An update on bimatoprost (Lumigan®) in glaucoma therapy

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The prostamide bimatoprost (Lumigan®, Allergan Inc.) has been proven highly effective as monotherapy, adjunctive, and replacement therapy for lowering intraocular pressure (IOP) and providing good diurnal control of IOP in patients with open-angle glaucoma and ocular hypertension. Target pressure results from large, randomized, multicenter clinical trials comparing bimatoprost with timolol, latanoprost (Xalatan®, Pharmacia & Upjohn), travoprost (Travatan®, Alcon laboratories), fixed combination timolol/dorzolamide (Cosopt®, Merck Inc.) or latanoprost and timolol gel have been analyzed. In each of the analyses, patients were more likely to achieve low target pressures with bimatoprost than with the other medications. Patients on bimatoprost therapy achieve low IOP levels that are maintained throughout the day and night, and long-term trials have shown that the efficacy of bimatoprost is sustained. Bimatoprost has been proven to be safe and well tolerated in postmarketing surveillance and, as a once-daily drug, allows for patient convenience resulting in better treatment compliance. Bimatoprost may be the most effective medication available for protecting the visual field in patients with glaucoma or ocular hypertension.

Keywords:
bimatoprost, glaucoma, intraocular pressure, ocular hypertension, open-angle glaucoma

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Overview of glaucoma

The American Academy of Ophthalmology (AAO) defines glaucoma as "a multifactorial optic neuropathy in which there is a characteristic acquired loss of retinal ganglion cells and atrophy of the optic nerve" [1].

The disease is characterized by progressive retinal ganglion cell (RGC) loss, gradual optic disk cupping, and associated visual field deficits. Elevated intraocular pressure (IOP) is not currently included in the definition, but it is still listed as an important contributing factor. It is a common disease occurring worldwide [2], and remains a leading cause of blindness [3].

Several other risk factors for the development of glaucoma have been identified including; advanced age, African ancestry, a family history of glaucoma, severe myopia, and ocular trauma. In many cases, the immediate causes of damage and death of retinal ganglion cells in glaucoma are unknown. Lowering IOP is presently the only proven treatment modality for halting the progression of glaucomatous damage in open-angle glaucoma (OAG), and normal tension glaucoma (NTG).

Rationale for lowering & stabilizing IOP

The paradigm for the management of glaucoma has evolved considerably in recent years as new evidence from clinical trials has become available. Physicians are now targeting greater IOP reductions and lower IOP levels for their patients than thought necessary in years past. It has been suggested by the AAO that, for patients with mild damage (optic disc cupping but no visual field loss), the initial target pressure should be 20 to 30% lower than baseline, while for patients with advanced damage the target pressure should be a reduction of 40% or more from baseline.

Studies have shown that low pressures are beneficial in preserving the visual field in glaucoma patients, even in patients with IOP in the normal range. In a study by Mao and colleagues, pressures less than 17 mmHg protected the optic nerve from damage in patients with early primary OAG, while pressures over 21 mmHg resulted in optic disc cupping and/or visual field loss [4]. In advanced glaucoma, pressures substantially lower than 17 mmHg may be required to prevent deterioration of the visual field. The Advanced Glaucoma Intervention Study (AGIS) investigators reported that after surgery to reduce IOP in advanced glaucoma, eyes with IOP less than 14 mmHg had less visual field loss than those with IOP higher than 17.5 mmHg, suggesting that very low target pressures are beneficial for these patients [5]. Similarly, reducing IOP to low target levels decreases the risk of glaucomatous progression

in patients with NTG. A 1998 study by the Collaborative Normal Tension Glaucoma Study Group reported that a 30% IOP reduction in patients with NTG had a significantly favorable effect on visual field stability [6].

Reducing IOP also decreases the risk of the development of glaucoma in patients with ocular hypertension (OHT) – defined as elevated IOP but no evidence of optic disc damage or visual field loss. A controlled trial involving 1636 patients with OHT (IOP between 24 and 32 mmHg in the most impaired eye) conclusively demonstrated that lowering IOP by 20% (or to no more than 24 mmHg) halves the risk of the development of OAG [7]. In the accompanying editorial [8], it is concluded that lowering IOP helps preserve visual function in OAG, NTG, and OHT, and for patients with each of these diagnoses, a 3 mmHg reduction in IOP roughly corresponds to a 50% reduction in the risk of the development or progression of glaucoma.

