Journal of the South East Asia Glaucoma Interest Group

SUPPLEMENT 4

Volume 8 Number 6 December 2006

Optic Nerve in Focus: the Asia Pacific Approach

21st Congress of the Asia-Pacific Academy of Ophthalmology

Singapore, 10 June 2006

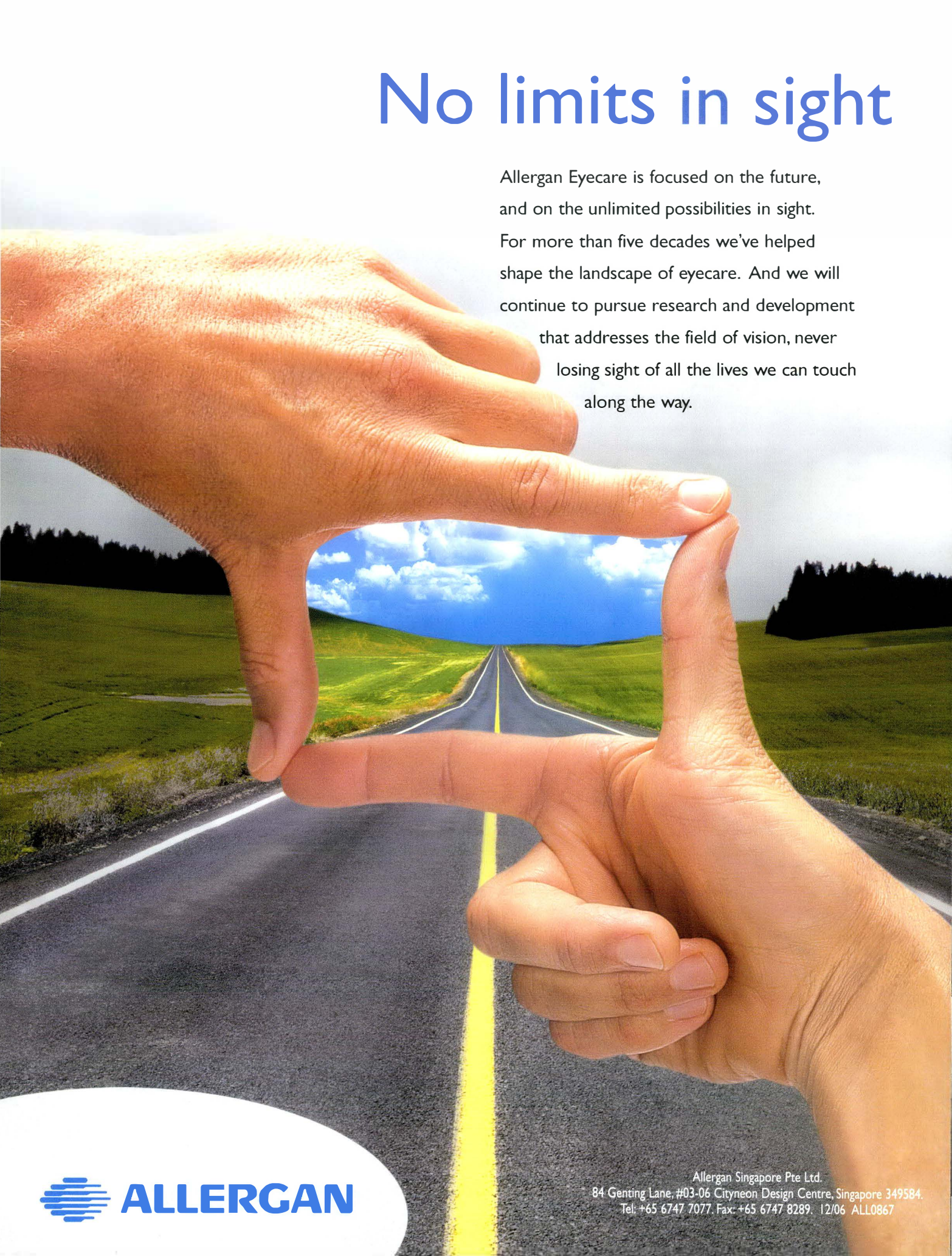
- *Treatment Principles and Concepts*
- *Predictive Factors for Glaucoma*
- *Detecting Damage*
- *Cost-effectiveness of Medical Therapy*
- *Circadian Intraocular Pressure*

Asian Journal of OPHTHALMOLOGY

Scientific Communications

No limits in sight

Allergan Eyecare is focused on the future, and on the unlimited possibilities in sight. For more than five decades we've helped shape the landscape of eyecare. And we will continue to pursue research and development that addresses the field of vision, never losing sight of all the lives we can touch along the way.



ALLERGAN

Allergan Singapore Pte Ltd.
84 Genting Lane, #03-06 Cityneon Design Centre, Singapore 349584.
Tel: +65 6747 7077. Fax: +65 6747 8289. 12/06 ALL0867

Optic Nerve in Focus: The Asia Pacific Approach

From the Optic Nerve in Focus: the Asia Pacific Approach Symposium held by Allergan Asia Pacific at the 21st Congress of the Asia-Pacific Academy of Ophthalmology (APAO), Singapore, 10 June 2006

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

ISSN 1560-2133

Glaucoma — Treatment Principles and Concepts

Ivan Goldberg
Eye Associates
Sydney Eye Hospital & the University of Sydney
Sydney, Australia

Abstract

The management of glaucoma is still clouded with insufficient knowledge of the disease and by inadequate access to resources. Significant advances have been made in diagnosis, from the discovery of factors affecting diagnostic interpretation such as central corneal thickness to the advent of new diagnostic technologies. Similarly, treatment options have improved with more effective, more convenient, and safer drugs available, and the emerging promise of neuroprotection. With these new treatment modalities, the core principles of glaucoma management are to individualise treatment and to balance it for different stages of the disease.

Clinicians need to diagnose patients who have glaucoma and treat them accordingly. The challenge lies in the limited knowledge of the disease, which may confound a definitive diagnosis, and various treatment controversies. For glaucoma suspects, clinicians also face the challenge of fitting such patients into the paradigm of glaucoma management.

Diagnosis of Glaucoma — Past and Present

Diagnosis of glaucoma is made by structural assessment of the optic nerve head and retinal nerve fibre layer and visual function testing.

Intraocular Pressure

Until recently, intraocular pressure (IOP) was an integral part of glaucoma diagnosis. Now, IOP has become irrelevant in the diagnosis of glaucoma. However, IOP remains vital for establishing baseline levels and therapeutic targets since it is the one parameter that is modifiable in the treatment of glaucoma.

Patients with elevated IOP without structural or functional damage associated with glaucoma were labelled as ocular hypertensives while those with glaucomatous damage were diagnosed with primary open angle or chronic simple glaucoma.[1] The term 'normal tension glaucoma' was used for patients with IOPs within normal ranges but who showed signs of glaucomatous damage.

Central corneal thickness (CCT) may be important in the interpretation of measured IOP. Goldmann applanation tonometry assumes an average CCT of 520 to 540 μm in healthy eyes. When CCT is significantly different from this, it must be taken into account when interpreting the importance of IOP levels.

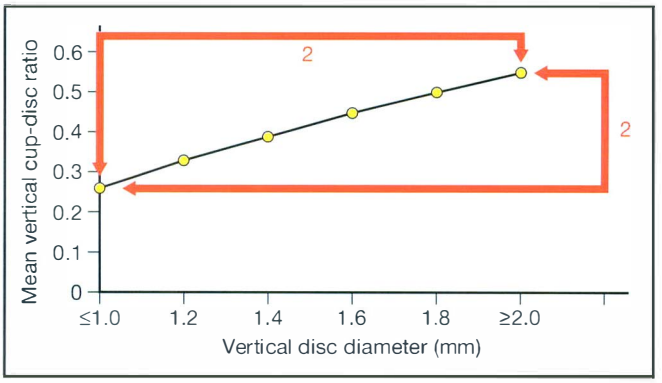
Assessing Structure

Conventionally, ocular structures are assessed with direct and slit-lamp indirect ophthalmoscopy. Direct ophthalmoscopy affords a magnified, upright, and monocular view of the optic nerve head, while slit-lamp indirect ophthalmoscopy through a dilated pupil provides an inverted, magnified, and stereoscopic view. More sophisticated techniques such as Heidelberg retinal tomography (HRT), laser polarimetry, and optical coherence tomography confirm damage when glaucoma damage is clear, but are often less helpful when there is doubt about the diagnosis. To date, HRT is the only modality with published efficacy for long-term follow-up.[2] The key principle of assessing structure is to 'look and record in a clinically meaningful way'. Clinicians should continue to record optic disc structure with photographs while more evidence for these modern devices is gathered.

Vertical Cup-disc Ratio

The Blue Mountains Eye Study showed that the cup-disc ratio has to be evaluated in the context of optic disc diameter.[3] Doubling of disc diameter is associated with a doubling of cup-disc ratio (Figure 1).[3] Thus, a large cup-disc ratio may not necessarily be pathological, particularly when the disc diameter is large.

Figure 1. Disc diameter versus cup-disc ratio.
From Healey PR, Mitchell P, Smith W, Wang JJ. Relationship between cup-disc ratio and optic disc diameter: the Blue Mountains Eye Study. Aust NZ J Ophthalmol. 1997; 25(Suppl 1):S99-101. Reprinted with permission. Copyright 1997, Blackwell Publishing.



Assessing Function

Visual function is categorised as normal or abnormal and, if abnormal, as stable or progressive. Kinetic and static techniques are available as subjective perimetry to assess the performance of visual function. Computerised static techniques range from standard white-on-white perimetry to more specific blue-on-yellow perimetry, as well as frequency doubling threshold (FDT) perimetry, which has good potential for screening for glaucoma. These computerised technologies can be enhanced with an improved algorithm to analyse collected data in a more sophisticated fashion.

Objective perimetry using multifocal multi-channel visual evoked potentials overcomes the difficulties associated with subjective perimetry, for which a patient's cooperation is vital for an accurate assessment. This type of objective perimetry is able to test the entire visual pathway from the retina through to the occipital cortex and requires no patient response except to maintain fixation at the centre of the screen. As it is non-invasive and can be performed on undilated pupils, it is relatively low-stress and requires a minimal learning curve for the patient. Patient preference (9 of 10 surveyed patients) [Graham S, personal communication, 2002.] and close correlation between objective and subjective perimetry in disc findings have made objective perimetry helpful in diagnosing glaucoma.

Detecting Structural and Functional Change

Damage to the optic nerve from glaucoma can be imagined conceptually to follow a downward curve (Figure 2). In advanced disease, detection of further structural changes is often very difficult, while detection of early functional loss depends critically on the sensitivity of current technologies. Initial damage is often best detected structurally; later damage progression is often best detected functionally.

Figure 2. Graphical representation of glaucomatous structural and functional change over time.

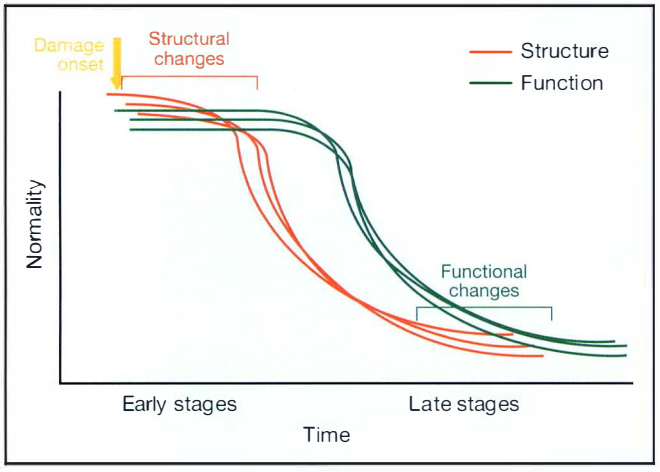
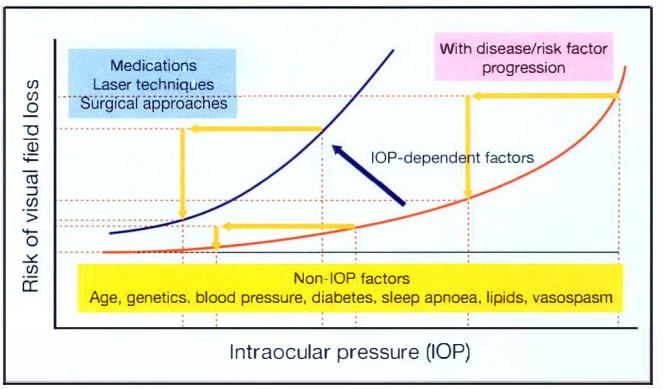


Figure 3. Association of visual field loss and intraocular pressure (IOP).



With the advent of new diagnostic modalities, clinicians now need to decide which technologies to use at the early, middle, and late stages of the disease to best detect change. For example, FDT perimetry may be excellent for detecting early changes but white-on-white perimetry is better for follow-up for patients with advanced disease. These technologies are unlikely to replace one another; in fact, they complement each other at different stages of the disease. This has significant economic implications since access to more than one imaging and functional testing modality may be needed to deliver the best care to patients.

Treatment of Glaucoma

The aims of treatment are to protect patients from disability after considering their life expectancy, the level and location of damage at time of diagnosis, and the measured rate of damage progression. The goal is to protect retinal ganglion cells by lowering IOP and intervening for associated vascular disease, as well as neuroprotection.

Conceptually, the risk of visual field loss and IOP are exponentially related for pressure-dependent factors (Figure 3). Lowering IOP using medication, laser techniques, or surgical approaches provides benefit to patients, but the extent of effectiveness depends on the location of the patient on this curve. In general, IOP reduction and minimising IOP fluctuation are valuable across the spectrum of the glaucoma continuum regardless of the means of achieving it. Intervention for non-pressure-dependent factors such as blood pressure, diabetes, sleep apnoea, hyperlipidaemia, and vasospasm can improve outcomes for patients with glaucoma.

The pressure-dependent damage curve may vary with a change in risk factors and disease status. As a patient's situation may be different in 5 or 10 years' time, the key approach is individualisation of the therapeutic effect.

Medical Therapy for Glaucoma

During the past 25 years, the medical treatment of glaucoma has been revolutionised. Newer medications employ once- or

Table 1. Vasoprotection approaches.

