between patients who will and will not benefit from IOP-lowering treatment.

Dr Shibal Bhartiya
MBBS MS*
Dr Colin Clement
BSc(Hon) MBBS PhD FRANZCO†§
* Fortis Memorial Research Institute, Sector 44, Gurgaon, Haryana, India
† Glaucoma Unit, Sydney Eye Hospital, NSW
§ Discipline of Ophthalmology, Central Clinical School, The University of Sydney, NSW

Ocular hypertension (OHT) is a risk factor for the development of glaucoma. The Ocular Hypertension Treatment Study (OHTS)[1] has shown intraocular pressure (IOP) reduction can reduce this risk by half. On face value, it would seem that all patients with OHT could benefit from IOP-lowering but a 'treat all' strategy is not necessarily the correct approach. This is because OHT is one of a number of risk factors for primary open-angle glaucoma (POAG) and it is their interaction that determines an individual risk. Therefore, not all cases of OHT carry the same risk and in some, the potential harm from treatment may outweigh the potential benefit.

With non-selective OHT treatment, up to 20 cases are needed to prevent a single case of POAG whereas selective treatment can potentially achieve the same results with the treatment of fewer patients. Similarly, between 12 and 83 ocular hypertensive patients will require treatment to prevent one patient from progressing to unilateral blindness over a 15-year period. The challenging issue remains distinguishing between those who do and do not need treatment.

OHTS has helped better define the risk factors that are associated with progression from OHT to POAG (Table 1). It is perhaps surprising to learn that baseline IOP is not the strongest risk factor in isolation.[2] In fact, OHTS found little difference in the mean baseline IOP of those who did or did not progress to POAG (25.6 mmHg vs 24.9 mmHg). However, if considered alongside other known risk factors, the importance of IOP becomes more apparent. For example, in eyes with thin corneas (<555 µm) a baseline IOP > 25.75 mmHg was associated with double the five-year risk of developing POAG (36 per cent) compared to eyes with a baseline IOP < 23.75 mmHg (17 per cent).

A risk profile can be generated from these findings for individual patients and this is the basis for the Scoring Tool for Assessing Risk (STAR) calculator.[3] Table 2 shows the risk profile generated by this calculator of three hypothetical patients, all of whom have the same baseline IOP (25 mmHg) but variations in other risk factors. Patient 1 has a 20.8 per cent chance of developing POAG over five years due to the combined effect of older age, raised IOP and mildly abnormal PSD on automated perimetry. In contrast, the five-year risk for patient 2 is comparatively low at 4.6 per cent due to a younger age and thicker cornea, despite the same baseline IOP. If the same patient were to have a much thinner cornea but also smaller cup-disc ratio (patient 3), the five-year risk would then be considered intermediate at 11.3 per cent.

An expert advisory panel has recommended individuals with a five-year risk of less than five per cent do not require treatment but when this risk exceeds 15 per cent, treatment is highly recommended. Those with intermediate risk (5–15 per cent) may benefit from treatment but other factors should be considered. Risk should be reassessed regularly as it will change over time.

The cost of treatment is a further consideration and a recent economic evaluation on the utility of treating ocular hypertension concluded that treating individuals with a ≥ 10 per cent five-year risk of developing POAG is cost-effective.[4] It is important to reiterate that predictive and economic models may aid in decision-making but are not a replacement for clinical judgment. Any clinical decision, therapeutic or otherwise, must take into account the individual patient's health, life expectancy, preferences and impact on quality of life.[5]

For instance, the threshold for initiating treatment will be lower for a young ocular hypertensive patient even if scored as a low risk, because of assumed long life expec-

Risk factor	Hazard ratio (confidence interval)
Baseline IOP (per mmHg)	1.10 (1.04 – 1.17)
Central corneal thickness (per 40 µm)	1.71 (1.40 – 2.09)
Increasing age (per decade)	1.22 (1.01 – 1.49)
Horizontal cup-to-disc ratio (per 0.1 larger)	1.27 (1.14 – 1.40)
Vertical cup-to-disc ratio (per 0.1 larger)	1.32 (1.19 – 1.47)
Pattern standard deviation (per 0.2 dB)	1.27 (1.06 – 1.52)
Disc haemorrhage	3.7 (3.6 – 10.1)

Table 1. Risk factors for developing open-angle glaucoma in OHT2

Risk factor	Patient		
	1	2	3
Age	65	45	45
Baseline IOP	25	25	25
CCT	550	590	490
PSD	1.50	1.0	1.0
Vertical CDR	0.6	0.6	0.4
5-year Risk (%)	20.8	4.6	11.3

Table 2. Scoring Tool for Assessing Risk (STAR) calculator five-year predicted risk of developing POAG

tancy. The same must always be evaluated against the negative impact of lifelong medication on quality of life. Conversely, an ocular hypertensive patient with poor general health might be kept under close follow-up instead of treatment, despite the fact that he might be at high risk of developing POAG.[4,5]

In case a decision to defer treatment has been made, the patient must be followed up regularly to detect any structural deterioration (on nerve fibre layer imaging and optic disc photos) and/or functional progression of the disease (visual fields). In the case of any disease progression, the results of imaging and visual fields must be used in conjunction for the same risk-benefit analysis to determine the further course of action. If an OHT is being treated, regular follow-ups provide an opportunity for compliance checks, and reassessment of risk, as well as target IOPs.

The other variable that may be considered in the treatment algorithm includes the degree of IOP fluctuation. A higher degree of short-term and/or long-term IOP fluctuation as measured by diurnal IOP measurements, and also between visits, may lower the threshold of treatment.

