Long-term Efficacy and Safety of Fixed-combination Timolol/Latanoprost

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Abstract

The fixed-combination preparation of timolol and latanoprost has been available in Europe since 2001. Evidence supporting its level of clinical efficacy has been slowly accumulating, with some studies suggesting clear benefit and others showing only a modest additional effect relative to its individual components. Studies demonstrating long-term protection of visual function are sparse and more work is required in this area. Several reports indicate that fixed-combination timolol/latanoprost is safe and well tolerated. Other similar combination products are now competing directly with fixed-combination timolol/latanoprost, and further comparative studies will be required to assess their relative merits.

Keywords

Fixed combination, prostaglandin analogue, beta-blocker, adverse effects, efficacy, protection

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In devising the 'ideal' glaucoma drop, it is almost intuitive that a combination preparation of two monotherapies should be a Holy Grail in the treatment of glaucoma. Indeed, the benefits seem clear: better patient compliance, fewer daily dosages and therefore fewer adverse effects, ideally synergy of the active components, less exposure to excipients, lower cost and effective intraocular pressure (IOP) control.

The concept of combining individual glaucoma drugs is not new.[1] Timolol and pilocarpine (Timpilo®), which became available in Europe in 1992, was the first true fixed combination, and timolol and dorzolamide (Cosopt®), launched in 1998, continues to be popular among glaucoma practitioners.[2]

When it appeared in 1977,[3] timolol became the gold standard in IOP control, and remained so for nearly two decades. On its appearance in 1996, latanoprost, a prostaglandin F2α analogue, began to usurp timolol's dominant position as the first line in glaucoma management, and is now the world's best-selling glaucoma drug.

Studies reporting the efficacy of the concomitant use of these monotherapies led to the development of fixed-combination timolol/latanoprost.[4,5] The fixed combination of timolol and latanoprost, marketed as Xalacom® in Europe, became commercially available in 2001 and was heralded by a series of short-term studies examining its efficacy, safety and tolerability. This article summarises the evidence to date on fixed-combination timolol/latanoprost and looks at the future for this fixed-combination glaucoma preparation.

Pharmacology and Function of Fixed-combination Timolol/Latanoprost

Fixed-combination timolol/latanoprost consists of 0.5% timolol as the isopropyl ester maleate and 0.005% latanoprost, a prodrug of a 17-phenyl substituted F2α analogue. The individual components have different modes of action in the control of IOP in humans. Latanoprost is highly selective for the FP receptor, one of several prostaglandin receptor sites in humans and primates, to increase uveoscleral outflow,[6] although there is some evidence that the conventional outflow pathway is also involved.[7] Its mode of action is thought to involve the induction of matrix metalloproteinases (MMPs) in the ciliary body smooth muscle and possibly also in ciliary melanocytes.[8–10] MMPs then break down the ciliary body extracellular matrix and reduce hydraulic resistance to uveoscleral outflow. Meanwhile, timolol acts at β-adrenergic receptors in the ciliary body to decrease production of aqueous humour,[11] but its exact mode of action remains unclear.

Pressure-lowering Efficacy of Fixed-combination Timolol/Latanoprost

Both timolol and latanoprost have proven efficacy as monotherapies in the lowering of IOP. The initial small, short-term studies[4,5] combining timolol and latanoprost established that these individual drugs used together achieved greater pressure reduction than the monotherapies alone.[4,5] An important consideration is whether the time of day at which the fixed combination is administered affects the results obtained. To date, no study comparing morning and evening dosing of fixed-combination timolol/latanoprost has ever been carried out. However, a

study comparing the unfixed components given concomitantly in the morning and evening, compared versus timolol, gave greater daytime reduction with evening dosing and lower night-time pressures with morning dosing.[12] Latanoprost had previously been shown to produce a greater daytime ocular hypotensive effect when dosed at night.[13] Some variability may therefore be attributed to the fact that morning dosing of fixed-combination timolol/latanoprost occurred in some studies,[14,15] while in others evening dosing was used.[16]

Morning Dosing of Fixed-combination Timolol/Latanoprost Produces Some Efficacy Improvements in Definitive and Other Supporting Studies