• Ensure systemic hypertension is being treated but not over- or under-treated
• Exclude nocturnal hypotension, a significant risk factor for progressive optic neuropathy[5,6]
• Consider sleep apnoea
• Ensure dyslipidaemia is addressed to protect endothelial cells in capillaries around the optic nerve head
• Ensure glucose intolerance is detected and treated effectively
• Discourage smoking, a general toxin to all neurones and blood vessels
• Encourage a healthy lifestyle and exercise

twice-daily dosing with minimal local and systemic side effects, while providing greater hypotensive potency. Recently, there has been a shift in the use of drugs from β-blockers to prostaglandins, while the number of surgical procedures has declined.[4] However, non-compliance with treatment, dyscompliance (physical/technical barriers), and patient perseverance remain as challenges of medical therapy.

Concepts of Neuroprotection

Glaucoma is an optic neuropathy, which arises from several contributory mechanisms. The survival of retinal ganglion cells (RGCs) is dependent on vasculature input of nutrients and removal of waste products, the supply of neutrophins from the lateral geniculate nucleus, the supporting structures around the RGCs, and the function of neighbouring cells such as astrocytes and Muller's cells. Neuronal death is a result of a chain reaction in response to a primary, and possibly secondary, insult to any of these factors maintaining the survival of RGCs. Clinicians could improve vasoprotection of RGCs by adopting the approaches listed in Table 1.

Neuroprotection is a therapeutic paradigm for slowing or preventing the death of RGCs and their axons, and maintaining their function. The concept of neuroprotection is to enhance cell survival signals at a cellular basis and will be useful regardless of the cause of injury. For neuroprotection to be effective, the agent should bind to receptors in the retina that mediate neuronal survival and achieve a sufficient concentration in the retina following clinical dosing. The neuroprotective potential of memantine and brimonidine was promising in the laboratory; they are currently being evaluated in clinical studies. It is envisaged that neuroprotective agents will augment hypotensive agents for the treatment of glaucoma in the future.

Conclusion

Based on currently available knowledge of glaucoma, clinicians should try to avoid the imbalance of over-treating patients who do not need treatment and under-treating patients who require treatment. Clinicians should strive to achieve this therapeutic balance at every stage of the disease for each individual patient.

References

1. Graham P, Hollows FC. Sources of variation in tonometry. Trans Ophthalmol Soc UK. 1964;84:597-613.
2. Philippin H, Unsoeld A, Maier P, et al. Ten-year results: detection of long-term progressive optic disc changes with confocal laser tomography. Graefes Arch Clin Exp Ophthalmol. 2006; 244:460-4.
3. Healey PR, Mitchell P, Smith W, Wang JJ. Relationship between cup-disc ratio and optic disc diameter: the Blue Mountains Eye Study. Aust NZ J Ophthalmol. 1997;25 (Suppl 1):S99-101.
4. Australian Health Insurance Commission. Laser and drainage procedures performed between 1993 and 2003. 2004.
5. Hayreh SS, Podhajsky P, Zimmerman MB. Role of nocturnal arterial hypotension in optic nerve head ischemic disorders. Ophthalmologica. 1999;213:76-96.
6. Tokunaga T, Kashiwagi K, Tsumura T, et al. Association between nocturnal blood pressure reduction and progression of visual field defect in patients with primary open-angle glaucoma or normal-tension glaucoma. Jpn J Ophthalmol. 2004;48:380-5.

Predictive Factors for Glaucoma — Progression of Disease

Joseph Caprioli
University of California Los Angeles
School of Medicine
California, USA

Abstract

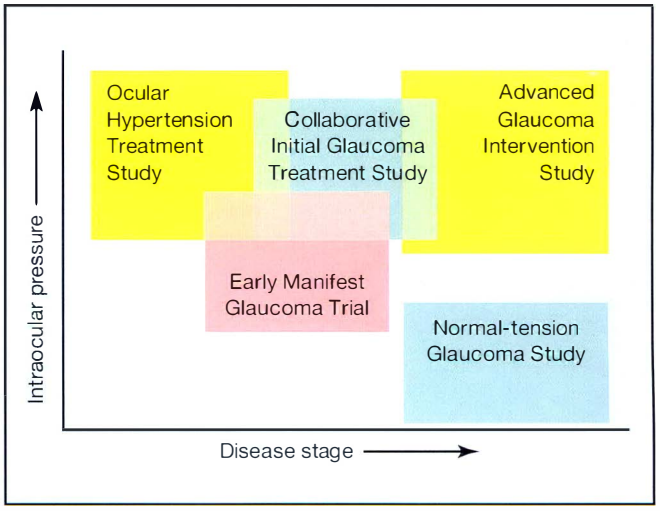
Intraocular pressure has been shown in landmark studies to play an important role in preventing progression of glaucoma, regardless of the pressure level and disease stage. The magnitude of intraocular pressure reduction has been found to be a major predictive factor for outcome. Recently, a robust analytical technique with rigorous criteria has been used to evaluate the significance of various risk factors on visual field progression in patients with advanced disease in a large post-hoc analysis. Intraocular pressure fluctuation between clinic visits consistently emerged as the most important modifiable risk factor associated with visual field progression.

Advances in glaucoma research in the past 50 years have changed the perception of glaucoma from a disease thought to arise from high intraocular pressure (IOP) to one that is now known to be caused by optic neuropathy. Attention has since focused on the outcomes of the optic nerve and visual field. Recently, a wealth of evidence from large clinical trials has demonstrated that lowering IOP helps to prevent glaucoma, hailing a return of interest in targeting IOP. Although treating IOP is important, the primary goals of preventing optic nerve damage and visual field loss should not be overlooked.

Evidence for Lowering Intraocular Pressure

During the past few years, reports from landmark trials that evaluated a large range of IOP levels and disease stages have consistently showed that treatment of raised IOP helps to prevent progressive glaucomatous damage (Figure 1). For patients with elevated IOP at risk for developing primary open angle glaucoma (POAG), the Ocular Hypertension Treatment Study (OHTS) demonstrated the effectiveness of topical hypotensive drugs in preventing the onset of POAG.[1] At the other end of the disease spectrum, the Normal-Tension Glaucoma Study (NTGS) was the first prospective randomised trial to discover that lowering IOP in patients with advanced disease who had normal pressures was beneficial for preventing further damage and progression.[2]

Figure 1. Landmark trials that have shown the benefits of intraocular pressure reduction by disease stage.



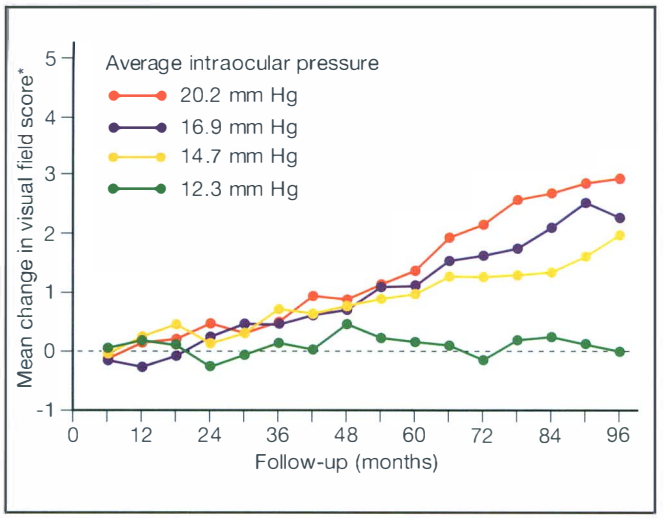
Both the Collaborative Initial Glaucoma Treatment Study (CIGTS)[3] and the Early Manifest Glaucoma Trial (EMGT)[4] showed that IOP reduction using medical or surgical treatment for patients with intermediate IOP and intermediate disease resulted in improved outcomes. The major factor that influenced outcome was the magnitude of initial IOP reduction.[4]

In advanced glaucoma with high IOP, the Advanced Glaucoma Intervention Study (AGIS) revealed a protective role of IOP reduction in the progression of visual field deterioration.[5] Lowering IOP, regardless of the surgical approach (argon laser trabeculoplasty versus trabeculectomy), prevented optic nerve damage in a dose-dependent manner.[6] The visual fields of patients who achieved a mean IOP of 12.3 mm Hg remained stable throughout the 8-year study period, while patients who had an average IOP of 20.2 mm Hg experienced the worst outcome in terms of visual field loss (Figure 2).

Does Intraocular Pressure Fluctuation Affect Outcome?

IOP findings from the AGIS raised the question of whether IOP fluctuation over a long period contributes to progressive visual field loss. There are suggestions that IOP fluctuation affects visual field outcome in patients with glaucoma. Asrani et al investigated the effect of diurnal IOP variations in patients who performed home tonometry for 5 years and found that diurnal fluctuations in IOP correlated with progression of open angle glaucoma.[7] In another prospective study with 2-year follow-up, Bergea et al showed that IOP variations (range and peak) and mean IOP were associated

Figure 2. Mean change in visual field score* with different quintiles of intraocular pressure.
* Higher score denotes worsening of visual field.



with worsening of glaucoma.[8] Similar observations were obtained in 2 other retrospective studies.[9,10]

Long-term Intraocular Pressure Fluctuation and Visual Field Progression

A post-hoc analysis of AGIS was performed to examine long-term IOP fluctuation and other risk factors predictive of visual field progression.[11] The analysis included a number of risk factors that have been shown to be significant in previous studies, as well as potential risk factors which were found to be significant with univariate analysis or could theoretically be associated with visual field progression (Table 1).

A pointwise linear regression was used to analyse the significance of these risk factors on visual field progression. This technique is designed to detect visual field loss specific to glaucomatous change and was found to be superior to the AGIS methods used in longitudinal evaluation of visual fields.[12] False positives were excluded by using a rigorous 2-point cluster change

Table 1. Risk factors and potential risk factors included in the post-hoc analysis of the Advanced Glaucoma Intervention Study (AGIS).

Risk factors	Potential risk factors
• Age	• Refractive error
• Sex	• Baseline visual acuity and AGIS score
• Race	• Baseline intraocular pressure and number of medications
• Educational level	• Average intraocular pressure during follow-up
• Presence or absence of diabetes	• Average number of medications
• Intervention sequence	• Intraocular pressure fluctuation
• Vertical cup-disc ratio	• Duration of follow-up
• Cataract surgery	• Number of glaucoma interventions

Table 2. Significant risk factors for visual field progression.

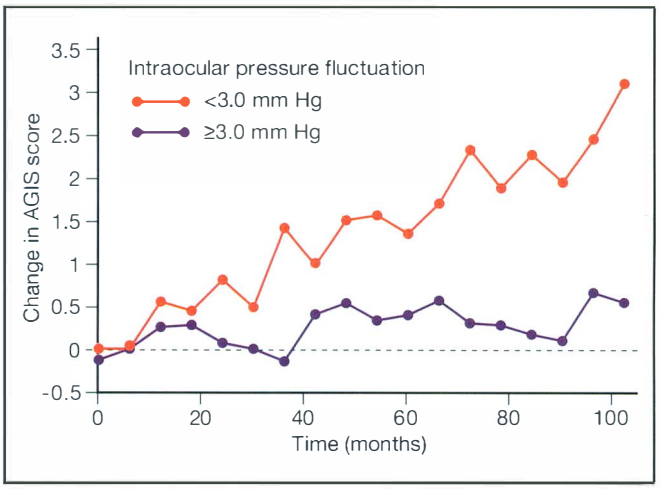
Variable	p Value	Odds ratio
Greater intraocular pressure fluctuation (SD of all intraocular pressures)	0.00002	1.30
Older age	0.00002	1.30
Longer follow-up	0.0006	1.20
Number of interventions	0.02	1.15

criteria that defines visual field progression as worsening of at least 2 test locations within a Glaucoma Hemifield Test cluster.[12] IOP fluctuation was defined as inter-visit IOP variations measured as standard deviation of all IOP measurements during follow-up, but did not denote fluctuations in diurnal IOP.

Patients were followed up for a mean of 7.4 years and had an average of 15 visual field examinations. The mean baseline AGIS score was 7.7 of 20, indicating moderate-to-advanced damage. The baseline IOP was 23.4 mm Hg. Similar to the findings from AGIS, approximately one-third of the patients showed progression of visual field damage. Based on multivariate logistic regression analysis, 4 variables were found to be significant risk factors for progression (Table 2). IOP fluctuation and age were the most important risk factors consistently associated with progression after adjusting for confounding factors such as comorbidity with cataract and cataract surgery. Surprisingly, mean IOP, despite being associated with progression, was less predictive than IOP fluctuation.

When patients were categorised according to the magnitude of the IOP fluctuations, those with a lower long-term IOP fluctuation had a statistically significant better visual field outcome than those with a greater IOP fluctuation (Figure 3). Only 5% of the differences

Figure 3. Change in Advanced Glaucoma Intervention Study (AGIS) score.*
From Nouri-Mahdavi K, Hoffman D, Coleman AL, et al; Advanced Glaucoma Intervention Study. Predictive factors for glaucomatous visual field progression in the Advanced Glaucoma Intervention Study. Ophthalmology. 2004;111:1627-35. Reprinted with permission. Copyright 2004, Elsevier, Inc.
* Higher score denotes visual field progression.



in IOP fluctuation could be explained by a difference in mean IOP. In fact, there was no significant difference in mean IOP between these 2 patient groups.

Conclusion

In conclusion, long-term inter-visit IOP fluctuation is a major risk factor for visual field progression in patients with advanced glaucoma, and perhaps in those with POAG. Compared with mean IOP, IOP fluctuation is more strongly associated with field progression.