The basic dictum for treating an ocular hypertensive patient is the same as it is for every other patient: customise the treatment plan for each patient's individual needs, and make sure you treat the patient and not the disease alone. It is also essential to ensure that the impact of the treatment on the quality of life of the patient is not worse than that of the disease itself. ■

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Is there a place for a one-eyed trial in glaucoma therapy?

Dr Brian Ang
FRCOphth FRANZCO
Royal Victorian Eye and Ear Hospital
Melbourne Eye Specialists

Overcome the problem of diurnal IOP fluctuation by treating one eye and using the fellow eye as a control.

Glaucoma is a leading cause of blindness worldwide and a major public health concern. As intraocular pressure (IOP) is well-recognised as an important risk factor for the occurrence and progression of glaucoma,[1-3] much of glaucoma management is focused on lowering and controlling IOP to reduce the risk of further optic nerve damage and subsequent vision loss.

Lowering IOP with eye-drops may sound simple in theory but in clinical practice, determining the efficacy of therapy can be difficult. One major reason for this difficulty is diurnal IOP fluctuation, which can be as high as 6 mmHg in some individuals. When a patient demonstrates an IOP reduction of 3 mmHg after commencing treatment, clearly the clinician needs to confirm that this is indeed true therapeutic IOP reduction as opposed to background fluctuation. The monocular, or one-eyed, trial of glaucoma therapy has been proposed as one way of overcoming this problem.

In the monocular trial, only one eye is started on therapy while the untreated fellow eye is used as control. At the follow-up visit, any change in IOP in the untreated fellow eye is considered to be the result of fluctuation. The observed IOP reduction in the treated eye is then adjusted to take into account the change in IOP in the untreated fellow eye.

For example, at baseline, the IOPs were 32 mmHg in the right eye and 30 mmHg in the left. Therapy was commenced to the right eye only and after four weeks, the IOPs measured 18 mmHg right and 24 mmHg left. In the treated right eye, the IOP reduction was 14 mmHg (32-18 mmHg). However, in the untreated left eye, there was also a lowering of IOP of 6 mmHg (30-24 mmHg), presumably due to fluctuation. Thus, of the 14 mmHg IOP reduction seen in the treated right eye, 6 mmHg can be attributed to spontaneous variation and the remaining 8 mmHg (14-6 mmHg) to the actual therapeutic IOP-lowering effect.

For the monocular trial to work, several assumptions have to hold true. First, it is assumed that using the medication in one eye will have no crossover or contralateral effect in the fellow eye. For instance, it is known that topical beta blockers do have a crossover effect,[4] thus precluding their use in a monocular trial. Another assumption is that the IOP in both eyes of the same individual fluctuate the same amount throughout the day. In this respect, it has been found that there is good correlation in the IOP fluctuation in both eyes in glaucoma patients but not in healthy subjects.[5,6]

Is the monocular trial valid?

Various studies have been conducted to evaluate the validity and usefulness of the monocular trial, with mixed results and contrasting conclusions. Differences in research design and methodology mean that it is not possible to make direct comparisons between studies. Most were retrospective analyses that were subject to bias and the

Continued page 16

One-eyed trial in glaucoma therapy

From page 15

inability to adequately account for diurnal variation and regression to the mean.[7] Additionally, the research question often posed was whether the monocular trial held any predictive value in determining the IOP reduction in the fellow eye, which is not really what the monocular trial is set out to determine.[8,9]

A prospective, randomised, masked study of 26 patients with open angle glaucoma or ocular hypertension (all previously treated but underwent a four-week wash-out period prior to randomisation) concluded that the monocular trial at one month was a poor predictor of IOP reduction at two to three months after latanoprost treatment was commenced.[10]

Similarly, when data was analysed from the 206 study participants in the observation arm of the Ocular Hypertension Treatment Study (OHTS) who were subsequently started on prostaglandin analogues, the monocular trial at one month was deemed to poorly determine IOP reduction up to 18 months later.[11] Predicting the medium-term or long-term outcome of therapy is not really the purpose of the monocular trial, either.

King and colleagues published perhaps the best conducted study so far in trying to determine the validity and usefulness of the classic monocular trial.[12] In their prospective, masked, intention-to-treat cohort study, 30 treatment-naïve patients with open angle glaucoma or ocular hypertension had their IOPs measured at the initial clinic visit and then subsequently at 11 am (±15 minutes) for seven consecutive weeks. At the third visit, the eye with the higher IOP was commenced on travoprost; at the fourth visit, the fellow eye was also started on travoprost. Visits 1 to 3 were the pre-treatment visits, while visits 5 to 7 were the post-treatment visits.

The adjusted IOP was the IOP change between the initial clinic visit and visit 4 in the treated eye, minus the IOP change in the untreated fellow eye over the same two visits (that is, the monocular trial). The true therapeutic IOP-lowering effect of travoprost was calculated as the difference in IOP between the three pre-treatment and the three post-treatment visits (the IOP at the initial clinic visit was not considered in this instance). By designing the study this way, the problems of diurnal variation, regression to the mean, crossover and selection bias are minimised. The authors found that not adjusting the IOP via the monocular trial meant that the true therapeutic effect was overestimated by a mean of 3.1 mmHg (or 36 per cent); this overestimation was less than 0.1 mmHg after IOP adjustment.

Way forward

The specific design of King and colleagues' work also means that the results are applicable only to a specific set of circumstances, namely travoprost treatment and IOP measurements at 11 am. It is not known if these results remain valid for IOP measurements at other time points, for instance, at 8 am or 6 pm. To be able to evaluate the monocular trial in a more comprehensive manner, future studies should ideally include IOP measurements at different times throughout the day and night, rendering them almost too impractical and resource consuming to be conducted in the first place.