Many of the studies that were definitive for the development of the fixed-combination timolol/latanoprost (0.5%/0.005%) used a regimen of morning dosing in comparison with comparator treatments at the same or other times of the day. The first study looking at the fixed-combination therapy showed that it gave enhanced IOP lowering compared with either component alone after four weeks of treatment.[17] The study used a morning dosing regimen and demonstrated a reduction in mean diurnal IOP of 6.1mmHg for fixed-combination timolol/latanoprost (0.5%/0.005%) compared with baseline. In addition, pressure reduction was 3.7mmHg with fixed-combination timolol/latanoprost (0.5%/0.001%) compared with 4.9mmHg for latanoprost alone and 2.1mmHg for timolol alone. These results were similar to those of a six-week study comparing fixed-combination timolol/latanoprost with placebo, in which there was a 4.7mmHg decrease in favour of the fixed-combination preparation.[18]

In the management of glaucoma, intraocular pressure lowering is merely a controllable surrogate for the ultimate goal of therapy, which is the prevention of the loss of visual function.

The fixed combination of timolol/latanoprost showed advantages in a number of critical studies. A three-armed double-masked, randomised, controlled study conducted in the US comparing the fixed combination given in the morning versus its individual monotherapies, involving 418 patients over 12 months, showed a modest 1.1–1.2mmHg decrease in IOP compared with latanoprost monotherapy.[14] A similar randomised, double-masked, multicentre study conducted in Europe with 436 patients again showed a 1.2mmHg reduction when switching from latanoprost monotherapy to fixed-combination timolol/latanoprost and a 1.9mmHg reduction when switching from timolol monotherapy to fixed-combination timolol/latanoprost.[15] Although there were consistent reductions in IOP in these large studies, the US Food and Drug Administration (FDA) requires that new combination products show a 2mmHg mean diurnal decrease in IOP compared with either individual component. This strict criterion has been a barrier to any fixed-combination medications for glaucoma containing prostaglandins gaining approval for sale in the US.

In a clinical study conducted in Glasgow, UK, a group of 59 patients switched from latanoprost monotherapy to fixed-combination timolol/latanoprost showed a mean reduction in IOP of 2.6mmHg.[19] Significant IOP reductions followed the switch to fixed-combination timolol/latanoprost for patients with primary open-angle glaucoma (n=49) and ocular hypertension (n=10), with mean decreases of 2.3 and 3.8mmHg for the two groups, respectively. A further 12-week study comparing the fixed combination with the individual components favoured the unfixed components by 1.1mmHg,[20] although it should be noted that the combination was applied once daily in the morning whereas the unfixed latanoprost was dosed in the evening.

A series of recent studies compared fixed-combination timolol/latanoprost versus other monotherapies and fixed combinations, with varying results. In an 18-week study of 32 patients,[21] fixed-combination timolol/latanoprost and fixed-combination timolol/dorzolamide were demonstrated to be statistically similar in their diurnal IOP-lowering effect. Similar results were seen in another cross-over study involving 33 patients comparing timolol/latanoprost once daily versus dorzolamide/timolol twice daily.[22] However, another study comparing these two fixed combinations showed a 1.0mmHg difference in the diurnal IOPs in favour of fixed-combination timolol/latanoprost.[23] A comparison of fixed-combination timolol/latanoprost with concomitant brimonidine and latanoprost therapy in 32 subjects showed that there was no statistical difference in the diurnal IOP reduction between the two regimes.[24]

A retrospective trial of 168 patients in Greece showed a statistically significant reduction in IOP in patients who switched from mono- and adjunctive therapies to fixed-combination timolol/latanoprost (switched from timolol alone -3.9mmHg; $p<0001$; from latanoprost alone -2.5mmHg; $p<0.001$; and from dorzolamide/timolol -2.7mmHg; $p=0.03$).[25] Another trial investigated switching to a fixed-combination timolol/latanoprost from other therapies and showed that fixed-combination timolol/latanoprost was as effective as latanoprost used with a dorzolamide/timolol fixed-combination but only for the two-month duration of the study.[26]

Switching glaucoma medication regimens was also investigated in a study looking at the IOP reduction when changing from timolol and another non-prostaglandin drug (either pilocarpine, an alpha-agonist, or a topical carbonic anhydrase inhibitor) to either latanoprost or fixed-combination timolol/latanoprost. Patients who were switched to latanoprost or fixed-combination timolol/latanoprost showed significant IOP reductions compared with their previous combination therapy with timolol and another non-prostaglandin drug. However, there was no statistically significant difference between latanoprost and fixed-combination timolol/latanoprost in terms of IOP lowering.[27]

In a randomised, double-masked trial in the US, 350 patients whose IOP was inadequately controlled by latanoprost were switched to fixed-combination timolol/latanoprost. After 21 days of treatment, switched patients showed a 2mmHg decrease in IOP compared with baseline and significantly more had IOP decreases ≥3, ≥4 or ≥5mmHg.[28]

