Reappraising first-line treatment in glaucoma management

Peter Phelan

Despite treatment, glaucoma patients may still suffer vision loss because of inadequate control of intraocular pressure or late presentation. This article reviews the latest evidence supporting a reappraisal of first-line treatment in the management of glaucoma, including a review of latanoprost, recently approved for first-line treatment of glaucoma and ocular hypertension.

Glaucoma is the second largest cause of irreversible bilateral blindness globally. It has been estimated that nearly 66.8 million people worldwide have primary glaucoma, with 6.7 million suffering from bilateral blindness (Quigley, 1996).

Glaucomatous optic neuropathy has been described as a progressive slow loss of retinal ganglion cells with a characteristic optic nerve appearance, such as cup enlargement, notching and rim loss. Factors that may contribute to the different clinical appearances of glaucomatous optic neuropathy include loss of neural tissue, vascular changes, and changes in the optic nerve support structures.

Elevated intraocular pressure (IOP) is the most important modifiable risk factor for optic nerve damage, with accumulating evidence confirming that the risk of progressive visual loss increases with increasing IOP (Odberg, 1987; Sommer et al, 1991; Collaborative Normal-Tension Glaucoma Study Group, 1998; AGIS Investigators, 2000). The aim of treatment is to reduce IOP to a target level that might prevent further glaucomatous damage.

Moreover, 5-year outcome data from the Ocular Hypertension Treatment Study demonstrated that topical ocular hypotensive medication was effective in delaying or preventing the onset of primary open-angle glaucoma in individuals with elevated IOP and no evidence of glaucomatous damage (Kass et al, 2002). The cumulative probability of developing primary open-angle glaucoma was reduced by 60% among participants randomized to receive topical medication (n=817) compared with those randomized to observation alone (n=819).

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MEDICAL THERAPY

The main treatment options for glaucoma include topical ocular hypotensive therapy, filtration surgery or laser treatment. Topical medications and filtering surgery are equally effective for IOP control as initial treatments for newly diagnosed open-angle glaucoma, according to up to 5 years of follow-up data in the Collaborative Initial Glaucoma Treatment Study (Lichter et al, 2001).

Medical therapy remains the initial first-choice strategy in seeking to lower and control IOP long term and preserve visual function (Hitchings, 1998). The treatment goal is to reduce and maintain IOP at an acceptable level to slow the progression of the disease and help preserve the patient's visual field, while maintaining the best possible quality of life of patients. This requires careful evaluation of the appropriate initial therapy choice. Efficacy, tolerability, safety, dosing frequency, cost effectiveness and long-term experience are some of the factors that should influence a practitioner's choice of glaucoma medication. Proper evaluation and assessment at the initial stage will reduce the likelihood of frequent treatment changes resulting from either inadequate IOP control or adverse ocular or systemic events.

TREATMENT OPTIONS FOR GLAUCOMA

Topical beta-adrenergic antagonists (beta-blockers) have been the mainstay first-line topical treatment for glaucoma for more than two decades. In many patients, topical beta-blockers alone do not sufficiently lower IOP, necessitating either the prescription of additional medications or a switch to another ocular hypotensive agent. Only around 30% of patients are effectively controlled on topical beta-blocker therapy alone long term (Kobelt-Nguyen et al, 1998).

Furthermore, studies have highlighted the potential cardiorespiratory side effects of beta-blockers. 'Hidden' airways disease such as chronic obstructive pulmonary disease and late-onset asthma is prevalent in the elderly glaucoma population and topical beta-blockers may cause significant systemic side effects (Renwick and Connolly, 1994; O'Donoghue, 1995). Physicians should remember the possibility of negative vasoconstrictive effects as a result of beta-blocker therapy. Ophthalmologists should also beware that physicians may incorrectly blame topical beta-blockers for other causes of respiratory and cardiac malfunction and constant feedback is needed between other medical specialists, physicians and ophthalmologists regarding systemic side effects to get the correct picture.