References

1. Kass MA, Heuer DK, Higginbotham EJ, et al. The Ocular Hypertension Treatment Study: a randomized trial determines that topical ocular hypotensive medication delays or prevents the onset of primary open-angle glaucoma. Arch Ophthalmol. 2002;120:701-13.
2. The Collaborative Normal-Tension Glaucoma Study Investigators. Comparison of glaucomatous progression between untreated patients with normal-tension glaucoma and patients with therapeutically reduced intraocular pressures. Collaborative Normal-Tension Glaucoma Study Group. Am J Ophthalmol. 1998;126:487-97.
3. Feiner L, Piltz-Seymour JR; Collaborative Initial Glaucoma Treatment Study. Collaborative Initial Glaucoma Treatment Study: a summary of results to date. Curr Opin Ophthalmol. 2003;14:106-11.
4. Heijl A, Leske MC, Bengtsson B, et al; for the Early Manifest Glaucoma Trial Group. Reduction of intraocular pressure and glaucoma progression. Results from the Early Manifest Glaucoma Trial. Arch Ophthalmol. 2002;120:1268-79.
5. The AGIS Investigators. The Advanced Glaucoma Intervention Study (AGIS): 7. The relationship between control of intraocular pressure and visual field deterioration. Am J Ophthalmol. 2000;130:429-40.
6. The AGIS Investigators. The Advanced Glaucoma Intervention Study (AGIS): 9. Comparison of glaucoma outcomes in black and white patients within treatment groups. Am J Ophthalmol. 2001;132: 311-20.
7. Asrani S, Zeimer R, Wilensky J, et al. Large diurnal fluctuations in intraocular pressure are an independent risk factor in patients with glaucoma. J Glaucoma. 2000;9:134-42.
8. Bergea B, Bodin L, Svedbergh B. Impact of intraocular pressure regulation on visual fields in open-angle glaucoma. Ophthalmology. 1999;106:997-1004.
9. Stewart WC, Kolker AE, Sharpe ED, et al. Factors associated with long-term progression or stability in primary open-angle glaucoma. Am J Ophthalmol. 2000;130:274-79.
10. O'Brien C, Schwartz B, Takamoto T, et al. Intraocular pressure and the rate of visual field loss in chronic open-angle glaucoma. Am J Ophthalmol. 1991;111:491-500.
11. Nouri-Mahdavi K, Hoffman D, Coleman AL, et al; Advanced Glaucoma Intervention Study. Predictive factors for glaucomatous visual field progression in the Advanced Glaucoma Intervention Study. Ophthalmology. 2004;111:1627-35.
12. Nouri-Mahdavi K, Caprioli J, Coleman AL, et al. Pointwise linear regression for evaluation of visual field outcomes and comparison with the advanced glaucoma intervention study methods. Arch Ophthalmol. 2005;123:193-9.

Detecting Damage

Ravi Thomas
LV Prasad Eye Institute
Hyderabad, India

Abstract

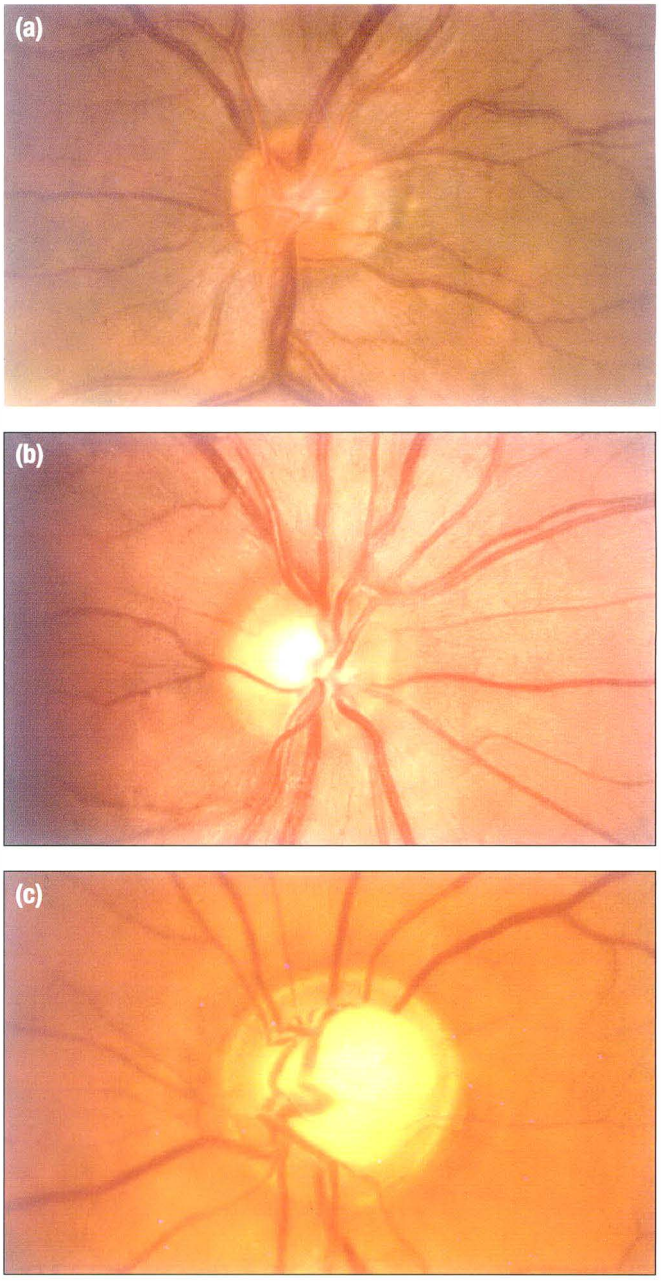
Optic disc examination remains an indispensable part of patient assessment for detecting glaucomatous damage. While the cup-disc ratio has been widely used as a surrogate for neuroretinal rim changes, observing the neuroretinal rim itself is the key to detecting damage. In addition, disc haemorrhage and retinal nerve fibre layer defects are important signs of glaucoma. Clinicians should critically assess their patients with the assumption that disc haemorrhage and retinal nerve fibre layer defects are present in all patients with glaucoma unless proven otherwise. The current evidence does not support the widespread clinical use of newer imaging techniques by general ophthalmologists; these should not replace optic disc examination in the diagnosis of glaucoma. Detection of damage should be based on a combination of signs; if the diagnosis is not confirmed but suspicion persists, the tests should be repeated at appropriate intervals.

Many optic disc changes have been described in glaucoma. These include variations in cup-disc ratio, loss of the inferior superior nasal temporal (ISNT) pattern in the neuroretinal rim, 'baring' of circumlinear vessels, disc haemorrhage, and defects in the retinal nerve fibre layer (RNFL).

Cup-disc Ratio

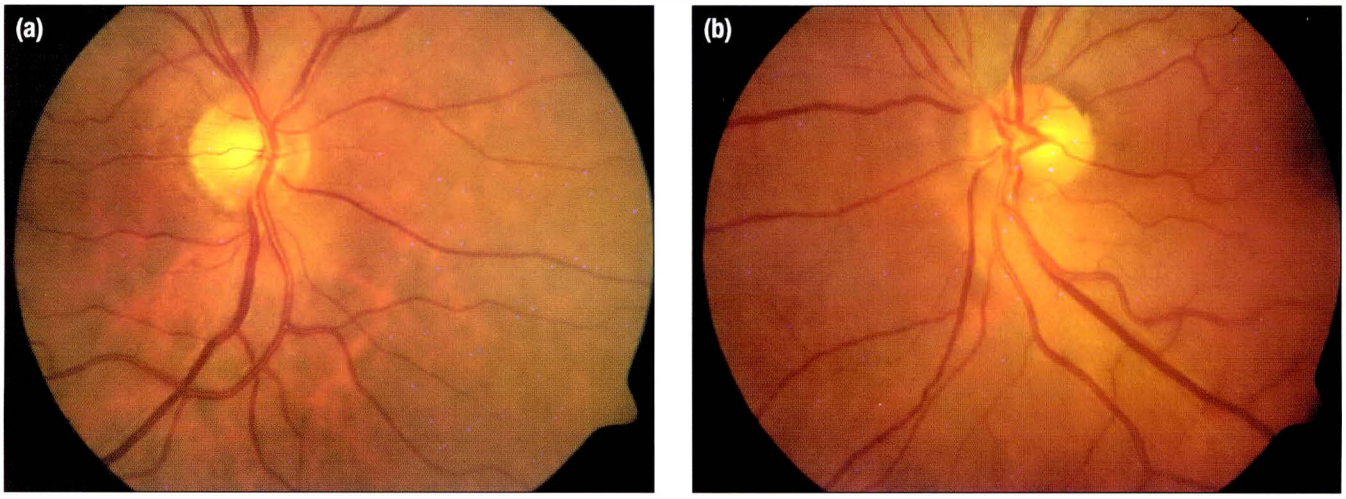
By itself, the cup-disc ratio is of no use in the detection of glaucoma damage. The disc size must always be considered when using cup-disc ratio. Approximately 1.2 million axons pass through each optic disc and the disc size varies between patients, and even within the same patient in the fellow eye. The cup could be regarded as the space that is 'left over' in the disc and this space has to vary with the size of the optic disc. The cup-disc ratio is a surrogate for the neuroretinal rim, which varies with disc size (Figure 1). A large cup may be normal for a large disc while a small cup may be abnormal for a small disc. It is meaningless to evaluate the cup-disc ratio without relating it to the disc size, which is best measured during routine clinical examination using a 60 D or similar lens. Documented increase in cup-disc ratio over time is a sign of glaucoma.

Figure 1. The cup size varies with disc size. (a) A small disc has no cup; (b) a medium-sized disc has a 0.4 to 0.5 cup; and (c) a large disc has a 0.8 cup.



Cup-disc ratio asymmetry could also be a sign of glaucoma. Asymmetry can be subtle and difficult to detect. The optic nerve may appear normal when assessed independently but can reveal a change in cup-disc ratio when compared with a fellow disc (Figure 2). Any difference in size between the 2 discs should be corrected before making comparisons of cup-disc ratios. In general, the cup-disc ratio is only useful when there is disease progression, asymmetry, and when its interpretation is related to the disc size.

Figure 2. Asymmetry of cup-disc ratio in (a) an optic nerve when compared with (b) a fellow disc.

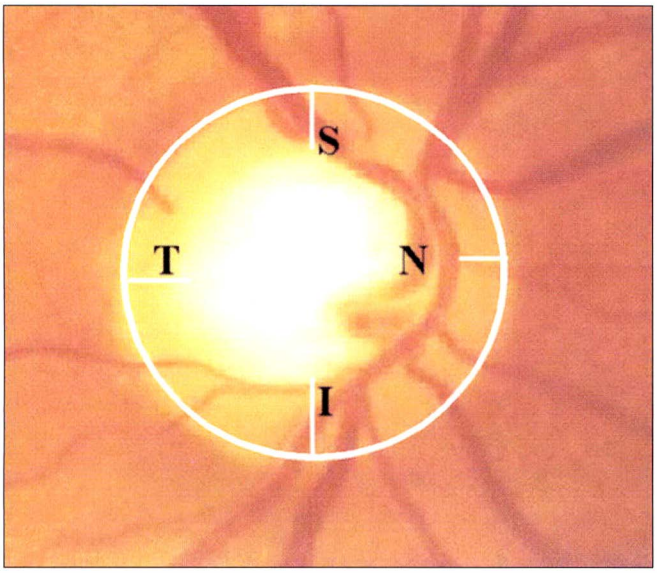


Neuroretinal Rim

While there have been doubts about the usefulness of cup-disc ratio in the management of glaucoma, the neuroretinal rim has been recognised as the key parameter to assess glaucoma since 1965.[1] The ISNT rule should be kept in mind when assessing the rim. The ISNT rule states that in 83% of the eyes, the inferior rim is the thickest, followed by the superior, nasal, and temporal rims (Figure 3).[2] It is also important to examine the ratio of the inferior and superior rims to the temporal rim (2:1 and 1.5:1, respectively). For example, the inferior rim in Figure 4 is thicker than the superior rim, but is thinner than the temporal rim; the superior rim too is markedly thinner than the temporal rim. The temporal rim should always be the smallest.

A less widely used sign of damage is to observe the circumlinear vessels. In approximately 50% of eyes, the circumlinear vessels can be seen hugging the neuroretinal rim and exit into the macula. A gap between the vessel and the rim implies loss of rim (Figure 5) and is fairly specific for the detection of glaucomatous damage.

Figure 3. The inferior superior nasal temporal rule of the neuroretinal rim.



Disc Haemorrhage

A splinter or flame-shaped haemorrhage at the border of the disc is associated with RNFL defects, notches, and focal perimetric loss. Disc haemorrhage is rare in healthy eyes and has a low incidence (4% to 7%) in patients with glaucoma.[3] Despite the low sensitivity of disc haemorrhage in glaucoma, it is extremely specific. Jonas and Xu suggested that until proved otherwise, all patients with glaucoma have an optic disc haemorrhage.[3] An optic disc haemorrhage lasts for approximately 10 to 35 weeks and clinicians need to check for optic disc haemorrhage in all glaucoma suspects. Red-free fundus photography may be required to detect subtle disc haemorrhages. Figure 5 also shows a resolving disc haemorrhage inferiorly.

Figure 4. The inferior superior nasal temporal rule is broken when the thickness of the inferior rim is less than the superior rim and the superior rim is less than the temporal rim.

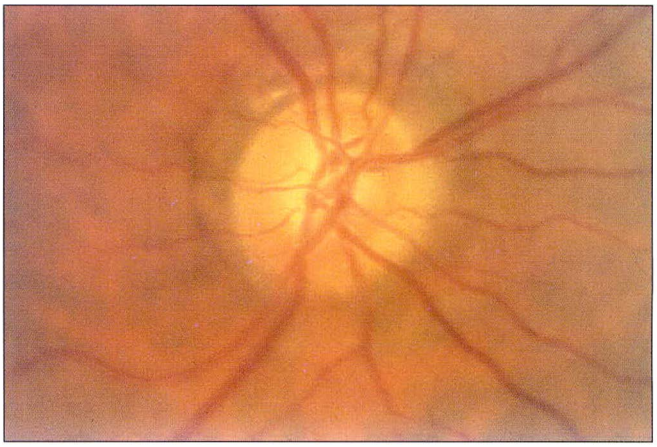
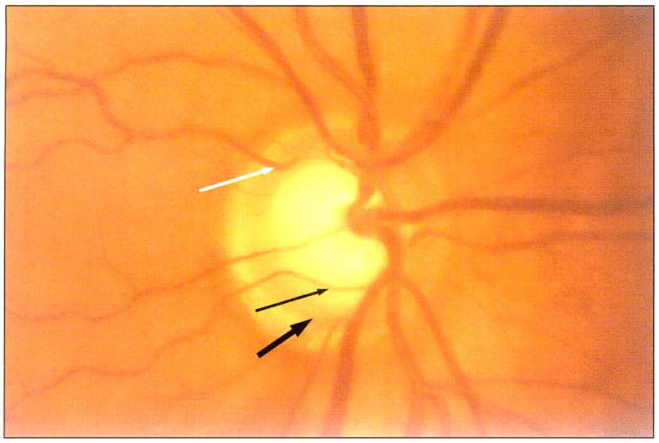


Figure 5. The white arrow shows a normal circumlinear vessel. As the rim is lost, a gap emerges between the vessel and the rim (black arrows). Note the other sign next to the lower, thicker black arrow.