Evening Dosing of Fixed-combination Timolol/Latanoprost Results in Marked Efficacy Improvements

Most of the clinical studies discussed here used morning dosing of the timolol/latanoprost fixed combination; however, a small number used evening dosing or directly compared dosing times. One such study

showed a pressure increment of between 1.5 and 2.9mmHg depending on the time of day.[29] In another study conducted in 2006, a comparison was made with fixed-combination timolol/latanoprost dosed once in the evenings against twice-daily timolol. Fixed-combination timolol/latanoprost was associated with an 8.6mmHg reduction from baseline; by contrast, timolol alone gave a 5.7mmHg reduction.[30] In a comparison of evening dosing of fixed-combination timolol/latanoprost with the concomitant use of its individual components in 502 patients in Germany, fixed-combination timolol/latanoprost was shown to be non-inferior to concomitant use.[31]

The timolol/latanoprost fixed combination was mostly more effective in reducing IOP than single or adjunct treatments. Generally, morning dosing produced a modest improvement in IOP, but evening dosing resulted in greater improvements. The results indicate that when assessing glaucoma treatment study results, it should be understood that the timing of doses affects the timing of the greatest changes in IOP during the following day/night. It is therefore important that different studies use similar dosing and assessment regimens in order to provide valid comparisons between treatments.

Long-term Efficacy of Fixed-combination Timolol/Latanoprost

While it is known that timolol shows a 'drift' in its effect over time, with IOP rising slowly after several years of use,[32] there are as yet no studies showing a corresponding latanoprost 'drift',[33] and evidence is emerging that the efficacy of the fixed combination may be retained in the longer term. Efficacy was maintained for one year in one study,[15] and a recent five-year study of the safety of fixed-combination timolol/latanoprost, the results of which have been presented in abstract form, suggested that the mean IOP reduction of 4.0mmHg varied only slightly over the five-year period.[34]

Why should studies of the efficacy of fixed-combination timolol/latanoprost produce apparently conflicting results? Inevitably, there is a rush to evaluate the new drug against its peers and this produces an almost bewildering variety of approaches and protocols. Large multicentre, randomised, double-blind studies may be considered to be the gold standard, but even these may not be completely free from bias or from phenomena such as the Hawthorne effect, whereby the performance of subjects (including compliance) improves simply by virtue of being included in a study. Retrospective studies may be particularly prone to the effect of 'regression to the mean', which tends to exaggerate the impact of a particular intervention.[35]

Another factor influencing variability may include the racial composition of the study population.[36] A pooled data analysis of eight clinical trials conducted in Asia, Europe and North and South America concluded that a greater difference in mean diurnal IOP reduction between latanoprost and timolol was seen in the Asian and Mexican patients than in the European and US patients. It was suggested that an apparently enhanced effect of latanoprost was associated with ethnic origin or eye colour differences. However, others have suggested that ethnicity has no influence on the effectiveness of latanoprost.[37]

The results of 24-hour efficacy studies may also be affected by the tonometry technique employed. Nocturnal readings will vary depending on the position in which they are taken – seated or supine[38] – and evaluation of IOP may also be affected by hospitalisation, exposure to light during night-time measurements, disturbed sleep and sudden awakening.[39]

The efficacy of evening dosing with timolol is dismissed by some researchers as negligible or non-existent,[40,41] while others implicate this as an important contributor to night-time systemic hypotension and, thereby, disease progression.[27,42]

Those opposed to fixed combinations in general may cite the fact that they leave no scope for altering the amount of the individual components prescribed. Many clinicians prefer to retain the flexibility of being able to change the dose of timolol; for example, this would allow a patient to be administered a dose ranging from 0.25 to 0.5%, rather than being bound by the fixed combination's composition.

Visual Field Protection and Fixed-combination Timolol/Latanoprost

In the management of glaucoma, IOP lowering is merely a controllable surrogate for the ultimate goal of therapy, which is the prevention of the loss of visual function. Nevertheless, several landmark studies[43–46] have shown that lowering IOP can reduce the risk of progression in glaucoma, with a fall in IOP of a single millimetre of mercury reducing the risk of progression by 10%.[45,46] While the documented pressure-lowering efficacy of fixed-combination timolol/latanoprost might reasonably be expected to confer protection of visual function, few studies are of sufficient duration to assess changes in the visual field over time. An early study of the individual monotherapies versus fixed-combination timolol/latanoprost recorded suspected visual field change in six of 140 subjects on the fixed combination compared with 10 of 147 on latanoprost and five of 149 on timolol as part of the drug's safety profile.[15]

It is only eight years since fixed-combination timolol/latanoprost was launched, and during this time it has established a good safety profile.