Other treatment options include alpha2-adrenergic agonists, topical carbonic anhydrase inhibitors and the prostaglandin derivatives latanoprost (Xalatan, Pharmacia Ltd, Milton Keynes), travoprost (Travatan, Alcon Laboratories Ltd, Hemel Hempstead) and bimatoprost (Lumigan, Allergan Ltd, High Wycombe). Of these, only latanoprost is approved for first-line treatment of glaucoma or ocular hypertension.

PROSTAGLANDIN DERIVATIVES IN GLAUCOMA

Prostaglandins are a series of naturally occurring fatty acids found throughout the body in almost every tissue, which possess numerous and diverse biological effects. The most common naturally occurring prostaglandins in the eye are prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) and prostaglandin E_2 (PGE_2). The former was first noted to reduce IOP in animals, but was found to cause clinically unacceptable conjunctival hyperaemia, irritation and foreign body sensation when first tried in humans (Camras et al, 1977; Camras and Bito, 1981; Guiffré, 1985).

To decrease ocular side effects, other $PGF_{2\alpha}$ analogues were synthesized and analysed (Resul et al, 1993, 1997). Researchers found that chemical modifications of the prostaglandin moiety itself dramatically enhanced the overall therapeutic index in the eye (Stjernschantz, 2001).

These principles led to the development of latanoprost (13,14-dihydro-17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$-isopropyl ester) as a new prostaglandin analogue for glaucoma treatment. Substitution of carbons 18, 19 and 20 on the omega chain with a phenyl ring in combination with saturation of the double bond between carbons 13 and 14 created a selective F-prostaglandin (FP) receptor agonist with virtually no sensory side effects in the eye and minimal conjunctival hyperaemia (Stjernschantz et al, 1995; Resul et al, 1997; Stjernschantz, 2001). In addition, the free acid was converted to an isopropyl ester to enhance corneal penetration, potency and tolerability.

LATANOPROST: EFFICACY AND SAFETY EVALUATIONS

Latanoprost *vs* timolol

In clinical studies comparing latanoprost 0.005% once daily *vs* the non-selective beta-blocker timolol 0.5% twice daily, it has been demonstrated that latanoprost generates a significantly greater reduction in mean IOP from baseline than timolol. Latanoprost produced a 6–8 mmHg reduction from a mean baseline of 24–25 mmHg, reducing baseline IOP by 27–35% (Alm et al, 1995; Camras et al, 1996; Watson et al, 1996). Diurnal IOP was also reduced 18% more with latanoprost than with timolol ($P<0.001$) (Hedman and Alm, 2000). Furthermore, patients treated with latanoprost have been shown to be more likely to reach target pressures than those treated with timolol (*Figure 1*) (Hedman, 1997; Hedman and Alm, 2000). Latanoprost treatment was associated with a withdrawal rate of less than 10%, similar to that seen with timolol.

Ocular side effects occurring at an incidence of 5–15% include blurred vision, burning or stinging, conjunctival hyperaemia, foreign body sensation, itching, iris pigmentation changes and punctate epithelial erosions. Only three ocular side effects occurred at an incidence greater than that observed with timolol treatment: conjunctival hyperaemia (10%), iris pigmentation changes and eyelash change. During 4 years of treatment with latanoprost, increased iris pigmentation occurred in about 30% of patients, predominantly occurring in mixed colour irides and usually within the first 8 months of treatment. There

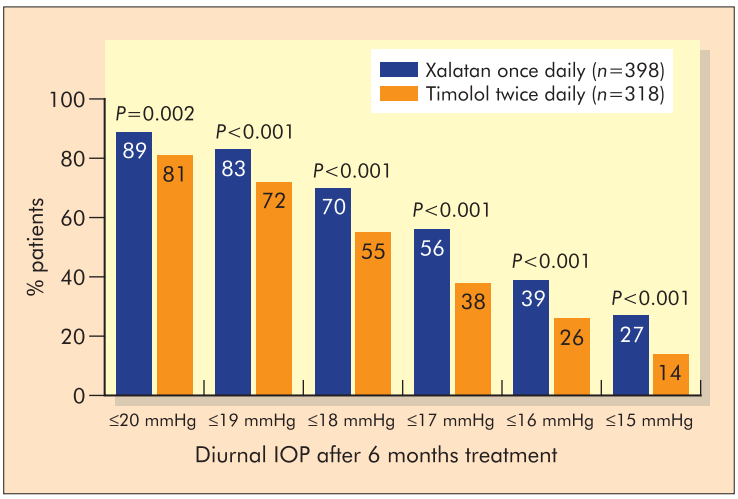

Figure 1. Percentage of patients who achieve specific intraocular pressure (IOP) after 6 months treatment. From Hedman (1997).