What does this mean for clinicians? The gold standard in determining the response to glaucoma medication is still measuring the IOP on multiple occasions before and after the decision to commence therapy. There is no doubt that the monocular trial, if performed correctly, can provide an accurate estimate of the actual therapeutic IOP lowering effect. However, both methods may not be practical in the day-to-day clinical setting.

The way forward has to be 24-hour IOP measurement in a way that is easy to administer, safe and accurate. Until then, monitoring of treatment response should be individualised and based on the characteristics of the patient being treated, including age, severity of glaucoma, adherence to treatment, appointment attendance, distance, cost to patient and patient preference. ■

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Does structure always precede function in glaucoma progression?

The relationship between structural abnormalities and visual field changes is still being debated.

Dr Tu Tran
MBBS, MPH, FRANZCO
Royal Victorian Eye and Ear Hospital, Melbourne

Understanding structure-function relationship in primary open-angle glaucoma is necessary for both grading the severity and understanding the natural history of the condition. Clinically, patients with similar neuroretinal rim loss may have different amounts of visual field loss. Some patients have evidence of glaucomatous optic neuropathy without detectable visual field abnormality, other patients have glaucomatous visual field without detectable structural abnormality. This can represent a diagnostic and management dilemma. The question arises of whether severity should be based on structure or function or a combination of both.

Imaging devices in common clinical use for measuring the structure of the optic nerve head (ONH) and retinal nerve fibre layer (RNFL) include confocal scanning laser ophthalmoscopy, scanning laser polarimetry and optical coherence tomography (OCT). These devices provide a quantification of the neuroretinal rim area (mm^2) or RNFL thickness (μm) and macular and ganglion cell complex thickness (μm). These measurements are taken in reference to normative values.

Clinically, measurement of visual function is by standard automated perimetry (SAP). It uses a constant size stimulus, the Goldmann size 3, at all test locations. Visual field sensitivity measures luminance of the stimulus relative to background, recorded in decibels (dB).

Analysing agreement between structural and functional parameters is complicated by different units of measurement. Perimetric sensitivities are reported in dB (non-linear units) and imaging measures are reported in linear units.

It is often stated that structural abnormalities precede visual field changes in glaucoma development. The term 'preperimetric glaucoma' was used if patients had clinically detected ONH changes in eyes without detectable visual field damage. Histologic ganglion cell data with normal visual field data from post mortem eyes supported this theory.[1,2] The concept of 'functional reserve' describes a functional latency period in the natural history of glaucoma where structural change occurred without a functional change.[3]

Several studies showed that the relationship between visual field measurements (dB) and structural measures (in linear units) is curvilinear.[4,5,6] This implies that in early POAG, structural loss appears greater than functional loss, whereas in more advanced disease, it appears as if function changes at a greater rate than structure. This curvilinear relationship may be a consequence of measuring visual function in logarithmic units, whereas ganglion cell measures are measured in linear units.[4,7] The correlation between structural and functional measures varies with severity of damage.

When functional abnormalities precede structural abnormalities

There is substantial evidence that abnormalities of the visual field can precede detectable abnormalities of the optic nerve head (ONH) or retinal nerve fibre layer (RNFL).

Data from large clinical trials illustrate that perimetric damage can precede ONH changes 35 per cent to 86 per cent of patients. In the Ocular Hypertension Treatment Study, a visual field end-point was reached first in 35 per cent of patients (structural change in 55 per cent).[8,9] The European Glaucoma Prevention Study and Early Manifest Glaucoma Trial showed that visual field was detectable first in 60 per cent and 86 per cent of patients, respectively.[10,11]

Identifying the relative frequency of structural and functional change within a study depends on the reference standard used to assess this change and the specificity and sensitivity criteria to define that the change has taken place.

One study aimed to establish the sensitivity of imaging devices to identify glaucoma and used visual function as the reference standard for classification of glaucoma and healthy eyes.[12] Another study aimed to establish the sensitivity of various vision function tests to identify glaucoma and used a structural definition of glaucoma as the reference standard.[13]

Both studies presented the sensitivity of the tests under consideration for specificity of 80 per cent. The studies found that the imaging devices had sensitivity to identify early glaucoma in 70 to 75 per cent and the visual function tests had sensitivity of about 50 to 65 per cent.

Thus, in first study, 25 to 30 per cent subjects with glaucomatous visual field loss had no detectable structural defect. In the second study, 35 to 50 per cent of patients with glaucomatous optic neuropathy had no detectable vision function loss. Therefore, the evidence points to either structural or functional loss being the first detectable sign of glaucoma in different patients.

Continued page 18

Does structure always precede function?

From page 17

Ganglion cells

The concept of ganglion cell dysfunction may explain why perimetric defects precede identifiable structural changes. In early stages of ganglion cell insult, cells may become dysfunctional, leading to reduction in visual field sensitivity, so that the measured structure may not be representative of functioning ganglion cell or axonal number.

Studies of electrophysiology support evidence for ganglion cell dysfunction. Investigations of pattern electroretinogram (PERG) show that the reduction in RGC signal is greater than predicted from RNFL thickness measurements alone[14] and that a reversible reduction of PERG amplitude can be induced by elevating IOP.[15]

Reasons for structure-function dissociation are diverse. There are expected sources of variability: intersubject variability, measurement imprecision, different measurement ranges and statistical boundaries for defining abnormality.