Safety and Tolerability of Fixed-combination Timolol/Latanoprost

Acceptable safety and tolerability profiles are prerequisites for any drug. These have been well documented for the individual components of fixed-combination timolol/latanoprost. Use of both timolol and latanoprost as monotherapies can bring about conjunctival hyperaemia, stinging, burning and itching, foreign body sensation, dry-eye sensation and superficial punctate keratopathy. With respect to hyperaemia, this occurs less frequently with timolol than with latanoprost,[14,15,47] but latanoprost causes less ocular hyperaemia than the other prostaglandin analogues.[48]

Timolol has well-known associated systemic effects such as bronchial spasm and bradycardia, and is contraindicated in bronchial asthma and severe chronic obstructive pulmonary disease (COPD), sinus bradycardia, second- or third-degree heart block, cardiac failure and

cardiogenic shock.[49] An oral beta-blocker taken at the same time can potentiate these cardiac effects.

The prostaglandin analogues have achieved notoriety for their association with iris and eyelid darkening and thickening and lengthening of the eyelashes. Darkening of the iris is thought to be due to an increase in the amount of melanin within a stable iris melanocyte population and is irreversible although entirely harmless.[6] However, one study has suggested that the iris pigmentation may be reversible on cessation of the drop.[50] Lengthening and thickening of the lashes is thought to occur least in latanoprost of all the prostaglandin analogues and is reversible on cessation of the drop. Patients often have a positive response to this change, although lashes may occasionally be so long as to interfere with spectacle wear and even accurate drop administration.[51]

Early studies on fixed-combination timolol/latanoprost cited the occurrence of burning, conjunctival hyperaemia, ocular itching, tearing, dry eye, eyelid laxity, blurred vision, floaters, blepharitis, diplopia, sinus allergies[35] and even back pain.[52] Other more serious adverse events can include changes in refractive error, upper respiratory tract infection, cardiac failure, tachycardia, blood pressure or pulse rate changes and increased iris pigmentation.[14,50] Patients were withdrawn from one study with finger and arm fractures.[13] Night-time use of a beta-blocker has been implicated as contributing to progression in some cases of glaucomatous optic neuropathy by the reduction of ocular perfusion pressure.[45]

However, significant adverse effects appear to be very uncommon. Glasgow Royal Infirmary's patient database provides 'real-life' data on patients being seen in clinics and suggests that fixed-combination timolol/latanoprost is among the best tolerated glaucoma medications, with only 8.6% of patients having to discontinue the drop due to adverse events.[53] A further study from the same database showed that fixed-combination timolol/latanoprost had the greatest persistency of use, with 64.2% of patients prescribed the preparation still using it at 60 months.[54] A large European five-year study looked at the incidence of iris pigmentation from baseline, darkening, lengthening and thickening of the eyelashes or pigmentation of peri-orbital skin and spontaneously reported adverse events or serious adverse events.[33] Presented in abstract form, this study, involving 974 patients, found that 42.6% of them developed overall increased iris pigmentation, 58.1% developed eyelash change and 5.2% developed peri-orbital skin changes. One patient developed cystoid macular oedema. Overall, this study concluded that, even after 60 months of treatment, fixed-combination timolol/latanoprost was safe and well tolerated for patients with primary open-angle glaucoma and ocular hypertension. This is believed to be the longest study to date examining these issues.

The Future for Fixed-combination Timolol/Latanoprost

It is only eight years since fixed-combination timolol/latanoprost was launched, and during this time it has established a good safety profile. Although evidence of its efficacy in lowering IOP has at times been conflicting, the benefits it offers in terms of ease of compliance and reduced exposure to preservatives have confirmed it as a useful addition to the therapeutic armamentarium in many parts of the world. Following the introduction of other combination beta-adrenergic receptor blocker/prostaglandin analogue products, such as fixed-combination travoprost/timolol and fixed-combination timolol/bimatoprost, as well as the adrenergic receptor blocker/carbonic anhydrase timolol/brinzolamide fixed combination, the market for fixed-combination products is becoming more crowded. Further high-quality comparative studies will be required to evaluate the long-term relative strengths and weaknesses of these products. ■

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