was little observed change in iris pigmentation after 2 years' treatment and no unexpected adverse effects have been noted during 4 years' safety monitoring. Increased iris pigmentation has not been shown to have any negative clinical sequelae based on 5 years' experience.

Reported ocular side effects include re-activation of uveitis and cystoid macular oedema in high-risk patients, but no cause-and-effect relationship between latanoprost and cystoid macular oedema has been proven (Schumer et al, 2000). Macular oedema has been reported rarely during latanoprost treatment. However, the occurrence of cystoid macular oedema, especially in an eye with multiple risk factors, may occur independent of the use of latanoprost (Schumer et al, 2000). The high selective affinity of latanoprost for the FP receptor makes retinal vascular actions for latanoprost unlikely even at high concentrations (Schumer et al, 2000). No systemic side effects associated with latanoprost have been proven.

Long-term evaluation of patients treated for more than 4 years has confirmed that latanoprost is a potent ocular hypotensive agent that is generally well tolerated in terms of ocular side effects and has few or no systemic effects. Previous studies demonstrate that there is no evidence of long-term drift of IOP control in patients evaluated for up to 2 years (Watson et al, 1998; Alm and Widengärd, 2000).

Monotherapy with latanoprost maintains stable IOP lowering control throughout the 24-hour circadian rhythm, an important consideration given that high 24-hour fluctuations are an independent risk factor for deterioration of visual field (Asrani et al, 2000).

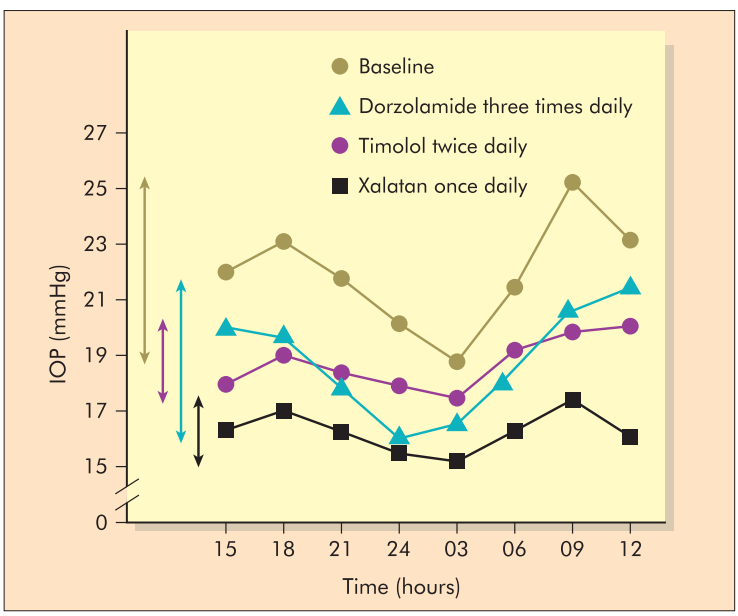

Figure 2. Tonometer intraocular pressure (IOP) readings (n=20). From Orzalesi et al (2000).