Retinal Nerve Fibre Layer

The RNFL is best seen inferiorly rather than superiorly as 'bright-dark-bright' fine striations as it fans out from the disc to the periphery. RNFL defect is highly specific for pathology since it is not observed in healthy eyes. Damage in the RNFL is present as a wedge or diffuse defect in approximately 20% of eyes with glaucoma. However, RNFL defect is also present in other pathological eye conditions such as drusen and ischaemia.

Diffuse RNFL defects are more difficult to detect than wedge defects. Suspicions should be raised when the inferior bright striations are less visible than the superior area. Usually, the bright-dark-bright pattern would be lost with the area between the disc and macula showing the same bright intensity as the superior and inferior arcuate. The vessels could be seen more clearly in diffuse defects.

Localised RNFL defects are important for early diagnosis of glaucoma because patients often show field loss on follow-up and this allows the clinicians to detect preperimetric glaucoma. It is therefore appropriate to presume that all patients with glaucoma and glaucoma suspects have an RNFL defect, as suggested by Jonas and Xu[3] and clinicians should attempt to detect the defect in these patients. RNFL defects can be seen on a slit lamp or on red-free fundus photography (Figure 6).

Detection of Damage in Myopia

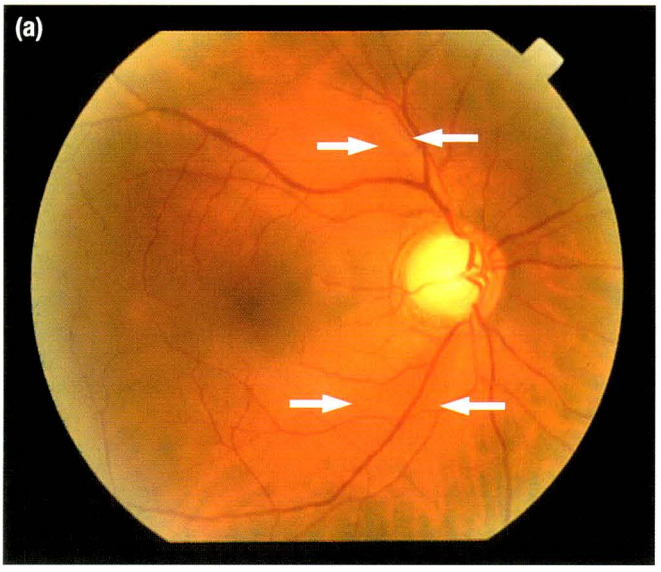
Detection of glaucomatous damage in myopia is difficult and a high index of suspicion is needed. To avoid under-diagnosis of glaucoma in this group of patients, Jonas and Xu suggested that clinicians regard all patients with myopia as glaucoma suspects and critically assess them.[3]

The Role of Imaging in Detecting Damage

Imaging techniques have been developed to improve the early detection of glaucomatous damage. For these technologies to be more sensitive than current clinical techniques, they should detect all early glaucomas in addition to moderate and severe disease. However, clinician assessment of imaging print-outs found that both their sensitivity and specificity were far lower than 100% (Table 1).[4] In addition, these instruments have limited agreement for detection at a specificity of 90%.[5] As many as 15% of patients with glaucoma were not diagnosed as having the disease by any of these 3 instruments shown in Table 1.

The Association of International Glaucoma Societies (AIGS) consensus concluded that the current literature does not provide the requisite evidence to validate any of these imaging instruments

Figure 6. Retinal nerve fibre layer defects as seen on (a) slit lamp; and (b) red-free fundus photography.



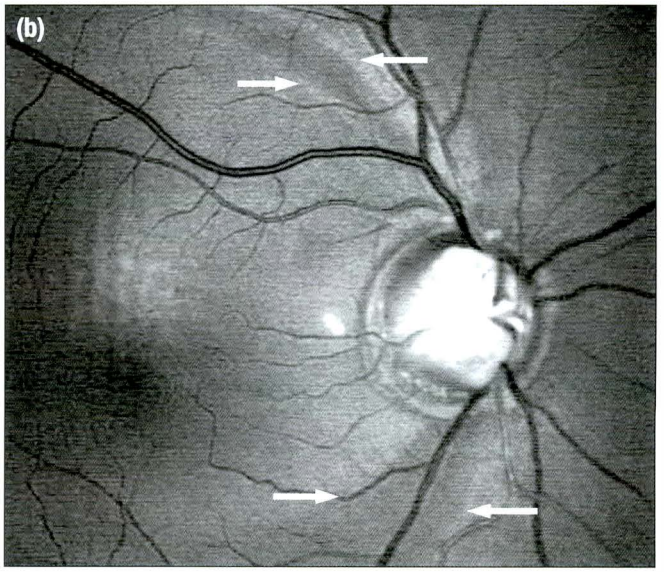


Table 1. Sensitivity and specificity of current imaging techniques.

	Optical coherence tomography (%)	Laser polarimetry (%)	Heidelberg retinal tomography (%)
Sensitivity	76-79	72-82	64-75
Specificity	68-81	56-82	68-80

for their widespread clinical use.[6] These instruments have not been shown to be better than standard clinical testing or a dilated examination from a trained clinician. For general ophthalmologists, there is a risk of misinterpretation of the results from imaging instruments, particularly when these are used in place of optic disc examination. However, in the hands of an experienced clinician who understands the strengths and limitations of the instruments, information may be helpful in many clinical situations.

Conclusion

Detection of damage in glaucoma should be based on a combination of signs. When the disc looks suspicious, it is prudent to confirm the findings with a visual field examination or short-wavelength automated perimetry. If there is still doubt, clinicians may want to request an independent second opinion and/or follow up the patients 6 months later for another examination. Every patient should have a comprehensive ophthalmic examination and that includes a dilated stereobiomicroscopic examination of the optic disc.

Acknowledgement

With grateful thanks to Dr Jost Jonas for provision of some of the slides.

References

1. Chandler PA, Grant WM. Lectures on glaucoma. Philadelphia: Lea & Febiger; 1965.
2. Ritch R, Shields MB, Krupin T. The glaucomas. New York: Mosby-Year Book; 1989.
3. Jonas JB, Xu L. Optic disc hemorrhages in glaucoma. Am J Ophthalmol. 1994;118:1-8.
4. Sanchez-Galeana C, Bowd C, Blumenthal EZ, et al. Using optical imaging summary data to detect glaucoma. Ophthalmology. 2001;108: 1812-8.
5. Zangwill LM, Bowd C, Berry CC, et al. Discriminating between normal and glaucomatous eyes using the Heidelberg Retina Tomograph, GDx Nerve Fiber Analyzer, and Optical Coherence Tomograph. Arch Ophthalmol. 2001;119:985-93.
6. AIGS Consensus Statements. 1st AIGS Consensus Meeting on Structure and Function in the Management of Glaucoma; 2003 Nov 13-14; San Diego, USA. Available at www.globalaigs.org. Accessed 25 June 2006.

Detecting Change in Damage

Luca Rossetti
University of Milan
Milan, Italy

Abstract

Glaucomatous progression can be detected by assessment of structure and function. However, the detection of progression is frequently complicated by the presence of long-term fluctuation. Test repetitions are often needed to identify real progression against the background 'noise'. Several methods exist for the detection of visual field progression, all of which have specific advantages and disadvantages. Qualitative assessment using optic disc photography remains the mainstay for detecting progression. There is insufficient evidence for the use of quantitative assessment (imaging techniques) to detect progression but the results for some techniques have been encouraging.

Identifying glaucoma progression is probably one of the most challenging tasks in the management of the disease. It is of primary importance because the earlier progression is detected, the greater the likelihood of treatment success. Both functional and structural assessments play an important role in the detection of progression. Due to the nature of the disease, structural changes are more easily detected in the early stage, whilst functional changes such as visual field loss are more suitable for monitoring progression in advanced disease.

Visual Field Progression versus Long-term Fluctuation

To identify visual field progression, the clinician must identify changes that exceed long-term fluctuation for that patient, that are consistent with primary open angle glaucoma (POAG), and correlate with optic disc appearance. Distinguishing progression of visual field loss from long-term variability can be difficult and usually requires repeated examinations. The retest rates can be higher in patients with more advanced visual field loss.

In the Ocular Hypertension Treatment Study (OHTS) involving more than 1600 patients, more than 14,000 visual fields were performed at 6-month follow-up visits, and more than 500 of these visual fields were retested because of conversion to glaucoma.[1] This study reported that more than 85% of initial visual field defects were not confirmed with retesting. Data from the same study showed that 66% of eyes that required consecutive visual field testing to confirm a defect had a subsequent normal visual field.[2] The authors concluded that for a greater specificity and stability, a visual field POAG endpoint should be confirmed by at least 3 consecutive reliable visual field test results.

Another landmark study, the Advanced Glaucoma Intervention Study (AGIS), investigated the worsening of visual field and the least number of confirming tests needed to identify progression of glaucomatous visual field defects.[3] There was considerable discrepancy in the percentage of eyes identified as having visual field progression based on different numbers of confirmatory tests conducted. The degree of variability was associated with severity of the disease. The greater the change in AGIS visual field score, the greater the number of confimatory retests were required. This study confirmed the need for test repetitions in order to reduce the number of false-positive results.

A recent review by Giangiacomo et al found that the variable pattern of visual field defects are consistent with long-term fluctuations in test results, particularly in advanced glaucoma.[4] Several repetitions of the tests are needed to evaluatue long-term fluctuation and to understand the noise against which real progression of the visual field can be properly identified.

Methods of Detecting Visual Field Progression

To date, a widely accepted standard for evaluating visual field progression is lacking. Various randomised clinical trials have used different criteria and methods for detecting visual field progression. There are 4 common methods of evaluating the progression of visual field loss — subjective clinical judgement, classification systems, trend analysis or linear regression, and event analysis.

Subjective clinical judgement is the most common, flexible, and easy method but it is prone to errors and bias. As expected, large variations in consistency of judgements made by different evaluators and over time are inevitable. This method was used in the Collaborative Normal-Tension Glaucoma Study (CNTGS)[5] in which suspected progression had to be confirmed by 4 of 6 subsequent follow-up visits to distinguish from long-term variations.

Classification systems are useful for indicating different severities of visual field damage. They are easy to use because a single value can often describe the entire visual field. However, they are not necessarily linear; the difference between grades 1 and 2 may not be the same as between grades 3 and 4. Moreover, classification systems are not derived from population statistics

but are often determined by expert opinion or subjective decision criteria. Classification systems have been used in AGIS and the Collaborative Initial Glaucoma Treatment Study (CIGTS).[6]

Linear regression techniques examine changes as a function of time. These techniques are applicable to either visual field indices or individual locations. A visual field is regarded as progressing if it had a point that exhibited a statistically significant slope of –1 dB per year. This is an objective quantitative method but its main disadvantage is that it requires many visual fields to be analysed to achieve good performances. In general, it provides good sensitivity and specificity when 10 fields are evaluated.

Event analysis compares follow-up visual fields with baseline on a point-by-point basis using glaucoma change probability (GCP). In GCP, changes at each test location are calculated and compared with a series of fields from a group of stable glaucoma eyes. Changes that are greater than the long-term fluctuations are denoted as open triangles, indicating an improvement in the test location, or closed triangles, indicating a worsening in the location (Figure 1). In addition to sensitivity, the GCP takes into account the increase in variability at more peripheral eccentricities. The GCP pattern of variability was used in the Early Manifest Glaucoma Trial (EMGT).[7]

Comparison of Methods for Detecting Visual Field Progression

Boden et al compared 3 progression criteria — GCP using total deviation and pattern deviation plots and clinical criteria — to determine typical patterns of repeatable glaucomatous visual field progression.[8] All eyes progressed by a deepening or an expansion of existing scotoma but a modest agreement was found. In a study by Nouri-Mahdavi et al, pointwise linear regression (PLR) was compared with the AGIS method and GCP analysis.[9] Progression detected by PLR, GCP analysis, and the AGIS method at 8 years was 35%, 31%, and 22%, respectively. PLR (PROGRESSOR software) was compared with clinical judgement of standard Humphrey printouts in a study by the Moorfields Institute of Ophthalmology.[10] This study revealed an inconsistency between clinical judgement and visual field progression status. The agreement between clinicians was substantially higher when PROGRESSOR software was used to interpret the visual fields compared with interpretation using Humphrey printouts.

Using the same longitudinal dataset from large prospective studies, Katz et al have shown that different rates of visual field progression can be obtained depending on the methods used for analysis.[11] A comparison of methods used in AGIS, CIGTS, and EMGT demonstrated that rates of progression could vary by a factor of 2 or more depending on the criteria used.

Alternative Perimetry for Detecting Glaucoma Progression

The role of alternative perimetry such as frequency doubling threshold (FDT) perimetry and blue-on-yellow perimetry for detecting glaucoma progression is not well studied to date. Among the few longitudinal studies available, it seems that both techniques might be sensitive for detecting early progression of the disease.[12,13] More research is required to understand its role in advanced disease.

Qualitative Assessment of Glaucoma Progression

Apart from visual field tests, the mainstay of detecting glaucoma progression is by assessment of the optic nerve head and retinal nerve fibre layer (RNFL). Optic nerve head photography is widely used in current practice although promising new techniques are becoming more common in clinics. Optic nerve head photography can be monoscopic, sequential stereoscopic, and simultaneous stereoscopic. Simultaneous stereoscopic photography is preferable because it allows better estimation to be made. Stereochronoscopy and flickerchronoscopy have been introduced to simplify the process of identification of progression, while some new techniques permit the viewing of stereophotographs in 3 dimensions directly on the computer screen.