Imaging measurements of neuroretinal rim in ONH and thickness of RNFL include non-neural elements such as glial tissue and blood vessels. It has been suggested that neuroretinal rim area measured by HRT correlate with ganglion cell counts in animal eyes and therefore, provide a measure of ganglion cell loss in glaucoma eyes. However, studies of relationship between disc topography and optic nerve fibres have included fewer than 15 eyes and correlations between rim area parameters and optic nerve fibres are about r = 0.85 (Pearson's correlation), indicating that rim area is not a perfect marker for ganglion cell count.[16]

Spectral domain OCT enables imaging a structure directly related to RGC numbers—the RGC layer in the macula.

Relating structure and function in patients with glaucoma requires knowledge about the anatomical correspondences of peripapillary RNFL sector with visual field test locations. There is considerable variability around ONH entry point for a given visual field; typically spanning 20-30 degrees.[17] This is likely to be a major source of imprecision in the evaluation of the quantitative structure-function relationship.

Visual field and structural measurements are subject to significant variations between subject and test-retest variability, which are sources of imprecision in structure-function comparisons.

Sources of variability in structural measurements include poor image quality, lens opacity and cylindrical error, poor acuity, low analysis confidence in OCT images and operator and instrument variability.[18,19]

Combining structural and functional testing improves the diagnostic ability to detect glaucoma and assessing progression. The exact nature of the structure-function relationship is still under debate but there is evidence that structure and function changes can occur concurrently in some patients, whereas structural or functional change can occur first in other patients. We await further research on this subject to better understand the structure-function relationship. ■

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Effect of lateral decubitus position on intraocular pressure in glaucoma patients

IOP-elevation asymmetry in lateral decubitus position (LDP) has been found to be associated with asymmetric visual field (VF) loss in glaucoma patients.

A prospective, cross-sectional study involved 98 eyes (n = 49 consecutive, bilateral glaucoma patients) with asymmetric VF loss. IOP was measured when sitting, supine, right LDP and left LDP. A questionnaire on the preferred lying position during sleep was administered to patients.

IOPs of the worse and better eyes showed no significant difference when sitting ($p > 0.05$). IOP of the worse eye was significantly higher than the better eye in supine position (16.8 ± 3.0 mmHg vs 15.1 ± 1.8 mmHg; $p < 0.05$). IOPs of the worse and better eyes in their dependent LDP were 19.1 ± 3.0 mmHg and 17.6 ±2.3 mmHg, respectively; 75.5 per cent of patients preferred the LDP and of these, 75.7 per cent preferred the worse eye dependent-LDP.

The authors concluded that the LDP habitually preferred by glaucoma patients may be associated with asymmetric VF changes.

Ophthalmology 2012; Dec 20, Epub ahead of print.

Longitudinal reproducibility of optical coherence tomography measurements in children

Global optical coherence tomography (OCT) measurements have been shown to be reproducible and not affected by normal increases in axial length in normal and glaucomatous eyes of children.

In this two-setting, prospective study, OCT was used to obtain fast retinal nerve fibre layer (RNFL) and macular thickness scans. In Setting 1, normal eyes (n = 8) from children were scanned on presentation, two weeks and three years; axial length was measured at the first and final visits. In Setting 2, OCT scans were performed in children over four years as clinically indicated in normal (n = 27) and glaucomatous (n = 37) eyes.

In Setting 1, axial length increased 0.11 ± 0.04 mm/year over an average of 3.3 years ($p < 0.05$); there was no significant change in RNFL thickness. In Setting 2, intraclass correlation coefficients across the four years for total macular volume were 0.80-0.91 and for average RNFL were 0.73-0.95.

The authors concluded that OCT is a promising objective tool for the longitudinal assessment of RNFL and macular volume in children.

J AAPOS 2012; 6: 523-528.

Dr Laura Downie
BOptom PhD(Melb)
PGCertOcTher FACO
DipMus(Prac) AMusA

Abstracts

Structural brain abnormalities in patients with advanced primary open angle glaucoma

Three-dimensional (3D) magnetic resonance imaging (MRI) has demonstrated the presence of wide-spread abnormalities in the central nervous system (CNS) of patients with open angle glaucoma (OAG).

A clinical, observational study involved 15 patients with bilateral, advanced OAG and an equal number of age-matched normal controls. Retinal nerve fibre layer (RNFL) thickness was measured with ocular coherence tomography. 3D MRI was used to quantify the cross-sectional area of the optic nerve, optic chiasm and grey matter volume of the brain.

Compared with controls, OAG patients showed significant ($p < 0.05$) reductions in bilateral grey-matter volume in multiple brain regions. The cross-sectional area of the optic nerve and optic chiasm and RNFL-thickness were also significantly decreased in the OAG group. These findings indicate that the integrity of the CNS is compromised in advanced OAG.

Invest Ophthalmol Vis Sci 2012; Dec 20, Epub ahead of print.

Ocular benzalkonium chloride distribution following topical administration in an experimental animal model

In this experimental rabbit model, the ocular distribution of topically-instilled benzalkonium chloride (BAK) , a commonly-used preservative in topical glaucoma therapy, was analysed using mass spectrometry imaging.

Three groups of rabbits were analysed: controls (no instillation), low-chronic model (0.01% BAK twice daily for five months), high sub-chronic model (0.2% BAK once daily for one month); n = 3 per group.

Immunological analyses showed a greater toxic effect in the five-month group than the one-month model, suggesting that the duration of treatment is more significant than the BAK concentration. BAK penetrated healthy eyes even after a short duration of exposure; it was detected on the ocular surface and deeper tissues, especially in areas involved in glaucoma pathophysiology, including the trabecular meshwork and optic nerve. BAK was also associated with pathogenic Müller glial cell activation.