A randomized, crossover study examined circadian IOP control with timolol, dorzolamide, a carbonic anhydrase inhibitor, and latanoprost in patients with primary open-angle glaucoma or ocular hypertension (Orzalesi et al, 2000). Although all the drugs reduced IOP at all time points, the effect of timolol on IOP during the night was about half that during the day. The efficacy of latanoprost was fairly uniform, providing stable IOP control throughout the circadian cycle (*Figure 2*). In another study comparing latanoprost and once-daily dosing with timolol 0.5% gel, latanoprost was found to be more effective in reducing the mean 24-hour IOP and mean daytime and night-time IOPs ($P<0.001$) (Larsson, 2001). These findings suggest that strategies primarily based on beta-blockers may mean that patients are less well protected during the critical night-time period. Both IOP and the rate of aqueous humour flow have a circadian rhythm and higher IOP may be recorded during the night. Moreover, the nocturnal decrease in systemic blood pressure may make the nocturnal IOP even more critical (Orzalesi et al, 2000).

Latanoprost *vs* other antiglaucoma medications

Efficacy evaluations have demonstrated that once-daily dosing with latanoprost is significantly ($P<0.001$) more effective than dorzolamide, brimonidine, an alpha2-agonist, and provides similar IOP lowering compared with a fixed combination of dorzolamide 2% and timolol 0.5% in patients inadequately controlled on current therapy (Fechtner et al, 1999; Emmerich, 2000; Kampik et al, 2000).

Latanoprost *vs* dorzolamide: The results of an efficacy and safety evaluation comparing latanoprost 0.005% once daily with dorzolamide 2% three times daily during 3 months of treatment in patients with open-angle glaucoma or ocular hypertension demonstrate that once a day latanoprost generated a greater IOP-lowering effect (O'Donoghue, 2000). Latanoprost monotherapy reduced diurnal IOP by 31% from baseline, or 8.5 mmHg, while dorzolamide monotherapy reduced diurnal IOP by 20% or 5.6 mmHg. The percentage of patients who reached a diurnal IOP of 21 mmHg or less at 3 months was 82% in the latanoprost group (n=109) and 42% in the dorzolamide group (n=104).

Latanoprost *vs* brimonidine: Six-month data from a randomized, observer-masked multicentre study (n=379) comparing the efficacy and safety of latanoprost with brimonidine in patients with open-angle glaucoma and ocular hypertension demonstrated that latanoprost once

daily was significantly (P<0.001) more effective than brimonidine twice daily in reducing mean IOP at 6 months (Kampik et al, 2000). After 6 months of treatment, latanoprost reduced mean IOP by 7.1 mmHg (28%) compared with 5.2 mmHg (21%) for brimonidine from an overall baseline mean IOP of 25.0 mmHg. Ocular and systemic adverse events were more frequently reported in the brimonidine treatment group (n=192). There were a total of 48 patient withdrawals, five (2.7%) in the latanoprost group and 43 (22.4%) in the brimonidine group.

Newer prostaglandin derivatives

Since the commercial introduction of latanoprost in 1996, three other prostaglandin derivatives have been clinically evaluated for the lowering of IOP: unoprostone (Rescula, Novartis Ophthalmics, Duluth, GA), bimatoprost and travoprost. All three of the newer topical prostaglandin-related derivatives have been directly compared with latanoprost.

Latanoprost *vs* unoprostone: Results of prospective, randomized trials showed that latanoprost administered once daily was significantly (P<0.001) more effective in reducing IOP compared to unoprostone twice daily in patients with primary open-angle glaucoma or ocular hypertension (Aung et al, 2000; Susanna et al, 2001). From an overall baseline IOP of 24.1 mmHg, latanoprost reduced mean IOP at 8 weeks by 27% while unoprostone reduced mean IOP by 14% (Susanna et al, 2001).

Latanoprost *vs* bimatoprost: In a 3-month comparative evaluation of bimatoprost and latanoprost, no significant between-group differences in IOP reduction were noted (Gandolfi et al, 2001). Conjunctival hyperaemia occurred more frequently with bimatoprost than with latanoprost (36.1% *vs* 14.2%, P≤0.001).

Latanoprost *vs* travoprost: In phase III clinical studies, travoprost once daily produced reductions in IOP of 7–8 mmHg from a mean baseline IOP of 25–27 mmHg, a similar effect to that noted for bimatoprost or latanoprost (Netland et al, 2001). However, there also appear to be marked differences in ocular tolerability. The percentages of patients with a clinically significant change from baseline in ocular hyperaemia was 49.9% for travoprost, 27.6% for latanoprost and 14.0% for timolol. Treatment withdrawal as a result of all adverse events was more than double the rate observed with latanoprost over the 12 months' evaluation.