Achieving a low target pressure at a single time point is insufficient to prevent the progression of glaucomatous damage as it is likely that even transient elevations of IOP can cause damage to the optic nerve. Therefore, for the best protection of the visual field of glaucoma and OHT patients, low pressures must be sustained through 24 h. IOP normally fluctuates throughout the day and night in a circadian rhythm [9], and pressure peaks can occur at any time during the day or night [10–12].

Glaucoma patients typically have larger diurnal variations in IOP compared with normal subjects. Large diurnal IOP fluctuations are a clinical concern, because they have been associated both with an increased risk of the development of glaucoma and an increased risk of glaucomatous progression. In concurrence with earlier studies, Asrani and colleagues demonstrated that large diurnal IOP fluctuations are a risk factor for visual field loss in glaucoma independent of the level of IOP [13]. Thus, treatment that prevents fluctuations in IOP should improve the prognosis of glaucoma patients.

Although other treatment strategies may eventually be used for glaucoma patients, such as neuroprotection, the current goal of glaucoma therapy is to lower and stabilize IOP. In clinical practice, many physicians set a target pressure for their patients to achieve on long-term therapy. Factors that should be considered in setting an appropriate target pressure include the IOP level at which optic nerve damage occurred, the rate and extent of glaucomatous damage, patient age and expected lifespan, and the presence of other risk factors for glaucoma such as family history and race [14,15].

Pharmacological approaches to IOP lowering

The medications available for reducing IOP in glaucoma patients include topical β-adrenergic antagonists (e.g., timolol, betaxolol), carbonic anhydrase inhibitors (e.g., dorzolamide [Trusopt®, Merck & Co.], brinzolamide [Azopt®, Alcon Laboratories]), cholinergics (e.g., pilocarpine), α-adrenergic agonists (e.g., brimonidine [Alphagan®P, Allergan Inc.]), prostaglandins (e.g., latanoprost [Xalatan®, Pharmacia & Upjohn], travoprost [Travatan®, Alcon laboratories]), and the prostamide bimatoprost (Lumigan®, Allergan Inc). In choosing among these medications, both efficacy and safety/tolerability issues should be considered. Except for β-blockers, which have been associated with rare but serious cardiopulmonary events [16], the ocular hypotensive agents commonly used seem to be systemically safe and are generally well tolerated. The most appropriate medication, therefore, will often be the one that is most efficacious in lowering and stabilizing IOP.

In evaluating the IOP-lowering efficacy of a medication, it is important to consider both mean IOP lowering and reliability of the medication in helping patients achieve target pressures. Further, the mechanism of IOP lowering may also be a key consideration in evaluating drug efficacy. The elevated IOP in glaucoma is caused by impaired aqueous outflow [17]. A medication that lowers IOP by decreasing aqueous production does not treat the physiological pathology in glaucoma, and it might cause additional damage to the outflow channels [18]. Conversely, a medication that increases tonographic outflow facility (trabecular meshwork ouflow) corrects the deficit that leads to elevated IOP. A medication that enhances outflow facility may also be preferred for therapy, as it could be best able to dampen pressure spikes and provide flat diurnal IOP curves [19,20].

Among the ocular hypotensive medications that are currently available, bimatoprost stands out for its IOP-lowering efficacy.

Background on bimatoprost

Bimatoprost is a synthetic prostamide analog that reduces IOP by increasing aqueous humor outflow through a dual mechanism of action, improving both pressure-dependent (presumed trabecular, via Schlemm's canal and the episcleral

veins) and pressure-independent (presumed uveoscleral, ciliary muscle) outflow pathways [19]. Once-daily (q.d.) bimatoprost has proven to be a powerful ocular hypotensive agent that provides large mean IOP reductions in clinical trials [21–25]. Moreover, it has been shown to control IOP throughout the day, maintaining a flat diurnal curve [26].

The cellular mechanism of action of bimatoprost is less well understood. It has been reported to have no meaningful affinity for receptors that are known to be involved in IOP regulation, including adrenergic, dopaminergic, cholinergic, cannabinoid, and prostaglandin receptors [27]. It has also been confirmed that bimatoprost does not bind to prostaglandin F2α (FP) receptors at physiological (sub-μmolar) concentrations [28]. However, bimatoprost demonstrates inherent activity in the cat iris sphincter isolated preparation [27]. Bimatoprost is not a prodrug in this model system as it does not need to be metabolized in order to cause iris constriction. Together, the results of radioligand binding assays and bioassays suggest that the actions of the drug are mediated through novel receptors that have not yet been identified [27]. Importantly, a recent study showed that bimatoprost and the prostaglandin latanoprost produce additive IOP lowering in glaucomatous monkey eyes [29]. These results strongly suggest that bimatoprost and the prostaglandins activate different receptors and have distinct cellular mechanisms of action.