These preliminary findings confirm the penetration of BAK to deep ocular structures involved in glaucomatous optic neuropathy in an animal model, and suggest that preservative-free compounds may be the most appropriate first-line therapy for patients with glaucoma.

PLoS One 2012; 7: 11: e50180.

Effect of topical intraocular pressure-lowering medication on IOP spikes after intravitreal injection

A significant reduction in the magnitude and duration of the intraocular pressure (IOP) spike that occurs following intravitreal injection (IVI) has been reported with the use of prophylactic IOP-lowering topical medication.

This prospective study involved 250 antivascular endothelial growth factor IVI (ranibizumab) treatments that were divided into five groups (n = 50 per group): Group 1 (Control): no IOP-lowering treatment, Group 2: apraclonidine 1%, Group 3: acetazolamide, Group 4: brimonidine + timolol, Group 5: dorzolamide + timolol. IOP was measured before, immediately after (T1), 15 minutes after (T15) and 45-minutes (T45) after IVI.

In Controls, the mean IOP peak was 46.4 ± 10 mmHg at T1, 27.1 ± 10.2 mmHg at T15 and 15.4 ± 8.6 mmHg at T45; the effect was not correlated with axial length or lens status (that is, phakic versus pseudophakic).

Topical IOP-lowering medications produced a significant reduction in IOP at each time-point; there were no significant differences in the mean reduction of IOP between Groups 2-4, with an average decrease of about 9 mmHg at T1.

In conclusion, post-IVI IOP-spikes were high but transient. Pre-treatment with topical anti-glaucoma medication resulted in a significant reduction in both the magnitude and duration of the IOP spike. The authors suggested that it would be advisable to pre-treat patients undergoing IVI VEGF treatments with a topical IOP-lowering agent, in particular in the context of coexistent glaucoma or multiple IVIs.

Eur J Ophthalmol 2012; Nov 15, Epub ahead of print.

Position of the central retinal vessel trunk and pattern of remaining visual field in advanced glaucoma

The pattern of perimetric loss in advanced glaucoma is related to the position of the

Continued page 20

Abstracts

From page 19

central retinal vessel trunk (CRVT); eyes with a central visual field (VF) island tend to have the CRVT at the temporal optic disc region.

This clinical observational study included patients with end-stage glaucoma and a remaining central VF island (CI group, n = 21) or temporal VF remnant (TI group, n = 22); both groups did not differ significantly in age, gender, refractive error, central corneal thickness, axial length or mean retinal nerve fibre layer (RNFL) thickness. The position of the CRVT exit on the lamina cribosa was evaluated with optic disc photographs. RNFL thickness was measured using optical coherence tomography.

RNFL in the temporal region (48.1 ± 5.5 µm vs 37.2 ± 7.9 µm; $p < 0.05$) was significantly thicker and RNFL in the nasal region (41.6 ± 8.3 µm vs 48.0 ± 7.8 µm; $p < 0.05$) was significantly thinner in the CI group than TI group. The CRVT was located in the temporal disc part significantly more often in the CI group than in the TI group (6/21 vs 0/22; $p < 0.05$).

An optic disc region close to the CRVT appears to have a lower risk of glaucomatous optic nerve damage than an optic disc region more distant to the CRVT. These results may suggest that the local glaucoma damage susceptibility within the optic nerve head depends on the position of the CRVT. It remains unclear whether this association is due to a structural reason or a vascular cause.

Br J Ophthalmol 2013; 1: 96-100.

Increased choroidal thickness in angle closure glaucoma

Eyes with angle closure (AC) have been shown to have a significantly thicker choroid than normal eyes or those with open-angle (OA) glaucoma.

In a study, controls (n = 40), OA eyes (n = 106) and AC eyes (n = 79) underwent measurements of: posterior choroidal thickness by spectral domain optical coherence tomography, intraocular pressure (IOP), blood pressure (BP), axial length (AL) and central corneal thickness (CCT).

Following adjustment for relevant variables, choroidal thickness was significantly greater in AC than OA and normal eyes ($p < 0.05$). Multivariate analysis showed that thinner choroidal thickness was associated with older age, longer AL, higher IOP and thicker CCT ($p < 0.05$ for each parameter). In glaucomatous eyes, there was no significant association between CT and cup-to-disc ratio or visual field mean deviation ($p > 0.05$).

These findings support the hypothesis that choroidal expansion contributes to the development of AC glaucoma. Age, AL, CCT and IOP were also significantly associated with CT; however, the severity of the glaucoma was not.

Invest Ophthalmol Vis Sci 2012; 53: 12: 7813-7818.

Retinal vessel calibre is associated with the 10-year incidence of primary open-angle glaucoma

A recent population-based cohort study has shown that retinal arteriolar narrowing, quantitatively measured from retinal photographs, is associated with the long-term risk of open-angle glaucoma (OAG).

These data derive from The Blue Mountains Eye Study, which examined 3,654 persons at baseline and 2,461 at either five years or 10 years, or both time intervals. After excluding 44 subjects with OAG at baseline, 2,471 participants at risk of OAG at the five- or 10-year examinations were included. Retinal vessel calibres were measured using a computer-based program and summarised as central retinal-artery and retinal-vein equivalents (CRAE, CRVE). There were 82 persons (104 eyes) who developed OAG over the 10-year follow-up period. After adjusting for age, sex, family history of glaucoma, smoking, diabetes, hypertension, hypercholesterolaemia, body mass index, spherical equivalent refraction and cup-to-disc ratio, narrower CRAE was associated with a higher risk of incident OAG (adjusted odds ratios [OR], 1.77; 95% confidence interval [CI], 1.12-2.79, per standard deviation decrease in CRAE).