Latanoprost, bimatoprost and travoprost produce greater IOP reductions than timolol and avoid the systemic side effects commonly associated with non-selective beta-blockers. However, bimatoprost and travoprost are associated with a significantly higher incidence of ocular side effects than latanoprost – principally conjunctival hyperaemia and eyelash growth – whereas timolol and latanoprost are better tolerated locally.

BENEFITS OF TOPICAL MONOTHERAPY

Treatment effectiveness is uniformly judged on its ability to reduce IOP to a target level acceptable for the patient's disease. Cost effectiveness is undoubtedly an important consideration in the choice of glaucoma treatment. Overall costs in glaucoma are driven by a number of interrelated factors beyond the acquisition cost of the drug itself. These include time of intervention, treatment effectiveness, time to failure, the frequency of treatment change, the sequence of treatments and patient management. Resource utilization might be improved by influencing such cost drivers. However, published evidence is sparse; health economic studies are notoriously difficult to undertake and sources of error are numerous.

The frequency and number of treatment changes are driven largely by inadequate IOP control but also by discontinuation of initial therapy because of adverse drug reactions. In clinical practice, each treatment failure leads to treatment change, intensifying patient management and increasing overall costs. Better and more stable IOP control, together with effective long-term monotherapy where appropriate, lowers the probability of treatment change, leading to better patient compliance, less intensive patient management and better overall value (Kobelt-Nguyen et al, 1998). Moreover, a better effect on IOP early in the treatment leads to a lower probability of frequent treatment changes including surgery (Kobelt, 1998).

A meta-analysis for example showed that after 2 years' monotherapy treatment with latanoprost, only 7% of patients required a treatment change because of poor IOP control (Hedman and Alm, 1998). Therefore an effective initial treatment has a large beneficial impact on total disease management cost. To maximize compliance, effective IOP-lowering medications with minimal side effects should be preferred. Moreover, achieving a better initial treatment effect in terms of IOP control reduces overall management costs, enabling better use of limited resources.

COMBINATION TREATMENT OPTIONS

Where additional IOP lowering is warranted, multiple topical medications may be considered. However, the greater the number of drops per day, the poorer patient compliance becomes. The

simpler the treatment regimen, and the fewer the side effects, the greater the likelihood of good patient compliance.

Xalacom (latanoprost, timolol ophthalmic solution, Pharmacia Ltd, Milton Keynes) was introduced in 2001 as the first topical combination therapy for glaucoma available as a once-daily drop. This offers patients even greater IOP-lowering efficacy than that offered by either of its components (latanoprost and timolol) administered alone.

Two large randomized, double-blind multicentre studies have independently investigated the efficacy and safety of Xalacom compared with individual therapies over 6 months. Both were followed by 6 months of open evaluation to determine the efficacy of the fixed combination for up to 12 months.

Both studies found that, compared with the individual therapies, Xalacom produced a greater mean diurnal IOP reduction across week 2 to week 26 and this difference was statistically significant (Pfeiffer et al, 2000; Higginbotham et al, 2002). At 6 months' follow up in the US phase III trial (n=418), treatment with once-daily Xalacom resulted in an incremental 13.9% IOP reduction from pre-treatment baseline diurnal IOP compared with a 9.2% reduction for those patients randomized to Xalatan monotherapy and a 1.3% reduction for patients randomized to twice-daily timolol (Higginbotham et al, 2002). Xalacom was significantly more effective that either agent alone (Xalacom *vs* timolol $P<0.001$; Xalacom *vs* latanoprost $P=0.005$). IOP levels were maintained with no upward drift over 12 months of treatment with Xalacom. Both studies demonstrated that all treatments were well tolerated both locally and systemically, and adverse events were generally mild to moderate in severity.