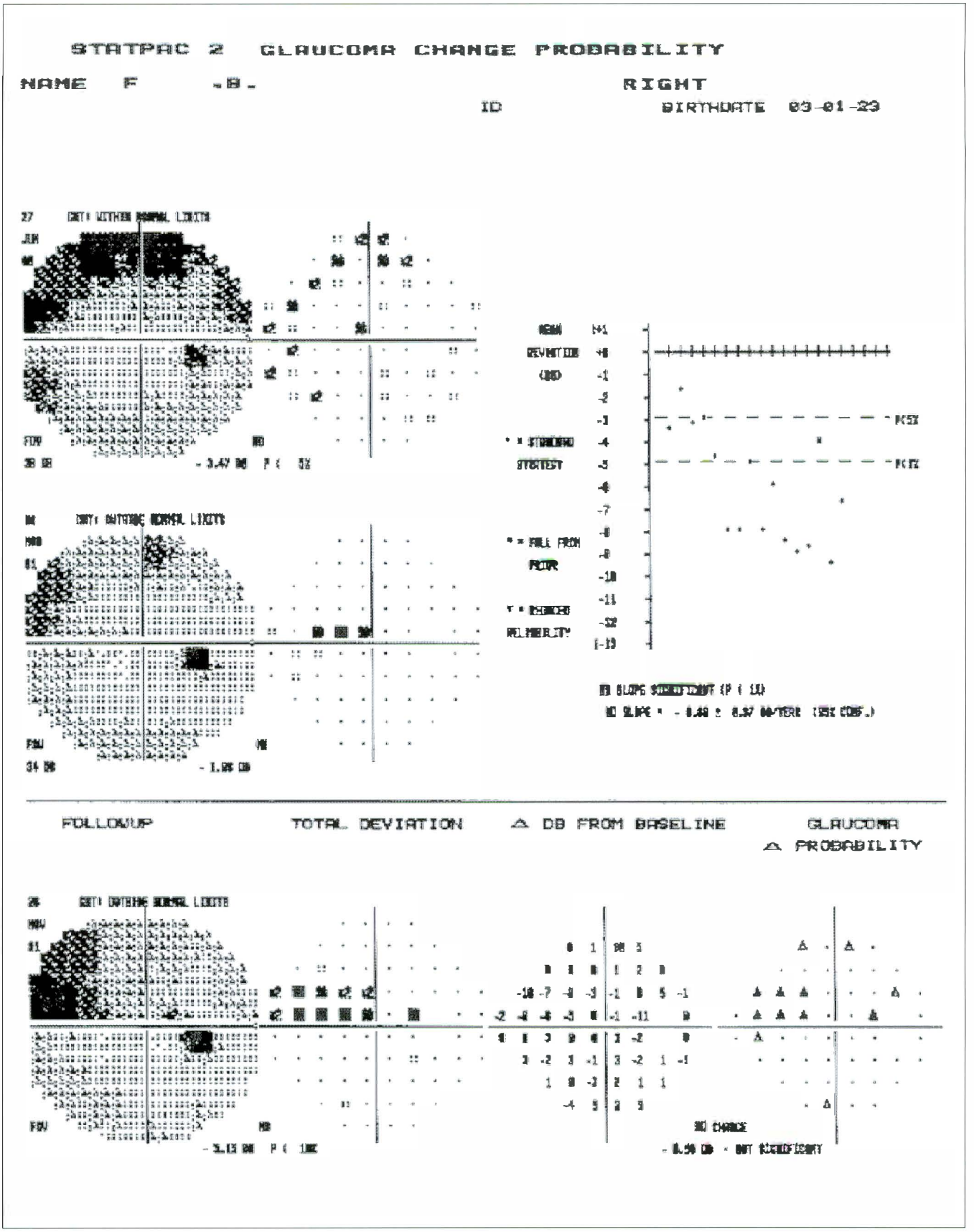
The reproducibility of qualitative assessment has been examined. The optic disc reading centre (ODRC) for OHTS was evaluated for agreement of repeat gradings and sensitivity and specificity of progression.[14] The ODRC was found to have a specificity of 98% to 100% with a sensitivity of 64% to 81%. The test-retest agreement in OHTS was good over 5 years.

Quantitative Assessment of Glaucoma Progression

Quantitative assessment of glaucoma progression usually refers to the use of automated imaging devices such as scanning laser tomography (SLT), scanning laser polarimetry (SLP), and optical coherence tomography (OCT). Currently, the clinical role of planimetry is limited due to high rates of variation between observers.

The ability to discriminate between healthy eyes and those with glaucoma and good measurement reproducibility makes SLT a good candidate for progression detection. With SLT, progression may be identified with an event or trend analysis. In a study by Chauhan et al, the threshold of SLT was determined with an analysis of the variance to quantify the variability of 3 measurements within one session.[15] This technique was tested longitudinally versus visual field progression. The results suggested that SLT has a high sensitivity and specificity.

Figure 1. An example of glaucoma change probability evaluation.



Structure versus Function in the Detection of Glaucoma Progression

Artes and Chauhan studied the relationship between visual field changes (measured by standard automated perimetry and high-pass resolution perimetry) and optic disc structural changes (measured by SLT) in glaucoma.[16] SLT and perimetry showed poor agreement and the study concluded that both techniques assessing function and structure are needed to detect progression.

There are limited data on SLP and OCT. In a small study by Boehm et al, RNFL changes in the eyes of patients with glaucoma and optic disc haemorrhage using scanning laser polarimetry (SLP) were compared with those noted on perimetry.[17] No significant change in SLP image was found, even in the 59% of eyes that progressed. Further research is needed to determine the role of SLP in the detection of progression. On the other hand, in a study comparing OCT with automated perimetry, OCT was found to have a greater likelihood of identifying progression than perimetry (22% versus 9%).[18] However, the study results should be interpreted with caution as they might reflect a hypersensitivity of OCT.

Conclusion

Both function and structure assessments are needed to detect progression. Repeated tests may reduce the 'effect' of long-term fluctuation and help to identify progression. Trend analyses seem to be promising and alternative perimetry such as short-wavelength automated perimetry and FDT are likely to help in future, but more research is needed to confirm their role. Results from the OHTS indicated that optic disc photography is necessary to detect progression. Quantitative imaging devices may become necessary in the near future.

References

1. Keltner JL, Johnson CA, Cello KE, et al; Ocular Hypertension Treatment Study Group. Classification of visual field abnormalities in the ocular hypertension treatment study. Arch Ophthalmol. 2003;121: 643-50.
2. Keltner JL, Johnson CA, Levine RA, et al. Normal visual field test results following glaucomatous visual field end points in the Ocular Hypertension Treatment Study. Arch Ophthalmol. 2005;123:1201-6.
3. Kim J, Dally LG, Ederer F, et al; AGIS Investigators. The Advanced Glaucoma Intervention Study (AGIS): 14. Distinguishing progression of glaucoma from visual field fluctuations. Ophthalmology. 2004;111: 2109-16.
4. Giangiacomo A, Garway-Heath D, Caprioli J. Diagnosing glaucoma progression: current practice and promising technologies. Curr Opin Ophthalmol. 2006;17:153-62.
5. The Collaborative Normal-Tension Glaucoma Study Investigators. Comparison of glaucomatous progression between untreated patients with normal-tension glaucoma and patients with therapeutically reduced intraocular pressures. Collaborative Normal-Tension Glaucoma Study Group. Am J Ophthalmol. 1998;126:487-97.
6. Musch DC, Lichter PR, Guire KE, et al. The Collaborative Initial Glaucoma Treatment Study: study design, methods, and baseline characteristics of enrolled patients. Ophthalmology. 1999;106:653-62.
7. Heijl A, Leske MC, Bengtsson B, et al; for the Early Manifest Glaucoma Trial Group. Reduction of intraocular pressure and glaucoma progression. Results from the Early Manifest Glaucoma Trial. Arch Ophthalmol. 2002; 120:1268-79.
8. Boden C, Blumenthal EZ, Pascual J, et al. Patterns of glaucomatous visual field progression identified by three progression criteria. Am J Ophthalmol. 2004;138:1029-36.
9. Nouri-Mahdavi K, Caprioli J, Coleman AL, et al. Pointwise linear regression for evaluation of visual field outcomes and comparison with the advanced glaucoma intervention study methods. Arch Ophthalmol. 2005;123:193-9.
10. Viswanathan AC, Crabb DP, McNaught AI, et al. Interobserver agreement on visual field progression in glaucoma: a comparison of methods. Br J Ophthalmol. 2003;87:726-30.
11. Katz J, Congdon N, Friedman DS. Methodological variations in estimating apparent progressive visual field loss in clinical trials of glaucoma treatment. Arch Ophthalmol. 1999;117:113-42.
12. Haymes SA, Hutchison DM, McCormick TA, et al. Glaucomatous visual field progression with frequency-doubling technology and standard automated perimetry in a longitudinal prospective study. Invest Ophthalmol Vis Sci. 2005;46:547-54.
13. Bayer AU, Erb C. Short wavelength automated perimetry, frequency doubling technology perimetry, and pattern electroretinography for prediction of progressive glaucomatous standard visual field defects. Ophthalmology. 2002;109:1009-17.
14. Parrish RK 2nd, Schiffman JC, Feuer WJ, et al; Ocular Hypertension Treatment Study Group. Test-retest reproducibility of optic disk deterioration detected from stereophotographs by masked graders. Am J Ophthalmol. 2005;140:762-4.
15. Chauhan BC, Blanchard JW, Hamilton DC, et al. Technique for detecting serial topographic changes in the optic disc and peripapillary retina using scanning laser tomography. Invest Ophthalmol Vis Sci. 2000;41: 775-82.
16. Artes PH, Chauhan BC. Longitudinal changes in the visual field and optic disc in glaucoma. Prog Retin Eye Res. 2005;24:333-54.
17. Boehm MD, Nedrud C, Greenfield DS, et al. Scanning laser polarimetry and detection of progression after optic disc hemorrhage in patients with glaucoma. Arch Ophthalmol. 2003;121:189-94.
18. Wollstein G, Schuman JS, Price LL, et al. Optical coherence tomography longitudinal evaluation of retinal nerve fiber layer thickness in glaucoma. Arch Ophthalmol. 2005;123:464-70.

Cost-effectiveness of Glaucoma Medical Therapy

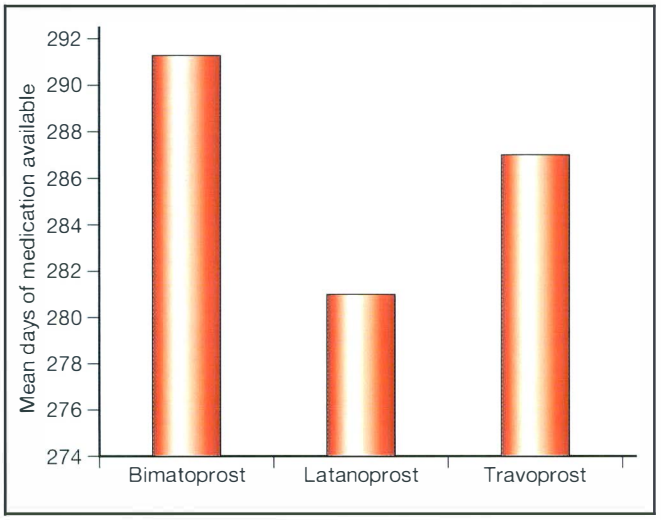
Rossana Romani
Allergan Australia Pty Ltd
Sydney, Australia

Abstract

Cost-effectiveness ratio is used to compare the costs of treatments that have different rates of efficacy on a predefined outcome. Cost-effectiveness can be defined as cost per treatment success. However, the success of a treatment is influenced by several factors such as patients' persistency and compliance. Current evidence indicates that persistency is equivalent among prostaglandin derivatives. The difference lies in the cost-effectiveness of these agents, for which bimatoprost has been shown in several large pharmacoeconomic analyses to have a lower cost per treatment success than other prostaglandins and β-blockers.

When assessing the value of an ocular medication, several factors that will contribute to the overall success of a treatment should be considered. Cost-effectiveness is an important factor in the management of a disease but is not the primary factor. The efficacy of the medication and persistency of patients in refilling the prescription are all interlinked for treatment success.

Figure 1. Mean number days for which medication was available for bimatoprost, latanoprost, and travoprost.
* $p \leq 0.05$ for bimatoprost versus latanoprost.



Persistency with Glaucoma Therapy

The success of pharmacologic therapy for glaucoma is highly dependent on patients' persistency in filling their prescriptions and compliance in taking their medications as directed.[1] Studies of persistency among patients with glaucoma have mainly been based on retrospective analysis of pharmacy claims data. Older data revealed a very low overall 1-year persistency (≤33%) across all medications.[1–3] However, these studies had multiple limitations such as inclusion of small sample sizes and no consideration for different bottle sizes.

The most recent study by Wilensky et al that evaluated a large patient sample receiving bimatoprost, latanoprost, and travoprost showed that approximately 70% of patients persisted for 1 year across all medications.[4] The study used the IMS Health LifeLink, a USA employer-based database covering approximately 1.8 million people, to measure persistency for the 3 prostaglandin derivatives. Persistency was found to be equivalent among all 3 derivatives. A comparison of the mean number of days for which patients had medication available for use suggests a better adherence with bimatoprost than with latanoprost (Figure 1).

Cost-effectiveness Comparisons of Glaucoma Medications

Cost-effectiveness is defined as cost per treatment success, which can be calculated by dividing the cost of treatment by a measure of effectiveness. This allows for comparisons of treatment with

Figure 2. Treatment and cost-effectiveness model.

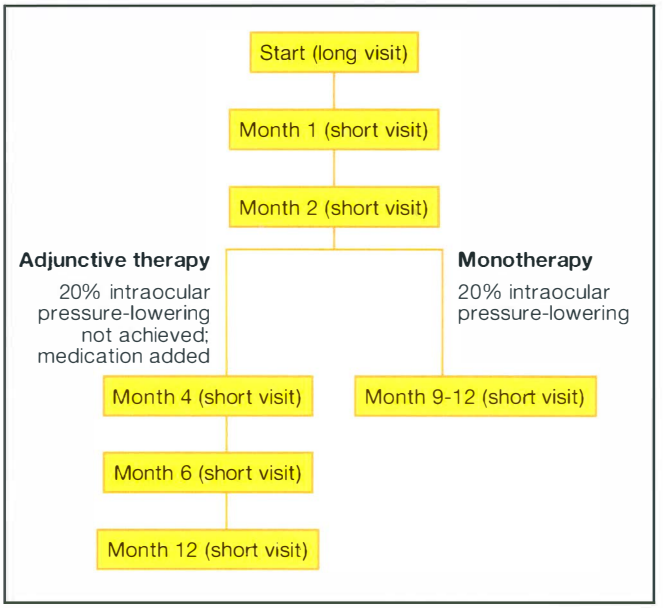
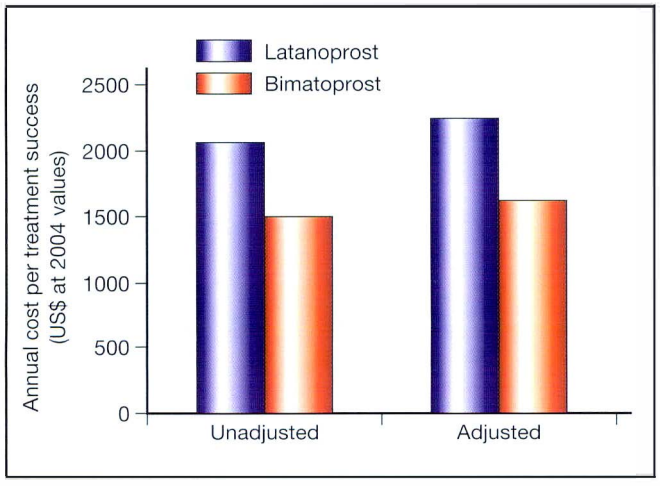


Table 1. Calculation of estimated annual costs per patient.