These data support the concept that early vascular changes are involved in the pathogenesis of OAG and suggest that computer-based measurements of retinal vessel calibre may be useful to identify people with an increased risk of developing the clinical stage of glaucoma.

Ophthalmology 2012; Oct 9 (Epub ahead of print)

Balance control is impaired in patients with glaucoma

Patients with glaucoma have impaired postural stability compared with patients who do not have ocular disease.

In a study, age-matched subjects with glaucoma (n = 24) and without eye disease, controls (n = 24) had their postural stability measured using a force-balance platform under four conditions: eyes open/closed standing on a firm surface and eyes open/closed standing on a foam surface. Average magnitude of centre of foot displacement was calculated in the antero-posterior direction. The Romberg Quotient (RQ) was used to evaluate the visual contribution to balance. The difference in sway between firm and foam standing evaluated the relative somatosensory contribution to balance. The binocular mean deviation (Bin MD) score was calculated from Humphrey 24-2 SITA strategy tests.

Glaucoma patients had a lower visual contribution to sway and higher relative somatosensory contribution to sway. BinMD was a significant predictor of balance.

These findings indicate that glaucoma patients display differences in their visual and somatosensory contributions to quiet standing balance compared with control subjects, associated with the degree of binocular visual field loss; therefore, balance control may by compromised in patients with glaucoma.

Invest Ophthalmol Vis Sci 2012; 53; 12: 7795-7801.

Longitudinal effect of topical anti-glaucoma medications on central corneal thickness

Topical prostaglandin analogues have been shown to have a small but significant effect on reducing central corneal thickness (CCT) over time.

This case-control study with retrospective and prospective data collection involved 187 eyes from glaucoma patients being treated with topical anti-glaucoma medications for at least three years, with no history of surgery or laser treatment. This group was compared with age-matched untreated controls subjects (n = 100) who were glaucoma suspects with normal intraocular pressure (IOP) and no treatment. The mean follow-up period was 6.92 ± 1.67 years for glaucomatous eyes and 6.58 ± 1.93 years for controls.

CCT was found to reduce significantly ($p < 0.05$) with time in treated eyes but not in control eyes (treatment group: mean CCT reduction of 12.29 ± 13.65 µm vs control group: 1.17 ± 8.75 µm). Among treated eyes, CCT reduction was significant ($p < 0.05$) only in eyes treated with prostaglandin analogues or combination therapy with prostaglandins and beta-blockers.

These findings suggest that serial CCT measurements may be necessary in glaucoma patients, in particular those managed with topical prostaglandin therapy.

Clin Experiment Ophthalmol 2012; Sep 7, Epub ahead of print. ■

Glaucoma is a 24-hour disease

The most effective therapies control intraocular pressure throughout the full diurnal cycle.

Dr Joseph Sowka
OD FAAO Diplomate
Professor, Nova Southeastern University, FL USA

It has long been thought that intraocular pressure (IOP) tends to be highest in the early morning, decreases throughout the day and is lowest while patients are sleeping.[1] This thinking comes from both the understanding that there is a reduction in aqueous production while patients sleep as well as studies of the diurnal IOP measurement of patients. However, this information typically came from studies performed in artificial clinical settings during typical office hours. In these studies, measurement of IOP occurred with the patient seated upright in the examination chair.

Based on this information, in determining a diurnal pressure curve for a patient, a clinician would take several IOP measurements during office hours, either throughout one day or on separate days, preferably in the morning and early and late afternoon, in order to understand the pressure trend of an individual patient. At the end of this exercise, it was felt that the true pressure response of a given patient on a given day was known.

This provincial thinking regarding the diurnal IOP curve has been challenged in recent years. Newer information has provided a better assessment of what actually happens to IOP during the full diurnal cycle. Nakakura and colleagues examined patients with glaucoma being treated concurrently with three IOP reducing medications (latanoprost, a beta blocker and a topical carbonic anhydrase inhibitor). Using Goldmann tonometry with the patients sitting upright, they found that the peak IOP occurred during the night outside of typical office hours in 61 per cent of tested eyes.[2] Although this study was done under artificial circumstances with patients being admitted to a study hospital and awoken from sleep and made to walk to a biomicroscope for pressure evaluation, the findings were compelling enough to lead to further studies.

In an effort to better identify natural diurnal IOP values, Liu and associates developed a sleep laboratory in which trained observers using night vision goggles and a pneumotonometer measured IOP with patients sitting upright in the 16-hour waking cycle and supine during the eight-hour sleep period with minimal disruption to their habitual body position.[3-5] Measurements of IOP were taken every two hours in the sitting position during the diurnal/wake period (7:00 am to 11:00 pm) and in the supine position during the nocturnal/sleep period.[4-5] In contrast to the previous thinking that IOP was lowest during the sleep period, it was found that IOP actually peaked during this time.[3-5] This was true for healthy patients as well as for those with glaucoma.[6]

The reason for IOP elevation during the supine sleep period is not clear. A popular conjecture is that when patients are supine, there is a gravitational effect increasing episcleral venous pressure. For aqueous to flow, there must be a pressure differential with IOP highest in the posterior chamber, reducing in the anterior chamber, reducing further in Schlemm's canal and beyond. As episcleral venous pressure rises, the resistance to aqueous outflow increases. Such an effect is seen in patients with Sturge Weber syndrome and cavernous sinus fistula.