The possibility that bimatoprost might be metabolized to compounds with activity at prostaglandin receptors has been extensively investigated [30], although differences in drug metabolism between species make it difficult to extrapolate these results to humans. Conflicting results have been obtained in studies of the metabolic stability of bimatoprost in homogenates of human ocular tissue. In one study using homogenates of iris–ciliary body obtained from healthy donor eyes within 4 h post-mortem, there was no measurable conversion of bimatoprost to the free acid metabolite in human iris–ciliary body homogenates, suggesting that it is not a prodrug in human eyes [27]. In contrast, a preliminary report using homogenates of iris–ciliary body as well as cornea and sclera from human donor eyes within 15 h post-mortem suggested that bimatoprost could be hydrolyzed to a free acid metabolite [31].

The results of these *in vitro* metabolism studies might reflect the situation in patients *in vivo*. There have been several recent presentations addressing this question, though this data is not yet published in peer reviewed literature. Cantor and colleagues reported that low levels of the free acid hydrolysis product were detected in the aqueous humor of cataract patients in a presentation at the American Glaucoma Society Meeting in March of 2004 (CA, USA). In addition, these same authors also presented evidence on the hydrolysis of bimatoprost and latanoprost to their free acids in the aqueous humor of cataract patients at the European Glaucoma Society Meeting in May of 2004. Both of these studies were consistent with low levels of the free acid of bimatoprost in the aqueous humor following single dose administration in eyes scheduled for cataract surgery. Furthermore, the systemic levels of bimatoprost and its metabolic degradation products have been monitored after clinical dosing, and the potential C-1 acid metabolite of bimatoprost was not detected in the blood of patients who were treated with once- or twice-daily (b.i.d) bimatoprost for up to 1 year (quantification by validated liquid chromatography tandem mass spectrometry, limit of detection = 50 pg/mL) [32]. These results strongly suggest that bimatoprost is not a prodrug, but rather, bimatoprost itself is the active moiety in human eyes.

Update on clinical studies of bimatoprost

Results of clinical studies to date have demonstrated that bimatoprost is highly effective as monotherapy, adjunctive, and replacement therapy for glaucoma and OHT patients. It has consistently lowered IOP throughout the day and night and provided flat diurnal and circadian IOP curves. Most patients achieved low target pressures on bimatoprost therapy with efficacy sustained over long-term use and found to be generally well tolerated systemically.

Comparison of bimatoprost with timolol

The object of a 2-year, double-blind, comparison of bimatoprost with timolol was to determine long-term efficacy in patients treated with bimatoprost q.d (n = 167), bimatoprost b.i.d (n = 131), and timolol b.i.d (n = 81) [33]. Patients who were given the q.d regimen of bimatoprost had significantly greater mean reduction from baseline in IOP. Bimatoprost q.d provided significantly lower mean IOP compared with timolol b.i.d at every time of the day on each study visit ($p \leq 0.001$). At 10 am (peak timolol effect) at month 24, the mean reduction in IOP from baseline in the bimatoprost q.d group was 7.8 mmHg

compared with 4.6 mmHg in the timolol group ($p < 0.001$). Patients treated with bimatoprost q.d sustained significantly lower mean IOP than timolol-treated patients at every follow-up visit throughout the 2-year study period ($p \leq 0.006$). At 10 am at month 24, a significantly greater proportion of bimatoprost q.d than timolol patients achieved target pressures of less than or equal to 13–18 mmHg ($p \leq 0.010$). Mean reduction from baseline IOP with bimatoprost b.i.d was not significantly different from that with timolol at month 24 at 10 am. The IOP lowering provided by bimatoprost in this study is consistent with other earlier trials [21,22,25] and confirm that bimatoprost q.d is superior to timolol in IOP lowering. Further, these findings demonstrate the IOP lowering provided by bimatoprost is sustained with long-term use.