Moreover, a recent 3-month evaluation study demonstrated that Xalacom is more effective than the twice-daily fixed combination dorzolamide and timolol (Cosopt, Merck Sharp & Dohme Ltd, Hoddesdon) in patients with glaucoma or ocular hypertension (Feldman et al, 2002).

Combination agents in a single bottle permit physicians to implement more aggressive yet convenient IOP-lowering strategies to help arrest glaucomatous progression in patients insufficiently responsive to a monotherapy trial with one glaucoma medication. Fixed-dose combinations also eliminate the possibility of reduced efficacy caused by the washout of sequential eye drops that is commonly experienced when two drugs are used separately, in immediate succession.

KEY POINTS

- Medical therapy remains the first choice for lowering and controling intraocular pressure (IOP) long term and preserving visual function.
- Beta-blockers have been the mainstay first-line topical treatment for more than two decades, but in many patients, the IOP-lowering effect is insufficient.
- Xalatan (latanoprost) produces greater mean diurnal IOP reductions than timolol, a widely prescribed beta-blocker, and lessens the systemic side effects commonly associated with ophthalmic beta-blockers.
- Xalatan is one of the most potent and well-tolerated ocular hypotensive agents; in the first-line setting this means that lower and more sustainable target pressures may be achieved with Xalatan monotherapy.
- Long-term efficacy and safety data confirm that Xalatan monotherapy maintains effective long-term IOP control which is stable throughout the 24-hour circadian rhythm.
- Securing effective early control of IOP with minimal adverse effects provides the best possible protection against further glaucomatous progression.

CLINICAL COMMENTARY

Latanoprost represents one of a new generation of medicines marked by a potent targeted physiological effect, offering an improved safety profile and a greater likelihood of improved compliance without negatively affecting quality of life. For these reasons, latanoprost has become the preferred treatment choice in many patients with glaucoma or ocular hypertension.

A medication's effectiveness, systemic safety and ocular tolerability are important factors which determine the success of therapy. Practitioners should initiate treatment with medications providing the optimal balance of these factors. In glaucoma care, greater attention is now directed at the impact of treatment on the patient's quality of life; this means taking all reasonable steps to avoid treatment failures, resulting from either unnecessary or inappropriate treatments or insufficient pressure-lowering control.

Securing effective early control of IOP with minimal adverse effects provides the best possible protection against further glaucomatous progression. The weight of evidence confirms that latanoprost is one of the most potent and well-tolerated ocular hypotensive agents. In the first-line setting, this means that lower and more sustainable target pressures may be achieved with latanoprost monotherapy. More experience is needed with newer ocular hypotensive agents to determine their role in glaucoma therapy. HM

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AGIS Investigators (2000) The advanced glaucoma intervention study (AGIS): 7. The relationship between control of intraocular pressure and visual field deterioration. *Am J Ophthalmol* **130**: 429–40

Alm A, Stjernschantz J, the Scandinavian Latanoprost Study Group (1995) Effects on intraocular pressure and side effects of 0.005% latanoprost applied once daily, evening