Outcome	Cost included
20% intraocular pressure reduction reached at month 3	12 months cost of monotherapy plus 4 clinic visits
20% intraocular pressure reduction not reached at month 3	12 months cost of monotherapy plus 9 months of adjunctive medication plus 6 clinic visits

Figure 3. Annual cost of bimatoprost and latanoprost per patient. Adjusted cost was estimated after the rate of discontinuations for adverse events subtracted from clinical success rate.



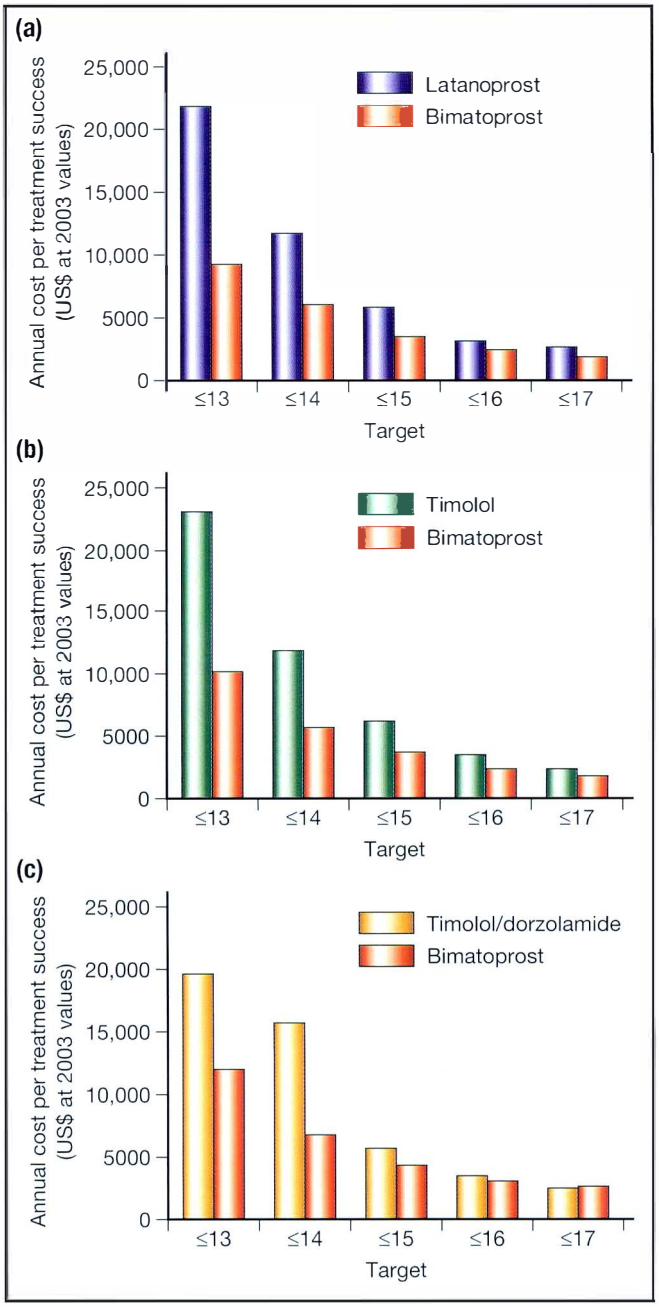
different success rates. For example, using 20% intraocular pressure (IOP) reduction as the endpoint, Fiscella and Walt compared the cost-effectiveness of bimatoprost with that of latanoprost after 6 months' treatment of glaucoma and ocular hypertension (Figure 2).[5]

The average annual cost per patient represents a weighted average of the cost of treatment with monotherapy for 12 months, adjunctive medications for 9 months (if IOP target was not reached at month 3) and cost of clinic visits (Table 1). The costs were extrapolated from a 6-month randomised trial[6] with the assumption that adjunctive therapy and more visits to ophthalmologists were required for patients who failed to achieve 20% IOP reduction at month 3.

The strength of this study stems from the design and analysis of the model that minimised potential bias in the estimation of cost-effectiveness ratios. This included determination of efficacy rates measured at 3 daily time points (8 am, 12 noon, and 4 pm), and adjustment of clinical success rates for patients who discontinued treatment due to adverse events. The results showed that bimatoprost is more cost-effective than latanoprost (Figure 3).

Another published cost-effectiveness analysis by Goldberg and Walt compared bimatoprost with latanoprost and timolol.[7] Efficacy data were extracted from randomised controlled clinical comparison studies ranging from 3 months to 1 year in duration.

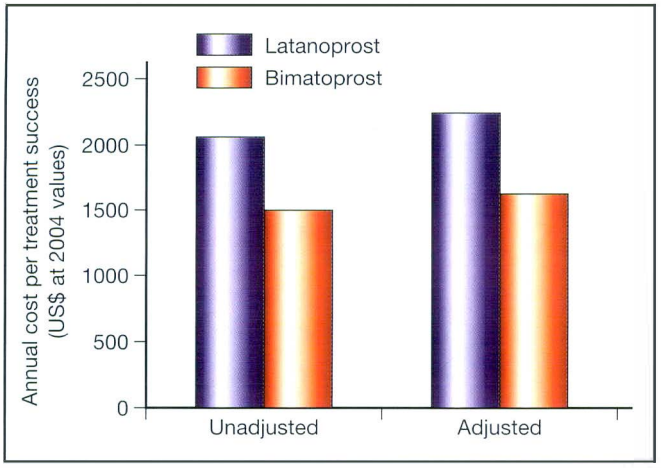
Figure 4. Cost per treatment success (target intraocular pressure; IOP) of bimatoprost compared with latanoprost, timolol, and fixed combination timolol/dorzolamide.



The cost of medication was based on average wholesale costs in 2003 and with the assumption that 1 bottle denotes 1 month's supply. The endpoint for treatment success was determined by the achievement of target IOP in the middle of the day (10 am or 12 noon).

Cost-effectiveness was evaluated using the average annual cost of treatment (weighted by the percentage of patients who met and did not meet the target pressure at month 3) divided by the percentage of patients who achieved the target IOP in the

Figure 5. Annual cost per patient for bimatoprost versus latanoprost monotherapy.



longest trial available. The results found a higher percentage of patients achieved target IOPs with bimatoprost than with each of the other medications. At most target pressures, the cost per treatment success for bimatoprost was less than that for other drugs (Figure 4).

The average annual cost of treatment for patients starting with bimatoprost monotherapy compared with latanoprost monotherapy was also assessed. The calculation was similar to that used in the analysis by Fiscella and Walt (Table 1).[5] Again, the cost of initiating bimatoprost monotherapy was consistently lower than that of latanoprost monotherapy across all target pressures (Figure 5).

Conclusion

Bimatoprost has a lower cost per treatment success than latanoprost, timolol, or fixed combination timolol/dorzolamide. Bimatoprost is the most cost-effective treatment to reduce IOP in glaucoma and ocular hypertension. The cost-effectiveness of bimatoprost is driven by its IOP-lowering efficacy.

References

1. Reardon G, Schwartz GF, Mozaffari E. Patient persistency with topical ocular hypotensive therapy in a managed care population. Am J Ophthalmol. 2004;137 Suppl:S3-12.
2. Reardon G, Schwartz GF, Mozaffari E. Patient persistency with ocular prostaglandin therapy: a population-based, retrospective study. Clin Ther. 2003;25:1172-85.
3. Day DG, Schacknow PN, Sharpe ED, et al. A persistency and economic analysis of latanoprost, bimatoprost, or beta-blockers in patients with open-angle glaucoma or ocular hypertension. J Ocul Pharmacol Ther. 2004;20:383-92.
4. Wilensky J, Fiscella RG, Carlson AM, et al. Measurement of persistence and adherence to regimens of IOP-lowering glaucoma medications using pharmacy claims data. Am J Ophthalmol. 2006; 141(1 Suppl):S28-33.
5. Fiscella R, Walt J. Estimated comparative costs of achieving a 20% reduction in intraocular pressure with bimatoprost or latanoprost in patients with glaucoma or ocular hypertension. Drugs Aging. 2006;23:39-47.
6. Noecker RS, Dirks MS, Choplin NT, et al; Bimatoprost/Latanoprost Study Group. A six-month randomized clinical trial comparing the intraocular pressure-lowering efficacy of bimatoprost and latanoprost in patients with ocular hypertension or glaucoma. Am J Ophthalmol. 2003;135:55-63.
7. Goldberg LD, Walt J. Cost considerations in the medical management of glaucoma in the US: estimated yearly costs and cost effectiveness of bimatoprost compared with other medications. Pharmacoeconomics. 2006;24:251–64.

Giving More with Less: Keys to Long-term Success

Joseph Caprioli
University of California Los Angeles
School of Medicine
California, USA

Abstract

Treatment of raised intraocular pressure by setting a target pressure is undoubtedly effective against glaucomatous damage and disease progression. However, the current definition of target pressure has its limitations due to an incomplete knowledge of the disease. A new concept of target pressure that includes a quality component in addition to quantitative measure has been proposed. It is suggested that target pressure should be kept constant to avoid long-term fluctuation, which is detrimental to the disease. The prostaglandin derivatives have robust effects on intraocular pressure and the approach of switching from latanoprost to bimatoprost has resulted in clinically useful reduction in intraocular pressure. Switching rather than adding prostaglandin derivatives is encouraged, to maximise treatment adherence.

Numerous major trials have demonstrated the benefits of reducing intraocular pressure (IOP) for improving patient outcomes. Aggressive IOP reduction by 30% resulted in a reduced visual field progression from 30% to 10% in the Normal-Tension Glaucoma Study (NTGS).[1] In early disease, treatment of IOP reduced the risk of developing damage from 10% to 5% over 5 years in the Ocular Hypertension Treatment Study.[2] In the Early Manifest Glaucoma Trial (EMGT), glaucomatous progression of patients with intermediate disease was reduced from 62% to 45% with treatment.[3] A quasi–dose-dependent relationship between the frequency of achieving an IOP target and progression has been shown in the Advanced Glaucoma Intervention Study (AGIS).[4] A post-hoc analysis of AGIS revealed that IOP fluctuations measured between clinic visits over a long duration may be important in progression, in addition to the mean IOP.[5] These findings have implications for the general concept of 'target pressure'.

Characteristics and Limitations of Target Pressure

According to the American Academy of Ophthalmology, the target pressure is an IOP range deemed unlikely to cause further optic nerve damage in an individual with glaucoma.[6] The characteristics of target pressure are that it is an estimate that provides a goal for protecting the optic nerve, and that it may vary among individuals and throughout the course of disease for an individual. However, there is no definitive way of determining the IOP below which optic nerve damage will be slowed. In addition, some patients may have a pressure-independent component of damage. If a variable target IOP is set in response to the course of disease, there is no evidence that it is effective in preventing progression and damage.

New Concept of Target Pressure

Target pressure should be defined not just quantitatively but also qualitatively. Instead of using the term 'IOP reduction', a new concept of 'IOP modulation' has emerged. A proposed notion for target pressure is to set a low target of 10 to 12 mm Hg to minimise the risk of progression and maximise the treatment effect. Additionally, there should be a quality component added to this target pressure. One should aim to achieve a consistent IOP reduction by targeting a constant IOP of less than 3 mm Hg standard deviation. This component avoids long-term IOP fluctuation, which has been shown to be a negative prognostic factor for glaucoma.[5]

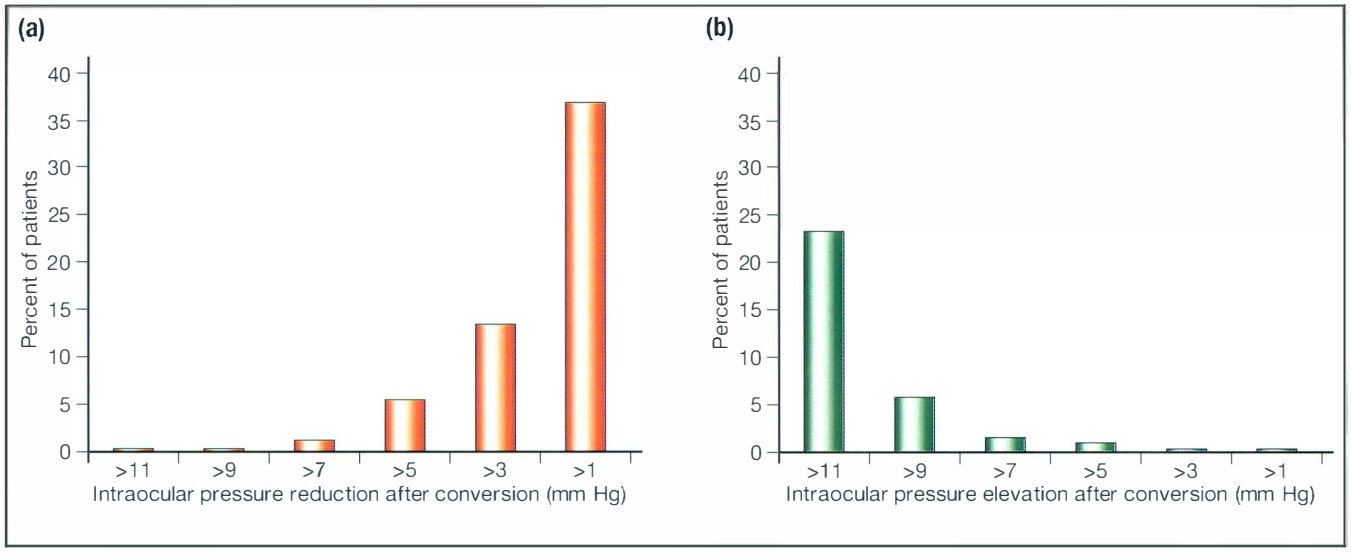
Effects of Prostaglandins in Intraocular Pressure Reduction

A retrospective comparison of intra-class prostaglandins conversion from latanoprost to bimatoprost was recently published.[7] This study evaluated more than 43,000 patients from a nationwide health maintenance organisation in the USA, where a closed formulary change led to conversion from latanoprost to bimatoprost for all patients taking prostaglandins. The purpose of the study was to assess the feasibility of conversion and to compare the efficacy of 2 prostaglandin derivatives.