Comparison of bimatoprost with latanoprost

A 6-month, multi-center, randomized, investigator-masked trial compared q.d bimatoprost with q.d latanoprost as monotherapy for patients with glaucoma or OHT [23]. Mean IOP at baseline was comparable between treatment groups at 8 am and 4 pm; at 12 pm mean baseline IOP was significantly higher for bimatoprost (24.0 mmHg) than for latanoprost (23.3 mmHg; $p = 0.028$). Bimatoprost lowered mean IOP statistically significantly more than latanoprost at all time points throughout the 6 months of this study. At every measurement throughout the study, mean changes from baseline IOP were significantly greater with bimatoprost than with latanoprost ($p \leq 0.025$). By the end of the study, mean changes from baseline were 1.2–2.2 mmHg greater with bimatoprost than with latanoprost ($p < 0.004$). At month 6, the mean decrease from baseline IOP was 1.5 mmHg greater with bimatoprost than with latanoprost at 8 am ($p < 0.001$), 2.2 mmHg greater at 12 pm ($p < 0.001$), and 1.2 mmHg greater at 4 pm ($p < 0.004$). More patients achieved low target pressures at all times of the day in the bimatoprost group than the latanoprost group. IOPs less than or equal to 20 mmHg were achieved in 82.0–91.0% of patients treated with bimatoprost compared with 68.4–79.4% of patients treated with latanoprost. IOPs less than or equal to 15 mmHg were achieved by 20.3–36.1% of patients treated with bimatoprost compared with 17.6–25.0% of patients treated with latanoprost. The target pressure analysis in this study suggests that bimatoprost may reduce the risk of disease progression in more glaucoma and OHT patients than does latanoprost. A decrease in IOP of 15–20% from baseline is frequently used to define a clinically relevant response to a glaucoma medication [34–36] and, in the present study, the responder rate at 6 months was statistically significantly higher in the bimatoprost group than the latanoprost group at all times measured regardless of whether a therapeutically relevant response was defined as a 15 or 20% IOP decrease. The results of this study were consistent with those of earlier trials in which bimatoprost was more effective than latanoprost in lowering IOP at all time points and statistically superior in achieving low target pressures [24,37].

In a study by Parrish and colleagues [38], the IOP lowering efficacy of latanoprost was compared with that of bimatoprost and travoprost. In this large scale 12-week clinical study, there were no significant among-group differences in mean IOP but it was concluded that all were potent IOP-lowering treatments. The reason for the failure of this study to find differences in efficacy between bimatoprost and either latanoprost and travoprost is unclear, but may be due to selection biases in the patient population selected for the Parrish study. For instance, approximately half of the patients in the Parrish study were previously treated with a prostaglandin analogue and the data presented suggests that the study may have been biased to select patients responsive to prostaglandins. Detailed examination of these data is difficult, however, because results of responder analyses and achievement of target pressures were not published.

Bimatoprost in nonresponders to latanoprost

The prevalence of nonresponders to latanoprost monotherapy in human glaucomas is not presently defined. Approximately 1% of subjects enrolled in two major clinical trials and treated with latanoprost monotherapy were withdrawn because of uncontrolled IOP [39–41]. To test the efficacy of bimatoprost in patients nonresponsive to latanoprost, 15 patients with a history of lack of response (≤10%) to latanoprost after 6–8 weeks of treatment were enrolled in a randomized, investigator-masked, crossover study [41]. One eye of each subject was randomly selected for treatment with either bimatoprost or latanoprost for 30 days followed by a 30-day washout and then crossover to the other drug for 30 days of treatment. The

other eye was treated with preserved artificial tears. Once switched to bimatoprost, 13 of the 15 nonresponders showed a decrease in IOP less than or equal to 20%. No IOP changes were detected in the other untreated eye. It has been postulated that prostamides to not activate the same receptors as prostaglandins [27,41]. The lack of response to latanoprost, a prodrug, may also involve poor deesterification of the prodrug to the pharmacologically active free fatty acid. A 2-month, open-label trial where bimatoprost (alone or in combination with other drugs at the physician's discretion) was used as a replacement for latanoprost for 1283 patients. In this study, bimatoprost provided a mean decrease in IOP of 3.4 mmHg after 2 months of therapy [42]. The percentage of patients achieving a target pressure of less than or equal to 18 mmHg doubled from 33–66% ($p < 0.001$). Moreover, the percentage of patients achieving a target pressure of less than or equal to 14 mmHg increased from 6% at baseline to 26% by month 2 and those achieving a target pressure less than or equal to 15 mmHg increased from 11% at baseline to 36% by month 2 ($p < 0.001$). A subgroup analysis showed comparable improvements in IOP control regardless of the previous treatment regimen of whether bimatoprost was used alone or in combination with other medications.

Another open-label trial of bimatoprost in 21 patients not responsive (<3 mmHg IOP reduction) to latanoprost after 3 weeks of treatment saw an additional mean IOP reduction of 3.5 mmHg after 8 weeks of treatment with bimatoprost [43]. Taken together, these studies indicate that bimatoprost helps many more patients reach low target pressures when used as a replacement for latanoprost in a variety of treatment regimens.