or morning: a comparison with timolol. *Ophthalmology* **102:** 1743–52
Alm A, Widengärd I (2000) Latanoprost: experience of 2-year treatment in Scandinavia. *Acta Ophthalmol Scand* **78:** 71–6
Asrani S, Zeimer R, Wilensky J et al (2000) Large diurnal fluctuations in intraocular pressure are an independent risk factor in patients with glaucoma. *J Glaucoma* **9**(2): 134–42
Aung T, Chew PTK, Yip CC et al (2000) A randomised double-masked crossover study comparing latanoprost 0.005% (Xalatan) with unoprostone 0.12% (Rescula) in patients with primary open angle glaucoma and ocular hypertension. *Invest Ophthalmol Vis Sci* **41**(4): S282 Abstract no 1484
Camras CB, Bito LZ (1981) Reduction of intraocular pressure in normal and glaucomatous primate (Aotus trivirgatus) eyes by topically applied prostaglandin $F_{2\alpha}$. *Curr Eye Res* **1**(14): 205–9
Camras CB, Bito LZ, Eakins KE (1977) Reduction of intraocular pressure by prostaglandins applied topically to the eyes of conscious rabbits. *Invest Ophthalmol Vis Sci* **16:** 1125–34
Camras CB, the United States Latanoprost Study Group (1996) Comparison of latanoprost and timolol in patients with ocular hypertension and glaucoma: a six-month, masked, multicenter trial in the United States. *Ophthalmology* **103:** 138–47
Collaborative Normal-Tension Glaucoma Study Group (1998) Comparison of glaucomatous progression between untreated patients with normal-tension glaucoma and patients with therapeutically reduced intraocular pressure. *Am J Ophthalmol* **126:** 487–97
Emmerich K-H (2000) Comparison of latanoprost monotherapy to dorzolamide combined with timolol in patients with glaucoma and ocular hypertension. *Graefe's Arch Clin Exp Ophthalmol* **238:** 19–23
Fechtner R, Clineschmidt C, Getson A, Adamsons I for the Cosopt Study Group (1999) A three month, parallel, randomized, observer-masked, multicenter study comparing Cosopt™ to Xalatan® in patients with elevated IOP. *Invest Ophthalmol Vis Sci* **40**(4): Abstract no 3513
Feldman R, Shin DH, the Xalacom/Cosopt Study Group (2002) Comparison of fixed combination of latanoprost and timolol (Xalacom®) with fixed combination of dorzolamide and timolol (Cosopt®) in patients with elevated intraocular pressure: a three-month, masked evaluator, Phase IIIB, multicenter study in the United States. Abstract. Presented at the Association for Research in Vision and Ophthalmology, Ft Lauderdale, USA: May 5–10
Gandolfi S, Simmons ST, Sturm R et al (2001) Three-month comparison of bimatoprost and latanoprost in patients with glaucoma and ocular hypertension. *Adv Ther* **18**(3): 110–21
Guiffré G (1985) The effects of prostaglandin $F_{2\alpha}$ in the human eye. *Graefe's Arch Clin Exp Ophthalmol* **222:** 139–41
Hedman K (1997) Results from a meta-analysis of three randomised, double-masked phase III clinical trials comparing latanoprost and timolol in patients with open-angle glaucoma and ocular hypertension. Presented at the XIth Congress of the European Society of Ophthalmology, Budapest, Hungary: June 1–5
Hedman K, Alm A (1998) The effect of latanoprost on intraocular pressure up to 24 months' treatment. Poster presented at the XXVIIIth International Congress of Ophthalmology, Amsterdam, The Netherlands: June 21–26
Hedman K, Alm A (2000) A pooled-data analysis of three randomized, double-masked, six-month clinical studies comparing the intraocular pressure reducing effect of latanoprost and timolol. *Eur J Ophthalmol* **10:** 95–104
Higginbotham EJ, Feldman R, Stiles M, Dubiner M, for the Fixed Combination Investigative Group (2002) Latanoprost and timolol combination therapy *vs* monotherapy. One-year randomized trial. *Arch Ophthalmol* **120:** 915–22
Hitchings R (1998) *Glaucoma management*. Focus - Occasional Update from the Royal College of Ophthalmologists, London
Kampik A and the European Study Group, Ludwig-Maximillians-University Eye Hospital, Munich, Germany (2000) A comparison of the efficacy and safety of latanoprost (Xalatan®) with brimonidine (Alphagan®) in patients with open angle glaucoma and ocular hypertension [ARVO Abstract]. *Invest Ophthalmol Vis Sci* **41**(4): S514. Abstract nr 2738