15,134 patients were switched from latanoprost to bimatoprost and IOP data from 309 of these patients were analysed. This subgroup analysis revealed a statistically significant mean reduction of 0.51 mm Hg in IOP ($p = 0.001$) and 13% of patients had an IOP reduction of more than 3 mm Hg. These results may have clinical significance as the EMGT showed that even small differences in IOP may contribute to an improved clinical outcome in the long term.[3] Overall, 90% of patients continued to take bimatoprost while 10% switched back to latanoprost because of intolerance.

More importantly, apart from a modest reduction in the mean IOP in the subgroup analysis, IOP changes within individual patients were evaluated by studying the distribution of patients who had a

Figure 1. Frequency distribution in patients with (a) lower intraocular pressure; and (b) higher intraocular pressure after the switch from latanoprost to bimatoprost. From Law SK, Song BJ, Fang E, Caprioli J. Feasibility and efficacy of a mass switch from latanoprost to bimatoprost in glaucoma patients in a prepaid Health Maintenance Organization. Ophthalmology. 2005;112:2123–30. Reprinted with permission. Copyright 2005, Elsevier, Inc.



resultant lower or higher IOP after the switch in therapy (Figure 1). The difference between the distribution of lower versus higher IOP was statistically significant in favour of lower IOP.

In summary, the conversion from latanoprost to bimatoprost was successful due to a high switch rate and a high percentage of patients continuing to use bimatoprost. In addition, a useful proportion of patients who switched had a clinically significant reduction of IOP.

Conclusion

It is well known that treatment of IOP is effective in preventing progression of glaucomatous damage. A low initial target IOP and aggressive treatment to maintain that target is needed, while reducing long-term IOP fluctuation. Fluctuations could be physiological, pathological, or due to poor compliance. It might be useful to study the degree and pattern of IOP fluctuation to properly assess treatment effects and progression. Prostaglandins play a central role due to their long duration of action and robust effects on IOP. To aid patients' adherence to treatment, it is important to limit the number and doses of medicines by practising switching medications before adding more medications.

References

1. The Collaborative Normal-Tension Glaucoma Study Investigators. Comparison of glaucomatous progression between untreated patients with normal-tension glaucoma and patients with therapeutically reduced intraocular pressures. Collaborative Normal-Tension Glaucoma Study Group. Am J Ophthalmol. 1998;126:487-97.
2. Kass MA, Heuer DK, Higginbotham EJ, et al. The Ocular Hypertension Treatment Study: a randomized trial determines that topical ocular hypotensive medication delays or prevents the onset of primary open-angle glaucoma. Arch Ophthalmol. 2002;120:701-13.
3. Heijl A, Leske MC, Bengtsson B, et al; for the Early Manifest Glaucoma Trial Group. Reduction of intraocular pressure and glaucoma progression. Results from the Early Manifest Glaucoma Trial. Arch Ophthalmol. 2002; 120:1268-79.
4. The AGIS Investigators. The Advanced Glaucoma Intervention Study (AGIS): 9. Comparison of glaucoma outcomes in black and white patients within treatment groups. Am J Ophthalmol. 2001;132: 311-20.
5. Nouri-Mahdavi K, Hoffman D, Coleman AL, et al; Advanced Glaucoma Intervention Study. Predictive factors for glaucomatous visual field progression in the Advanced Glaucoma Intervention Study. Ophthalmology. 2004;111:1627-35.
6. American Academy of Ophthalmology. Preferred Practice Pattern: Primary Open-Angle Glaucoma, 2005. Available at www.aao.org/education/library/ppp/index.cfm. Accessed 28 June 2006.
7. Law SK, Song BJ, Fang E, Caprioli J. Feasibility and efficacy of a mass switch from latanoprost to bimatoprost in glaucoma patients in a prepaid Health Maintenance Organization. Ophthalmology. 2005;112: 2123-30.

Giving More with Less: Control of Intraocular Pressure Reduction and Circadian Intraocular Pressure

Luca Rossetti
University of Milan
Milan, Italy

Abstract

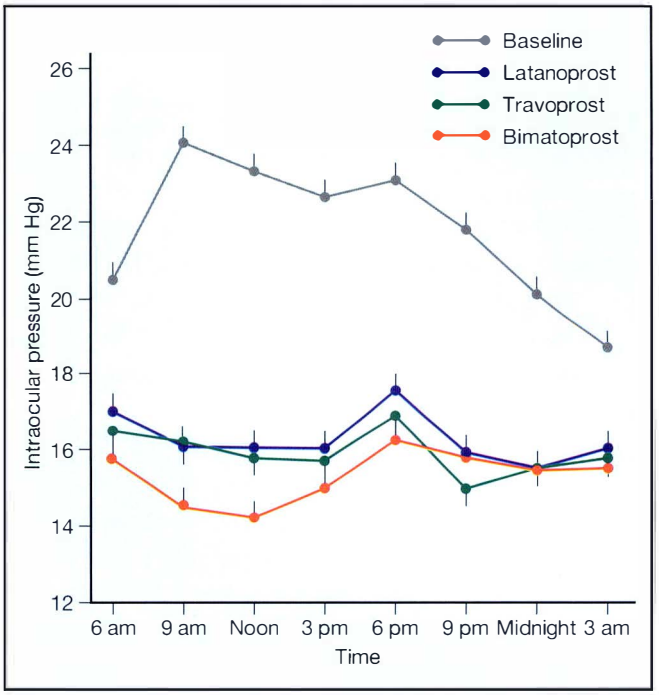
The control of 24-hour intraocular pressure beyond daytime intraocular pressure seen in the clinics is often overlooked. Research has documented considerable circadian fluctuation of IOP, particularly during the night. Thus, treatments that achieve 24-hour intraocular pressure control should be preferentially chosen. Target intraocular pressure from landmark studies is applicable to various types of patients in clinical practice. A difference of 1 mm Hg in intraocular pressure could have significant implications for risk of progression or damage. The efficacy of bimatoprost compared favourably with other prostaglandins and the fixed-dose latanoprost/timolol combination.

The diagnosis and treatment of glaucoma have always been based on the measurements of intraocular pressure (IOP) during the 'office hours' window at the clinics. Any fluctuations of IOP during the night have not generally been considered. However, fluctuation of IOP is important and the 24-hour IOP is a potentially important risk factor for glaucoma. Although circadian IOP fluctuation during the day is typical for patients with glaucoma as well as healthy people,[1] considerable circadian fluctuation of 24-hour IOP was found in one study, with 60% of treated patients having a 24-hour IOP fluctuation >5 mm Hg.[2]

Effects of Medical Treatment on 24-hour Intraocular Pressure

The importance of maintaining 24-hour IOP prompted researchers to examine the effects of medical therapy on IOP control beyond daytime measurements. The β-blocker timolol was found to have no effect on nocturnal IOP despite being effective in reducing diurnal IOP.[3] A randomised double-masked crossover study compared the 24-hour IOP reduction of latanoprost, travoprost, and bimatoprost.[4] All 3 medications were found to be equally effective in reducing 24-hour IOP (Figure 1).

Figure 1. 24-hour intraocular pressure readings for latanoprost, travoprost, and bimatoprost.
From Orzalesi N, Rossetti L, Bottoli A, Fogagnolo P. Comparison of the effects of latanoprost, travoprost, and bimatoprost on circadian intraocular pressure in patients with glaucoma or ocular hypertension. Ophthalmology. 2006;113:239–46. Reprinted with permission. Copyright 2006, Elsevier, Inc.



Approaches to Achieve Target Intraocular Pressure

The target IOP used in various landmark trials of different types of glaucoma is a useful guide for determining the extent of IOP reduction needed for a particular type of patient (Table 1). In Europe, the current practice is to start with a β-blocker such as timolol, and switch to a prostaglandin when the IOP reduction with timolol is not sufficient. The European Glaucoma Society guidelines recommend switching to another drug when monotherapy is not effective.[10] The reason for advocating a switch is 2-fold. Firstly, an individual patient may respond differently to different prostaglandins. Secondly, the different prostaglandins do not necessarily act in the same way.

In a pooled estimate of efficacy of bimatoprost compared with other prostaglandins in more than 1000 patients, bimatoprost was shown to be more effective than other prostaglandins by 0.6 to 1.2 mm Hg ($p < 0.00001$).[11] The approximate 1 mm Hg difference in efficacy is comparable to a 10% risk reduction, a

Table 1. Target intraocular pressures (IOPs) in landmark trials.

Study	Patient type	IOP reduction	Outcome
Ocular Hypertension Treatment Study[5]	Ocular hypertension	20%	54% reduction of progression versus the untreated group
Collaborative Normal-Tension Glaucoma Study[6]	Normal tension glaucoma	30%	3 times less progression (from 60% to 20%)
Early Manifest Glaucoma Trial[7]	Early glaucoma	25%	45% progression
Collaborative Initial Glaucoma Treatment Study[8]	Early glaucoma	35% to 48%	No progression
Advanced Glaucoma Intervention Study[9]	Advanced glaucoma	Mean intraocular pressure of 12.3 mm Hg and intraocular pressure always <18 mm Hg	No progression

derived estimate based on the evidence from the landmark studies listed in Table 1.

Bimatoprost versus Fixed-dose Combination Treatment

One of the most frequently prescribed fixed-dose combination medications is latanoprost/timolol (LTFC). However, the efficacy of fixed versus unfixed combinations is still debated and there is no data on the effects of switching from LTFC to bimatoprost. Thus, a randomised double-masked multicentre European study was conducted to compare the 24-hour average IOP after bimatoprost and LTFC after 12 weeks.

The study evaluated 200 patients with either primary open angle glaucoma (POAG) or ocular hypertension whose glaucoma was well-controlled (IOP <22 mm Hg) with the unfixed combination of latanoprost and timolol for at least 3 months prior to the baseline visit, or who were receiving monotherapy with either latanoprost or timolol and who were eligible for dual therapy due to uncontrolled IOP >21 mm Hg. Patients receiving monotherapy underwent a 6-week washout period with the unfixed combination of latanoprost and timolol.

The study hypothesised that bimatoprost is not inferior to LTFC for lowering IOP. Inferiority was defined as more than a 1 mm Hg difference in IOP. The analysis of covariance model was used for the primary efficacy variable. At study endpoint, the agents showed little difference (<1 mm Hg) in 24-hour IOP profile. Bimatoprost demonstrated a trend towards greater IOP reduction than LTFC but the differences were not statistically significant. The study concluded that bimatoprost is as effective as LTFC for controlling IOP. The medications showed similar safety profiles and no increase in hyperaemia was noted after the switch to bimatoprost.

Conclusion

Greater awareness should be given to the 24-hour IOP profile of patients with glaucoma, particularly when determining appropriate medical treatment, and when evaluating evidence from clinical trials. Switching rather than adding a second drug is recommended when monotherapy fails. Bimatoprost has demonstrated superiority to other prostaglandins in a meta-analysis and is as effective as LTFC in lowering IOP of patients with POAG or ocular hypertension.

References

1. Liu JH, Kripke DF, Twa MD, et al. Twenty-four-hour pattern of intraocular pressure in the aging population. Invest Ophthalmol Vis Sci. 1999;40:2912-7.
2. Fogagnolo P, Rossetti L, Mazzolani F, et al. Circadian variations in central corneal thickness and intraocular pressure in patients with glaucoma. Br J Ophthalmol. 2006;90:24-8.
3. Liu JH, Kripke DF, Weinreb RN. Comparison of the nocturnal effects of once-daily timolol and latanoprost on intraocular pressure. Am J Ophthalmol. 2004;138:389-95.
4. Orzalesi N, Rossetti L, Bottoli A, Fagagnolo P. Comparison of the effects of latanoprost, travoprost, and bimatoprost on circadian intraocular pressure in patients with glaucoma or ocular hypertension. Ophthalmology. 2006;113:239-46.
5. Kass MA, Heuer DK, Higginbotham EJ, et al. The Ocular Hypertension Treatment Study: a randomized trial determines that topical ocular hypotensive medication delays or prevents the onset of primary open-angle glaucoma. Arch Ophthalmol. 2002;120:701-13.
6. The Collaborative Normal-Tension Glaucoma Study Investigators. Comparison of glaucomatous progression between untreated patients with normal-tension glaucoma and patients with therapeutically reduced intraocular pressures. Collaborative Normal-Tension Glaucoma Study Group. Am J Ophthalmol. 1998;126:487-97.
7. Heijl A, Leske MC, Bengtsson B, et al; for the Early Manifest Glaucoma Trial Group. Reduction of intraocular pressure and glaucoma progression. Results from the Early Manifest Glaucoma Trial. Arch Ophthalmol. 2002;120:1268–79.
8. Feiner L, Piltz-Seymour JR; Collaborative Initial Glaucoma Treatment Study. Collaborative Initial Glaucoma Treatment Study: a summary of results to date. Curr Opin Ophthalmol. 2003;14:106-11.
9. The AGIS Investigators. The Advanced Glaucoma Intervention Study (AGIS): 7. The relationship between control of intraocular pressure and visual field deterioration. Am J Ophthalmol. 2000;130:429-40.
10. European Glaucoma Society. Terminology and Guidelines for Glaucoma, 2nd Ed. Italy: Dogma; 2003.
11. Van der Valk R, Webers CA, Schouten JS, et al. Intraocular pressure-lowering effects of all commonly used glaucoma drugs: a meta-analysis of randomized clinical trials. Ophthalmology. 2005;112:1177-85.

Case Study — Reducing Intraocular Pressure Fluctuation

Prin Rojanapongpun
Department of Ophthalmology
Chulalongkorn University and Hospital
Bangkok, Thailand

Abstract

A 48-year-old man presented with suspicion of glaucoma based on optic nerve changes. At presentation, his intraocular pressure was 20 mm Hg and baseline visual field was normal. After 3 years of regular follow-up, the patient presented to the emergency department with intraocular pressures of 28 mm Hg in the right eye and 24 mm Hg in the left eye. After a single-eye trial, binatoprost was prescribed for both eyes. To date, the intraocular pressure has remained controlled at 15 to 16 mm Hg with stable optic disc and visual field examinations.