Comparison of bimatoprost with travoprost

Travoprost has been shown to be more effective in black patients than in white patients, while bimatoprost has been shown to be equally effective. An investigator-masked, parallel-design trial compared bimatoprost with travoprost in African Americans with glaucoma or OHT [44]. After a washout, patients were assigned to bimatoprost q.d ($n = 16$) or travoprost q.d ($n = 15$) for 3 months. Study visits were at baseline and at months 1, 2, and 3. Primary outcome measures were the percentage of patients who achieved selected target pressures and the mean reduction in IOP from baseline at month 3. Both drugs comparably lowered IOP, but bimatoprost was more likely than travoprost to allow achievement of every target pressure from 12 to 19 mmHg at month 3. At 3 months, the mean IOP reduction from baseline was 8.4 mmHg (34%) in the bimatoprost group and 7.9 mmHg (30%) in the travoprost group. A second trial compared bimatoprost with travoprost in 26 patients with glaucoma or OHT for 6 months with comparable results [45]. After 6 months of therapy, both treatments provided significant mean reductions from baseline IOP at every time point ($p \leq 0.007$). Mean IOP reductions ranged from 7.4 to 8.8 mmHg (34–36%) with bimatoprost and from 4.6 to 7.2 mmHg (19–29%) with travoprost ($p \leq 0.057$) after 6 months of treatment. Again, more patients achieved low target pressures with bimatoprost than with travoprost at each time point and larger mean IOP reductions. These results are being further evaluated in larger, ongoing clinical trials.

Bimatoprost in replacement of timolol/latanoprost

When IOP is not adequately controlled with monotherapy, the physician may choose to add another medication to the patient's regimen or to replace the regimen with one that is more efficacious. The efficacy of bimatoprost monotherapy as replacement therapy was evaluated in a 4-month, open-label, multicenter, crossover evaluation of 83 patients with glaucoma or OHT [46]. Patients were treated with dual therapy with latanoprost and timolol gel-forming solution for 60 days. At day 60, patients were switched to bimatoprost monotherapy for an additional 60 days. The mean IOP at 8 am was comparable between day 60 (17.9 mmHg with timolol/latanoprost dual therapy) and day 120 (18.6 mmHg with bimatoprost monotherapy; $p = 0.084$). The majority of patients (50/83, 60.2%) achieved IOP lowering with bimatoprost monotherapy that was the same or better than that achieved with timolol/latanoprost therapy, and 76.3% of patients (61/80) were at least as satisfied with bimatoprost monotherapy as with dual timolol/latanoprost therapy. Patients were as likely to be clinically successful with bimatoprost monotherapy as with dual timolol/latanoprost therapy (65/79, 82.3% with bimatoprost compared with 68/82, 82.9% with dual timolol/latanoprost; $p > 0.999$). These findings indicate that in most patients, bimatoprost monotherapy controls IOP as effectively as dual timolol/latanoprost therapy.

Comparison of bimatoprost with timolol/dorzolamide

Bimatoprost was compared with fixed combination timolol/dorzolamide in a 3-month, randomized, controlled trial in 177 glaucoma or OHT patients who had inadequate IOP control after at least 2 weeks on timolol monotherapy [47]. Patients were randomly assigned to treatment with bimatoprost monotherapy q.d (n = 90) or timolol/dorzolamide fixed combination b.i.d (n = 87). Bimatoprost lowered mean IOP 6.8 mmHg to 7.6 mmHg from baseline at 8 am measurements, whereas combined timolol and dorzolamide lowered mean IOP 4.4–5.0 mmHg from baseline ($p < 0.001$). At the 3-month visit, patients had better diurnal IOP control with bimatoprost than with combined timolol and dorzolamide. At 8 am, the percentages of patients achieving IOPs of less than or equal to 13–16 mmHg were more than twice as great for bimatoprost than for timolol/dorzolamide (all $p \leq 0.008$). These results indicate that bimatoprost consistently provides significantly greater IOP lowering than combined timolol and dorzolamide.