Kass MA, Keuer DK, Higginbotham EJ et al (2002) 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* **120:** 701–13
Kobelt G (1998) Comparative data for all countries. In: Jönsson B, Krieglstein G, eds. *Primary Open-Angle Glaucoma. Differences in International Treatment Patterns and Costs*. Isis Medical Media Ltd, Oxford: 116–26
Kobelt-Nguyen G, Gerdtham UG, Alm A (1998) Costs of treating primary open-angle glaucoma and ocular hypertension: a retrospective, observational two-year chart review of newly diagnosed patients in Sweden and the United States. *J Glaucoma* **7:** 95–104
Larsson LI (2001) Intraocular pressure over 24 hours after repeated administration of latanoprost 0.005% or timolol gel-forming solution 0.5% in patients with ocular hypertension. *Ophthalmology* **108:** 1439–44
Lichter PR, Janz NK, Musch DC et al, CIGTS Study Group (2001) The Collaborative Initial Glaucoma Treatment Study (CIGTS) interim outcomes report with up to 5 years of follow-up. Free paper presented at the 105th annual meeting of the American Academy of Ophthalmology, New Orleans, LA, USA: November 11–14
Netland PA, Landry T, Sullivan EK et al (2001) Travoprost compared with latanoprost and timolol in patients with open-angle glaucoma or ocular hypertension. *Am J Ophthalmol* **132:** 472–84
Odberg T (1987) Visual field prognosis in advanced glaucoma. *Acta Ophthalmol* **65**(182): 27–9
O'Donoghue E (1995) Beta blockers and the elderly with glaucoma: are we adding insult to injury? *Br J Ophthalmol* **79:** 794–6
O'Donoghue EP (2000) A comparision of latanoprost and dorzolamide in patients with glaucoma and ocular hypertension: a 3 month, randomised study. *Br J Ophthalmol* **84:** 579–82
Orzalesi N, Rossetti L, Invernizzi T et al (2000) Effect of timolol, latanoprost and dorzolamide on circadian IOP in glaucoma or ocular hypertension. *Invest Ophthalmol Vis Sci* **41**(9): 2566–73
Pfeiffer N and the German Latanoprost Fixed Combination Study Group (2000) A comparison of the fixed combination of latanoprost and timolol with first individual components in patients with glaucoma or ocular hypertension. *Invest Ophthalmol Vis Sci* **41**(4): S754 Abstract no 4004
Quigley HA (1996) Number of people with glaucoma worldwide. *Br J Ophthalmol* **80:** 389–93
Renwick DS, Connolly MJ (1994) Prevalence and treatment of chronic airways obstruction (CAO) in older adults. *Age Aging* **23** (suppl): 6
Resul B, Stjernschantz J, No K et al (1993) Phenyl-substituted prostaglandins: potent and selective antiglaucoma agents. *J Med Chem* **36:** 243–8
Resul B, Stjernschantz J, Selén G, Bito L (1997) Structure-activity relationships and receptor profiles of some ocular hypotensive prostanoids. S*urv Ophthalmol* **41**(Suppl 2): S47–S52
Schumer RA, Camras CB, Mandahl AK (2000) Latanoprost and cystoid macular edema: is there a causal relation? *Curr Opin Ophthalmol* **11:** 94–100
Sommer A, Tielsch JM, Katz J et al (1991) Relationship between intraocular pressure and primary open angle glaucoma among white and black Americans. *Arch Ophthalmol* **109:** 1090–95
Stjernschantz JW (2001) From PGF_2-isopropyl ester to latanoprost: a review of the development of Xalatan. *Invest Ophthalmol Vis Sci* **42:** 1134–45
Stjernschantz J, Selén G, Sjöquist B, Resul B (1995) Preclinical pharmacology of latanoprost, a phenyl-substituted $PGF_{2\alpha}$ analogue. *Adv Prostaglandin Thromboxane Leukot Res* **23:** 513–18
Susanna R, Giampani J, Borges AS et al (2001) A double-masked, randomized clinical trial comparing latanoprost with unoprostone in patients with open-angle glaucoma or ocular hypertension. *Ophthalmology* **108:** 259–63
Watson P, Stjernschantz J, the Latanoprost Study Group (1996) A 6-month, randomized, double-masked study comparing latanoprost with timolol in open-angle glaucoma and ocular hypertension. *Ophthalmology* **103:** 126–37
Watson PG, the Latanoprost Study Group (1998) Latanoprost: two years' experience of its use in the United Kingdom. *Ophthalmology* **105:** 82–7