Continued page 22

Glaucoma is a 24-hour disease

From page 21

The result is an IOP that rises until it can overcome the back-pressure and re-establish forward flow. It appears that this increase in IOP reflects body position more than circadian rhythm. Supine measurements in the examination chair may yield IOPs 5 mmHg or more, greater than the sitting IOP in the same patient.[6]

It has been shown that lowering of IOP prevents or delays progressive glaucomatous damage.[7,8] Ideally, IOP should be lowered consistently at all times to affect the best outcome for patients. If the IOP is highest when patients sleep in the supine position, it is likely peak IOP measurement will remain undiscovered. We can speculate that the pressure measured during typical office hours possibly reflects a lower range of the diurnal IOP, reasoning that IOP is likely to be higher when most, though not all, patients sleep supine. Knowing that IOP is highest while patients sleep supine, it becomes imperative to choose therapies that have effects evenly throughout the 24-hour cycle.

It has been well shown that prostaglandin analogs are excellent in reducing IOP both during waking hours as well as during the supine sleep cycle with a sustained IOP lowering throughout the 24-hour diurnal cycle.[9-12] This could possibly be explained by the fact that prostaglandin analogs increase aqueous outflow through the uveoscleral pathway, which is independent of episcleral venous pressure.

What are less certain are the effects of other therapies in the 24-hour diurnal cycle. Although 0.1% brimonidine monotherapy significantly lowered IOP during the diurnal/wake period, it did not significantly lower IOP during the nocturnal/sleep period.[13] Similarly, once-daily gel-forming beta blocker monotherapy failed to provide IOP reduction from the untreated baseline during the sleep cycle though IOP was significantly reduced during the day.[9] When choosing adjunctive therapy to prostaglandin analogs, considerations for sleep time effects are warranted. It has been shown that brinzolamide seems to have an additional adjunctive effect during the sleep cycle while timolol does not.[14-16]

When choosing therapies to control IOP in glaucoma, it appears that the prostaglandin analogs and topical carbonic anhydrase inhibitors tend to be most effective through the full 24-hour cycle. When choosing additive therapy to prostaglandin analogs, it appears that topical carbonic anhydrase inhibitors tend to have the most sustained effects through the 24-hour cycle while other therapies are mostly effective during the waking period only and have minimal to no effects on patients during the supine sleep cycle. As glaucoma is a disease that is likely to pathogenically progress continuously through the entire 24-hour diurnal period, it is important to choose therapies that most effectively blunt IOP elevations through this same period. ■

> **Knowing that IOP is highest while patients sleep supine, it becomes imperative to choose therapies that are effective evenly throughout the 24-hour cycle.**

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Glaucoma and quality of life

Rate of visual field progression and life expectancy

Dr Tim Roberts
MBBS MMed FRANZCO FRACS
Clinical Senior Lecturer,
University of Sydney
Department of Ophthalmology,
Royal North Shore Hospital
Vision Eye Institute

The aim of management in any disease is to maintain or improve our patients' quality of life (QOL). What is it we are aiming to achieve in glaucoma—a better visual field test result, a lower IOP or minimising progressive symptoms that may adversely affect quality of life?

The goal of glaucoma treatment is to maintain the patient's visual function and related quality of life at a sustainable cost. Over-treating a patient with only a short while to live, where glaucoma is unlikely to impact QOL during their life, or under-treating a patient with many years to live, where glaucoma is likely to impact QOL during their life, are both poor management options.

Recent large, randomised controlled trials have provided excellent data regarding predictive risk factors for developing glaucoma or further glaucomatous damage. These studies also give an indication of the safety and efficacy of various therapies, allowing the risk/benefit analysis of various management options for each patient to be individualised depending on the stage of their disease stage and their risk factors, and treatment to be tailored accordingly.

The challenge

Glaucoma is the second leading cause of irreversible blindness globally and the most common cause of preventable blindness.[1] In Australia about 150,000 people aged over 50 years have glaucoma and this number is expected to double over the next 30 years.[2,3]

Despite significant advances in diagnosis and management, some of these people continue to lose their sight. About 50 per cent of those with glaucoma remain undiagnosed[4,5] and it is estimated that 15 per cent of individuals with glaucoma will become blind in both eyes and 20 to 40 per cent blind in one eye throughout their life.[6,7,8]

Two key factors predict a patient's risk of being adversely affected during their lifetime: the rate of glaucoma progression and their life expectancy.

The severity of glaucoma and general health can be determined at the initial visits, whereas an accurate assessment of progression can take up to two years and require five or more visual field tests. The principal role of visual field testing in glaucoma is in follow-up to determine the rate of progression, rather than in establishing the diagnosis which can usually be done following a careful clinical examination of the optic disc.

- Higher baseline IOP
- Greater glaucoma damage at diagnosis
- Pseudoexfoliation syndrome
- Larger IOP variation
- Disc haemorrhages
- Non-compliance with treatment

Heijl et al 2009

Table 1. Risk factors associated with glaucoma progression

Glaucoma progression

The goal of treatment is to prevent the patient from progressing to serious visual field loss in their better eye. Large trials have identified risk factors that may be associated with progression to blindness in open-angle glaucoma. These include older age, greater glaucoma damage at diagnosis, pseudoexfoliation syndrome, larger IOP variation, disc haemorrhages and non-compliance with treatment[9] (Table 1).

These studies have also shown us, somewhat disturbingly, that most patients progress even if the IOP is normal and that the rate of progression is extremely variable.[10] This paradigm shift highlights the complexities of glaucoma management and warns against a simplistic 'treatment by numbers' approach.