Comparison of bimatoprost with timolol & pilocarpine

A 3-month, masked study assessed the effect of changing 32 patients from concomitant timolol 0.5% b.i.d and pilocarpine 2% TID to bimatoprost 0.03% q.d on ocular blood flow and IOP in primary chronic angle closure glaucoma [48]. IOP and pulsatile ocular blood flow were recorded before and after starting bimatoprost and were followed up every 4 weeks. Bimatoprost provided statistically significant ($p < 0.05$) mean IOP reduction from 19.3 ± 6.6 to 13.5 ± 4.5 mmHg (30.5%) and there was improvement from 858 ± 260 to 1261 ± 321 μL/min (46.8%) in mean pulsatile ocular blood flow ($p < 0.05$). Bimatoprost improved ocular blood flow and provided a better diurnal IOP control than concomitant timolol/pilocarpine. The improvement of ocular blood flow with bimatoprost may be useful as it is possible that improving ocular blood flow may improve visual outcomes in patients with glaucoma. However, this mechanism is still the subject of debate and definitive clinical trials are needed to conclusively demonstrate the relationship between blood flow and improving visual outcomes.

Circadian IOP control with bimatoprost

A 1-month, randomized, multicenter, investigator-masked trial compared the ability of bimatoprost, timolol gel-forming solution, and latanoprost to provide 24-hour IOP control [26]. After washout, patients with OAG or OHT were randomly assigned treatment to receive bimatoprost 0.03% q.d (n = 38), or latanoprost 0.005% q.d (n = 38) between 7 and 9 pm, or timolol gel 0.5% q.d (n = 39) between 7 and 9 am for 1 month. The primary outcome measure was circadian IOP, measured at eight time points over the course of 24 h beginning at 8 am on day 28. In the overall analysis of circadian IOP, the mean IOP was significantly lower with bimatoprost or latanoprost than with timolol gel ($p < 0.001$). At 10 am (peak drug effect) on day 28, the mean IOP reduction from baseline was significantly greater with bimatoprost (9.3 mmHg, 40.3%) than with timolol gel (7.1 mmHg, 31.1%; $p = 0.024$) or latanoprost (7.4 mmHg, 33.3%; $p = 0.022$). The results of this trial indicate that q.d bimatoprost or latanoprost provides significantly better 24 h IOP control than timolol gel in patients with glaucoma or OHT.

Bimatoprost as adjunctive therapy

Because bimatoprost lowers IOP by increasing aqueous outflow through both pressure-sensitive (trabecular) and pressure-insensitive (uveoscleral) pathways [19], bimatoprost might be expected to show additive efficacy with β-blockers, which reduce IOP by lowering the rate of aqueous humor formation. The efficacy of bimatoprost as an adjunct to topical β-blockers was investigated in a 3-month, multicenter, double-masked, randomized, vehicle-controlled, parallel-group clinical trial with study extension for the active medication to 1 year [49]. Patients uncontrolled on topical β-blockers were given adjunctive bimatoprost q.d (n = 93), bimatoprost b.i.d (n = 97), or vehicle b.i.d (n = 95) for 3 months. During this 3-month initial treatment period, adjunctive bimatoprost provided clinically and statistically significant greater IOP lowering than vehicle. Mean IOP was 3.3 to 4.5 mmHg lower with bimatoprost/β-blocker q.d than with vehicle/β-blocker at all measurements. In the study extension, patients who were continued on adjunctive bimatoprost q.d showed sustained IOP lowering throughout 1 year of treatment. At the hour 0 measurement, adjunctive bimatoprost q.d consistently provided more than 30% additional IOP lowering from the β-blocker treated baseline. These results showed that bimatoprost has outstanding efficacy as an adjunct to β-blockers.

No controlled studies of bimatoprost used adjunctively with prostaglandin therapy have yet been reported.

Postmarketing surveillance

A 2-month, open-label, noncomparative surveillance trial was undertaken to evaluate the safety and efficacy of bimatoprost for the treatment of glaucoma and OHT in clinical practices throughout the USA and Puerto Rico [50]. There were 6767 patients enrolled at 1439 clinical sites. Physicians prescribed bimatoprost as monotherapy for newly diagnosed patients (n = 1946, 28.8%), as an adjunct to one or more other medications (n = 2640, 39.0%), or as a replacement for another medication (n = 2117, 31.3%). Bimatoprost treatment provided significant IOP reductions in all three groups of patients. For newly diagnosed patients, the mean IOP reduction after 2 months of bimatoprost monotherapy was 7.9 mmHg (30.7%, $p < 0.001$). For patients who had bimatoprost added to ongoing treatment regimens, the mean additional IOP reduction with bimatoprost was 5.0 mmHg (21.3%, $p < 0.001$). For patients who were given bimatoprost in replacement of another medication, the mean IOP reduction from baseline on the previous therapy was 4.2 mmHg (18.6%, $p < 0.001$). Patients were also significantly more likely to achieve low target pressures after 2 months of bimatoprost therapy ($p < 0.001$).