In 1998, a 48-year-old man was referred for suspicion of glaucoma based on optic nerve changes. The patient had no family history of glaucoma and his past medical history was good. His ocular examination was normal except for changes in the optic nerves (Figure 1). At presentation, his intraocular pressure (IOP) was 20 mm Hg. His baseline visual field was normal. The patient was observed for several years with 6-month follow-up for IOP measurement (Table 1). During follow-up, the patient was almost always seen in the afternoon after work. The IOP was in the range of 18 to 21 mm Hg, except for 1 occasion when the measurement took place in the morning; his IOP was 23 mm Hg. The patient also underwent annual examination of visual field, which had since remained normal.

Table 1. Intraocular pressure (IOP) measurements for 3 years.

Year	IOP level (mm Hg)	Time of visit
1998	19	4:00 pm
1999	19	3:00 pm
1999	18	3:30 pm
2000	18 (right eye), 20 (left eye)	4.30 pm
2000	21	3:00 pm
2001	18	4:30 pm
2001	23	11:00 am

In 2001, Humphrey visual field testing showed a localised visual field loss of his left eye with normal right visual field. He was started on timolol ophthalmic gel forming solution once daily in the morning. Subsequent 1-, 3-, and 6-month follow-up showed a stable IOP ranging from 17 to 18 mm Hg in the right eye and 15 to 16 mm Hg in the left eye. Again, the follow-up was conducted in the afternoon. In 2001, the patient presented to the emergency department at 7:30 am due to eye irritation

Figure 1. Disc photographs of (a) the right eye; and (b) the left eye in 1998. In the right eye, the rim is thin but intact inferiorly and in the left eye, the rim is thin but intact.

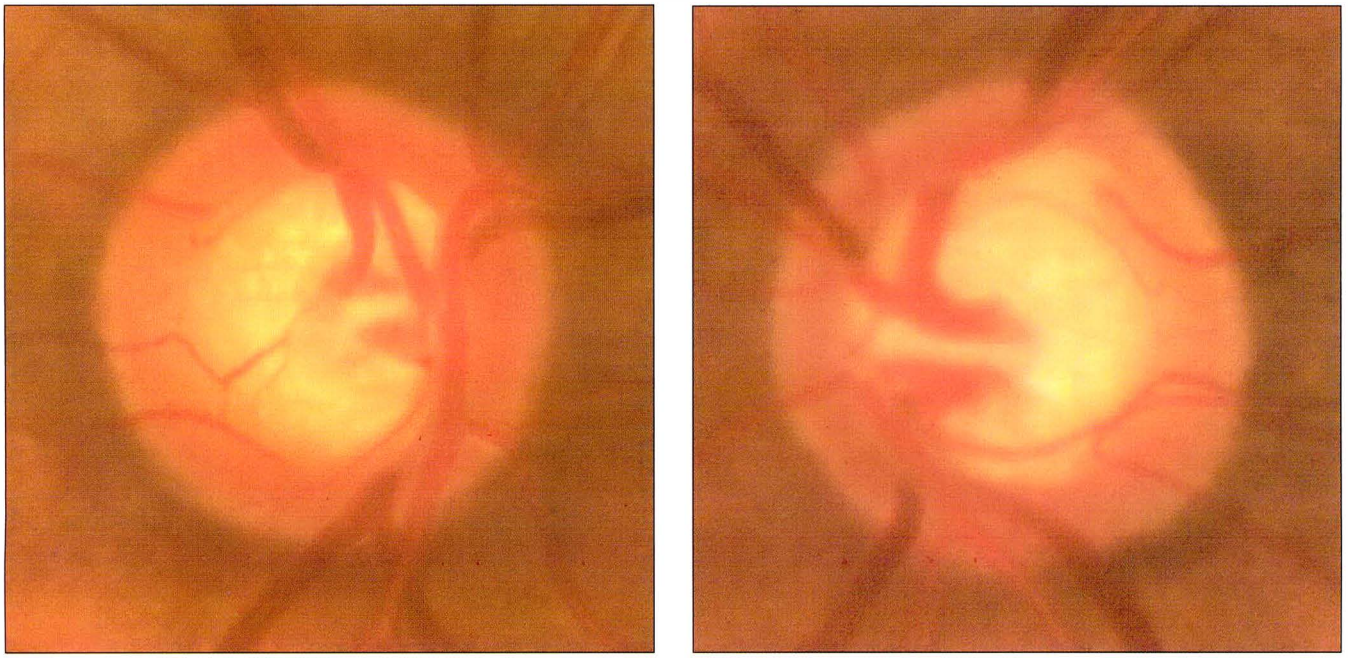
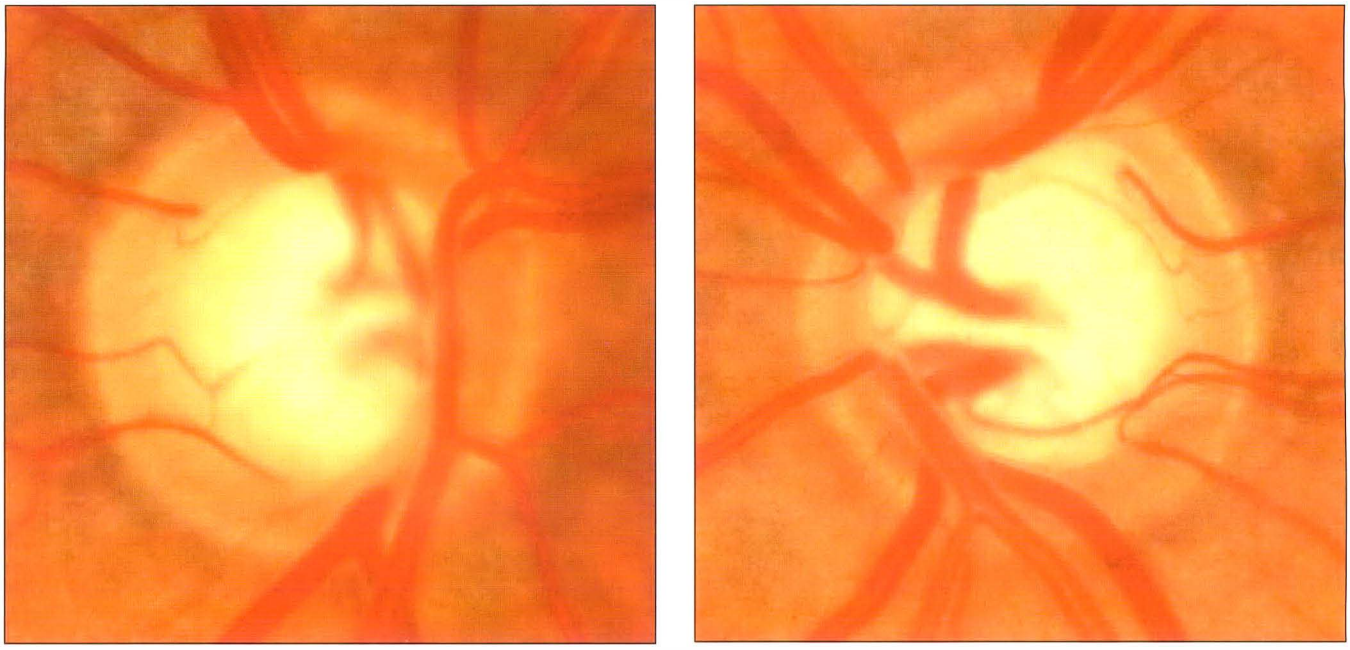


Figure 2. Disc photographs of (a) the right eye; and (b) the left eye in 2001. In the right eye, there was probably more thinning at 7 o'clock and there was a superior temporal notch at 1 o'clock in the left eye.



and possible foreign body. His IOP was found to be 28 mm Hg in the right eye and 24 mm Hg in the left eye, so he was referred to the Glaucoma Service for evaluation. Stereodisc photographs showed probable optic nerve changes (Figure 2) but the visual fields were unchanged from baseline.

The patient's diurnal tests revealed IOP fluctuations with very high IOP in the early morning (Table 2). His nocturnal IOP was not known. Based on the diurnal results, the patient was switched to bimatoprost once daily in the left eye. The South East Asia Glaucoma Interest Group Guidelines recommend a 1-eye trial for new medication to evaluate the effectiveness of the medication in a particular patient.[1] However, this patient returned with hyperaemia in the left eye. The symptom was effectively relieved by administration of artificial tears.

The diurnal IOP testing was repeated 3 weeks after the commencement of bimatoprost. The IOP of the left eye was reduced to 15 mm Hg. Although abnormality in the right eye was not detected by white-on-white perimetry, frequency doubling threshold perimetry revealed hints of early structural changes in the right eye and confirmed pronounced visual field loss in the left eye. Bimatoprost was initiated in both eyes and follow-up visits were scheduled at different times of the day. To date, the patient's IOP has remained controlled at 15 to 16 mm Hg with stable disc and visual field examination.

Table 2. Diurnal intraocular pressure levels.

Right eye	Left eye (mm Hg)	Time (mm Hg)	Comments
26	24	8:00 am	Pre-dosing
21	19	10:00 am	Peak
19	18	4:00 pm	

Conclusion

IOP reduction is important to improve patients' outcomes. Pharmacotherapy should be initiated at an appropriate time and, when it fails, it is important to switch to another medication instead of adding a second medication. Adverse effects may sometimes be confounded by concurrent dry eye conditions and the use of artificial tears can be helpful. Clinicians should be aware of the influence of diurnal variation on the ability to detect elevated IOP. Achieving consistently low inter-visit IOPs should be one of the aims of treatment.

Reference

1. South East Asia Glaucoma Interest Group (SEAGIG). Asia Pacific Glaucoma Guidelines. Singapore: SEAGIG; 2004.

Switch versus Add

Yupin Leelachaikul
Department of Ophthalmology
Ramathibodi Hospital, Mahidol University
Bangkok, Thailand

Abstract

Many pharmacological agents in different drug classes are now available for the medical treatment of glaucoma. When initial pharmacotherapy fails to reduce intraocular pressure, it is recommended that the initial agent is switched to a substitute rather than adding a second medication. Substitutions can be made from a different drug class or within the same drug class. It is appropriate to switch within the same drug class when the likelihood of improvement in efficacy, tolerability and/or compliance can be envisaged.

Many pharmacological agents in different drug classes are now available for the medical treatment of glaucoma. When initial pharmacotherapy fails to reduce intraocular pressure (IOP), clinicians tend to add a second agent. However, it is recommended that the initial agent is switched to a substitute in cases of inadequate pressure control or for patients who do not respond. Substitutions can be made from a different drug class or within the same class. The rationale for switching pharmacotherapy is 3-fold: to achieve greater efficacy; to avoid adverse effects; and to improve compliance.

Figure 1. The effects of bimatoprost on intraocular pressure of patients who do not respond to latanoprost.

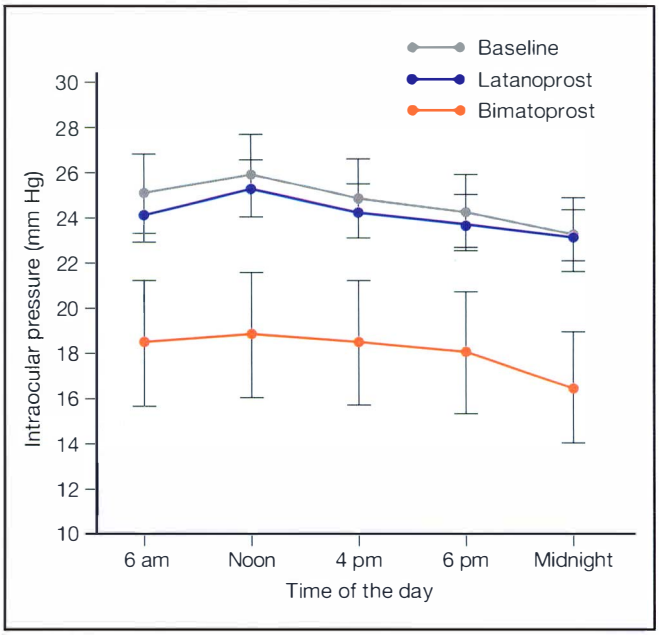


Table 1. Weighted mean intraocular pressure reduction of timolol and prostaglandin derivatives.

Agent	Weighted mean intraocular pressure reduction (%)
Timolol	22.2
Latanoprost	26.7
Travoprost	28.7
Bimatoprost	30.3

There is a general consensus that prostaglandin analogues and prostamides are the most efficacious drug class among the glaucoma medications in current use. Prostaglandin derivatives control IOP uniformly throughout the 24-hour cycle with a good safety profile, while providing the convenience of once-daily dosing. Studies comparing the efficacy of agents within this drug class have been conducted. An analytic review of 42 trials involving 9295 patients with primary open angle glaucoma evaluated the IOP-lowering effect of bimatoprost, latanoprost, and travoprost.[1] The prostamide bimatoprost seemed to be most efficacious in terms of IOP reduction (Table 1) and achievement of various target IOP levels. There were no significant differences between the drugs in the incidence of adverse effects.

Pharmacologically different from prostaglandin analogues, bimatoprost, being a prostamide, was postulated to act on a different receptor than prostaglandin analogues. This hypothesis may offer an explanation for the effectiveness of bimatoprost observed in patients who do not respond to latanoprost treatment (Figure 1).[2]

Conclusion

It is appropriate to switch within the same drug class, such as switching from prostaglandin analogues to a prostamide, when the likelihood of improvement in efficacy, adverse effects, and/or compliance can be envisaged. The decision of switching pharmacotherapy should be evidence-based and individualised for each patient.

References

1. Holmstrom S, Buchholz P, Walt J, et al. Analytic review of bimatoprost, latanoprost and travoprost in primary open angle glaucoma. Curr Med Res Opin. 2005;21:1875-83.
2. Gandolfi SA, Cimino L. Effect of bimatoprost on patients with primary open-angle glaucoma or ocular hypertension who are nonresponders to latanoprost. Ophthalmology. 2003;110:609-14.

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

IMPORTANT SAFETY INFORMATION

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

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

See LUMIGAN® Prescribing Information.

Visit us at www.lumigan.com

LUMIGAN®
(bimatoprost ophthalmic solution) 0.03%