Deterioration of the visual field is best understood in terms of the number of years it would take a patient to lose significant visual function. A slow progression rate (for example, 0.2 dB/year) would take about 150 years for the patient to go from a full normal field to perimetric blindness. In contrast, rapid progression (for example, 2 dB/year) would cause perimetric blindness in about 15 years.

The EMGT (Early Manifest Glaucoma Trial) found the average natural history progression rate in untreated glaucoma to be 0.36 dB/year; however, there was a

Continued page 24

Glaucoma and quality of life

From page 23

small group of rapid progressors.[11] Older patients consistently show more rapid progression than younger patients, and those with elevated IOP show more rapid progression (average 1.31 dB/year) than with low IOP. Eyes with pseudoexfoliation progress rapidly at more than 3dB/year (which untreated would lead to perimetric blindness in less than 10 years). The rate of progression in treated patients is lower. Some patients show almost no visual field progression (0 dB/year) whereas others progress up to -11 dB/year, indicating the highly variable rate between individual patients.

Other medical specialities such as oncology have clear categorical stages for disease classification but there is no consensus on what the stages of the disease are within the field of glaucoma. Glaucoma staging systems have been developed based on Humphrey Visual Field mean deviation scores, ranging from -0.01 to -5.00 dB (early glaucoma) to -20.01 dB or worse (severe glaucoma) (Table 2).

Ensuring good quality and reliable visual fields is crucial. This can be improved by:

- instructing new patients in what the test involves and clearly explaining why it is being done
- careful and correct interpretation of visual fields without getting lost in the detail
- looking at earlier fields if a suspicious result is found.

The ideal frequency and type of testing differs from patient to patient; however, it is recommended to perform a sufficient number of VF tests to assess progression and to estimate the rate of visual field progression. To identify rapid progression, some patients may need up to six visual field tests to be performed in first two years of follow-up (Table 3).

Stage	Description	VF MD Score
0	Ocular hypertension	0.00
1	Early glaucoma	-0.01 to -5.00
2	Moderate glaucoma	-5.01 to -12.00
3	Advanced glaucoma	-12.00 to -20.00
4	Severe glaucoma	-20.01 or worse
5	End-stage glaucoma/blind	No VF in worst eye

Mills et al 2006

Table 2. Staging system for glaucoma based on Humphrey visual field test

- Perform a sufficient number of visual field tests to assess progression, and identify rapid progressors
- Estimate the rate of visual field progression
- Use the same threshold test
- Pay attention to test quality

Chauhan et al 2008

Table 3. Recommendations for visual field testing

Conclusion

The goal of glaucoma management is to prevent our patients from progressing to serious visual field loss which may adversely affect their quality of life. The two key factors in predicting an individual's risk of visual morbidity are the rate of glaucoma progression and their life expectancy. Recent large trials provide excellent data regarding predictive risk factors for developing glaucoma or further glaucomatous damage. They also give an indication of the safety and efficacy of various therapies that allows us to individualise the risk/benefit analysis depending on disease stage and risk factors, and to tailor treatment accordingly.

New data show that most patients progress even if the IOP is normal and that the rate of progression is extremely variable. This highlights the complexities of glaucoma management and the need for a comprehensive individual assessment rather than a simplistic 'treatment by numbers' approach. ■

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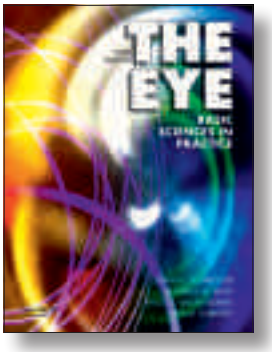

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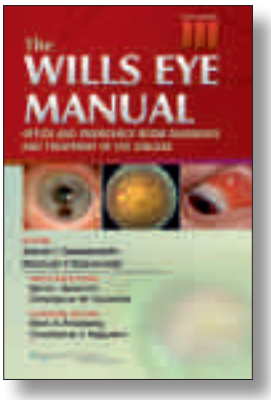

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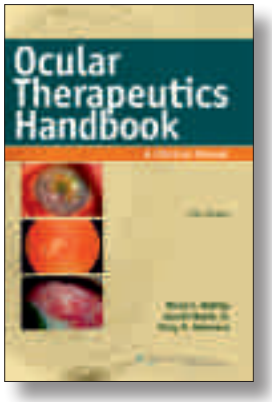

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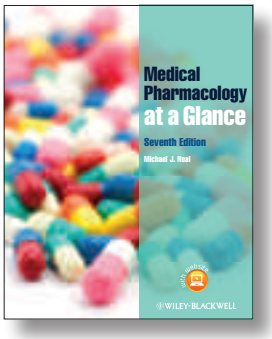

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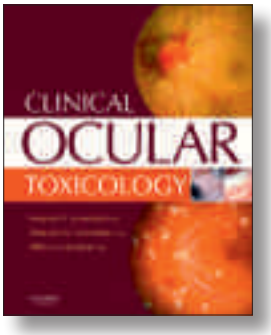

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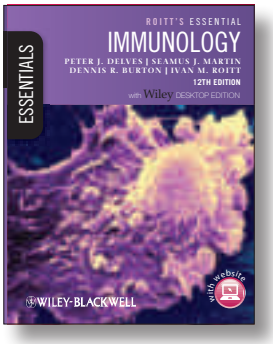

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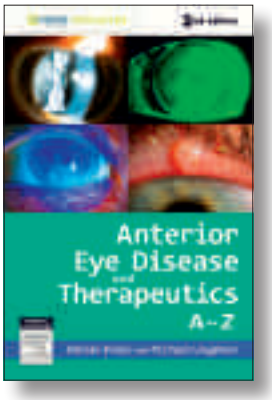

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