These trials suggest that bimatoprost is very effective when used in clinical practice for the treatment of glaucoma and OHT. Substantial IOP reductions can be anticipated, regardless of whether bimatoprost is used alone or adjunctively with other medications.

Safety & tolerability

Bimatoprost has been proven to be safe and well tolerated with a high rate of study completion in clinical trials [21,23–25,37,47,51,52]. The most commonly reported side effect of bimatoprost therapy is trace or mild hyperemia, which may occur in approximately 14% of patients [33]. A 28-day, open-label study evaluated the onset and progression of hyperemia associated with bimatoprost once daily in 39 patients with OAG and OHT [53]. Current glaucoma medication was either replaced with or augmented by bimatoprost. Previous users of bimatoprost were excluded. Mean hyperemia scale scores for each of the three vessel beds (ciliary, conjunctival, episcleral) peaked one day after the first installation of bimatoprost and consistently decreased throughout the study. At peak hyperemia (day 1), mean severity scores ranged from low mild-to-moderate and by day 28 had returned to near-baseline levels (in the trace range of the scale). The difference between day 28 and baseline hyperemia levels was statistically significant ($p = 0.002$) only in the conjunctival vessel bed (mean score near trace). Incidence analysis revealed that treatment-related hyperemia was predominantly trace, mild, or mild-to-moderate. Moderate-to-severe or severe hyperemia was limited to a few eyes and only at days 1 through 3 to 5. No statistically or clinically significant changes occurred in corneal fluorescein staining. Consistent with other clinical studies, in an earlier 1-year comparison of bimatoprost with timolol, mean conjunctival hyperemia scores were in the trace range by the 2-week follow-up visit. Hyperemia levels continued to decrease after 4 weeks, and by 6 months no further patients discontinued participation because of hyperemia [25]. In this study, mean conjunctival hyperemia scores were between trace and mild at day 14 and were trace at day 28. The majority of patients reported they were not troubled by their ocular redness, and investigators did not believe it warranted discontinuation of therapy. These findings, together with the failure of previous studies to show an association between hyperemia and intraocular inflammation, suggest that this hyperemia is not clinically significant. Bimatoprost is an extremely effective drug that lowers IOP to the level needed for long-term preservation of visual function, a capability that far outweighs the occurrence of short-term hyperemia.

Increased iris pigmentation occurs with low incidence (1–2% of patients after 1 year of treatment) in patients treated with bimatoprost. Patients should be warned about the possibility of increased pigmentation of the eyelashes and periorbital tissue. Cystoid macular edema has occurred with low incidence.

Regulatory affairs

Bimatoprost (Lumigan®, Allergan Inc.) ophthalmic solution 0.03%, is currently available in the USA, the UK, Germany, and Italy. It has received approval for marketing in the European Union and in six Latin American countries.

Conclusion

Bimatoprost has been demonstrated to be clearly superior to timolol and has consistently provided approximately 1 mmHg greater mean IOP lowering than latanoprost in clinical trials. The greater mean IOP lowering with

bimatoprost reflects a significant difference in the percentage of patients that reached target pressures. Bimatoprost has consistently allowed more patients to reach the low target pressures that best protect the visual field. Bimatoprost provides low, stable IOP throughout the day and night, and the efficacy is sustained with long-term use. It can be concluded that bimatoprost is very effective in both monotherapy and adjunctive therapy. No safety concerns have arisen in postmarketing surveillance. Bimatoprost has proven to be a valuable agent for glaucoma therapy.

Expert opinion

Today, a goal of therapy is to reduce IOP to a target level sufficiently low to halt glaucomatous progression and preserve the visual field. Physicians have been selecting lower IOP targets for their patients than in years past. The prostamides and prostaglandins lower IOP more effectively than medications that were previously available. It is now possible for physicians to achieve 30% or greater IOP lowering in most patients with a single medication.

Bimatoprost and the prostaglandins share a similar profile of side effects. Therefore, the choice of therapy will often be made on the basis of efficacy. There are several factors to consider in evaluating efficacy of these drugs. Until the relative effectiveness of medications in preserving retinal ganglion cells and the visual field can be determined, the measures of efficacy must involve IOP. The mean IOP lowering of a drug should be considered, as well as the likelihood that patients achieve low target pressures on the drug. Another consideration should be the reliability of patient response: there may be a relatively high rate of nonresponders to latanoprost, particularly among newly diagnosed (treatment naïve) patients [54]. It may also be necessary to consider the race of the patient.

Recent clinical trials have suggested that β-blockers are more effective in Caucasian than in African-American patients [25,55]. This does not seem to be true for the prostaglandins or bimatoprost. Travoprost, however, has been shown to be less effective in Caucasians than in African-American patients, while bimatoprost is equally effective in Caucasian and African-American patients [25,44,55]. Comparison of results from separate trials suggests that travoprost and bimatoprost may be similarly effective in African-American patients, while in Caucasian patients, bimatoprost is more effective than travoprost. It will be important to compare travoprost, arguably the most efficacious of the prostaglandins, with bimatoprost in large, head-to-head trials to confirm this.

The mechanism of action of a selected medication should also be considered when choosing ocular hypotensive regimens. Different classes of medications lower IOP by different mechanisms, such as decreasing aqueous production, increasing trabecular meshwork aqueous outflow, or increasing uveoscleral outflow. Reports have suggested that medications that lower IOP by increasing trabecular outflow (pressure-sensitive outflow) may provide more stable control of IOP [20]. Mechanism of action should also be considered when selecting adjunctive agents because agents with complementary mechanisms or dual mechanisms of action may provide greater additive IOP lowering.

Further studies investigating the adjunctive use of bimatoprost are also needed. Bimatoprost has been shown to provide substantial additional IOP lowering with used adjunctively with β-blockers [49]. Additive IOP lowering with bimatoprost and the prostaglandins might also be predicted because

- The drug classes have different cellular mechanisms of action
- IOP lowering with these medications has been shown to be additive in a primate model of glaucoma [29]

Patient convenience and compliance are also important factors in selecting an ocular hypotensive regimen. Whenever possible, it is preferable to control IOP with a single medication rather than multiple medications, because every medication added to the regimen has side effects, and each added medication increases the costs of treatment. Furthermore, multiple medications may increase the patient's exposure to benzalkonium chloride (BAK), a common preservative. BAK may accumulate in ocular tissues for a lengthy period of time and at high concentrations, promote cellular damage in a dose-dependent manner [56]. Moreover, patients are more likely to be compliant with their once-a-day monotherapeutic regimen than with multiple medications given in multiple doses. The stability of the medications varies, furthermore, and this may influence the convenience of their use. Latanoprost has to be protected from light until opened, when it can be stored at temperatures up to 25°C for up to

Highlights

- Glaucoma is a multifactorial optic neuropathy characterized by the loss of retinal ganglion cells.
- Although elevated intraocular pressure (IOP) is only considered to be a risk factor in glaucoma, lowering IOP remains the only proven method of preserving the visual field in patients with the disease.
- Bimatoprost (Lumigan®, Allergan Inc.), a prostamide, is not a prodrug and is inactive at prostaglandin receptors.
- Bimatoprost has been proven to provide highly effective IOP lowering in many patients.
- Numerous studies have demonstrated that bimatoprost provides greater IOP lowering than that provided by latanoprost (Xalatan®, Pharmacia & Upjohn).
- Bimatoprost is very effective as both monotherapy and adjunctive therapy.
- No safety concerns have arisen in postmarketing surveillance.
- Bimatoprost is a convenient, once-daily medication that requires no refrigeration. These attributes may promote enhanced patient compliance.
- Bimatoprost has proven to be a valuable agent for glaucoma therapy.

6 weeks. Patients should be cautioned that exposure of the medication container to sunlight or high temperatures causes degradation of the drug [57]. Travoprost does not require refrigeration if stored at or below 25°C. Bimatoprost is also stable, and it can be stored at room temperatures up to 25°C. Most patients can be switched from timolol/latanoprost dual therapy to bimatoprost monotherapy without experiencing a change in IOP [46], and bimatoprost monotherapy is as effective or more effective than timolol/dorzolamide fixed combination treatment [47].

A final factor that might influence treatment decisions is cost. Treatment with either latanoprost or travoprost treatment may cost approximately 30% more than treatment with bimatoprost [58].

Outlook

As our understanding of the pathophysiology of glaucoma continues to evolve, so too will our ability to treat and, perhaps one day, prevent this disease. Neuroprotection, or the ability to preserve the function of the retinal ganglion cells, may become an important part of the treatment of glaucoma in the future. Currently, however, the available data present a compelling argument that the preservation of the visual field in glaucoma is best accomplished through early and aggressive IOP-lowering and this is unlikely to change in the immediate future.

Disclaimer

Neither author has any proprietary interest in bimatoprost, Allergan, or any pharmacologic agent discussed in this review.

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