Patient considerations in ocular hypertension: role of bimatoprost ophthalmic solution

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Abstract: Glaucoma is a leading cause of irreversible blindness worldwide. The reduction of intraocular pressure has been well established as an effective treatment to prevent both the development and the progression of all forms of glaucoma. Bimatoprost 0.03% ophthalmic solution, introduced in 2001, is a synthetic prostamide with the unique mechanism of improving both uveoscleral and trabecular outflow. Comparative studies with other pharmacotherapies have shown favorable results for bimatoprost as a potent ocular hypotensive agent that is generally well tolerated. Common side effects include conjunctival hyperemia, eyelash growth, iris pigmentation and periorbital changes. Hyperemia rates were reduced following the introduction of bimatoprost 0.01%. Bimatoprost should be used with caution in those with higher risk of developing ocular inflammation and macular edema. However, the perceived risk of bimatoprost in these patient populations is likely greater than the actual risk observed in practice. Bimatoprost is currently in the center of several clinical trials including its use for dermatologic applications and sustained-release therapies for the treatment of ocular hypertension and glaucoma.

Keywords: bimatoprost, ocular hypertension, glaucoma

Introduction

Glaucoma is a group of diseases that is characterized by a progressive optic neuropathy that can result in permanent vision loss of varying severity. The pathology of glaucoma is an accelerated loss of the retinal ganglion cells and axons resulting in characteristic structural changes in the optic nerve, resulting in loss of peripheral and central vision, typically without symptoms until later stages. To date, there is no proven treatment to repair or replace the ganglion cell and axonal loss that occurs in glaucoma. Thus, the functional loss manifested by defects in visual field is permanent. Although there are many postulated contributory factors to the development of glaucoma, the precise mechanisms are not fully elucidated. There is robust evidence that for most patients, reduction of intraocular pressure (IOP) not only slows the rate of structural and functional progression in those with glaucomatous optic neuropathy but also reduces the development of glaucoma in those with ocular hypertension (OHT).3

Glaucoma is the leading cause of irreversible blindness on a global scale. Currently, glaucoma is estimated to affect >70 million people worldwide, 10% of whom are blind in both eyes.4 Population-based surveys have estimated that 4%–10% of those aged >40 years have OHT – or elevated IOP without glaucoma damage.5,6 In the setting of a rapidly growing and aging population, the prevalence of glaucoma is expected to nearly double from 2013 to 2040.7

The Ocular Hypertension Treatment Trial1 demonstrated the benefits of IOP lowering in reducing the development of glaucomatous damage in those with OHT.
Other robust and well-designed randomized controlled trials clearly demonstrated the role of IOP reduction in slowing the rates of glaucomatous progression.\textsuperscript{1–3,8–11} IOP remains the only proven modifiable risk factor, which is currently treated by various classes of medications, lasers and surgical modalities. The extent of IOP lowering is individualized to each patient based on a number of factors including, but not limited to, stage of disease, perceived rate of glaucoma progression and general health status/life expectancy. This IOP target must be readjusted based on the perceived stability or instability of a patient.\textsuperscript{12,13}

Medical therapy for glaucoma is considered a mainstay of treatment. As with medical therapy for any condition, the goal is high effectiveness, tolerability and access with minimal side effects. The different medication classes available currently modify IOP through different mechanisms of action. Currently, the five different classes of topical medications available are beta-blockers, carbonic anhydrase inhibitors (CAIs), sympathomimetics, prostaglandin derivatives and miotics. Among these, the prostaglandin analog class of medication has assumed the role of first-line medical therapy for glaucoma due to its demonstrated efficacy, high tolerability and low systemic side effects with once-daily dosing. Prior to this medication class, the available topical medications required more frequent dosing with a higher local and systemic side-effect profile. Although generally grouped together as a class of medication, there are molecular differences between the prostaglandin analogs. While beta-blockers, CAIs and alpha-agonists primarily affect aqueous humor production, the prostaglandin class enhances aqueous outflow via the uveoscleral passage.\textsuperscript{14}

In cases where treatment of OHT is chosen, the risk of glaucoma progression is judged to be sufficient to warrant the burdens of therapy. However, this treatment is preventative and will likely be prolonged. Therefore, there is a need to balance drug efficacy against drug tolerability and convenience. Once-daily prostaglandin analogs are often the drug of choice in OHT given the class’ efficacy, once-daily dosing and general tolerability for most patients.

Bimatoprost ophthalmic solution (Lumigan; Allergan Inc., Irvine, CA, USA) is a prominent member of the prostaglandin analog class of medications introduced in 2001 for the lowering of IOP in patients with glaucoma and OHT. It is commonly a first-line medication implemented in treatment. This study reviews the current properties and clinical effectiveness, as well as future applications of bimatoprost in the management of glaucoma and OHT.

**Pharmacology and mechanism of action**

Although often broadly categorized into the prostaglandin class, bimatoprost is actually a synthetic prostamide analog, which is structurally distinct from other prostaglandin analogs.\textsuperscript{14,15} In contrast to the acidic prostaglandins, prostamides lack a carboxylic acid group in their chemical structure, rendering them neutral in solution. Several studies have suggested the presence of unique prostamide sensitive receptors that differ from the receptors of other prostaglandin analogs.\textsuperscript{15–19} This has been subsequently supported by the discovery of prostamide antagonists.\textsuperscript{20} However, to date, no receptor unique for bimatoprost has yet been cloned, and this point remains controversial. After topical instillation, a significant quantity of intact bimatoprost has been found in the ciliary body.\textsuperscript{21,22} Bimatoprost has also been found in its hydrolyzed free-acid form in the aqueous, suggesting that it enters the anterior chamber via the cornea as a prodrug as well.\textsuperscript{23,24}

Like other medications in the prostaglandin class, bimatoprost primarily exerts its therapeutic effect by increasing uveoscleral outflow. However, several studies have shown a bimodal action with the improved trabecular outflow facility as well.\textsuperscript{22,25} The increased outflow is thought to occur by the remodeling of the extracellular matrix in the ciliary muscle.\textsuperscript{26} Other proposed mechanisms include modifying the permeability of tissues in the outflow pathways. It has also been suggested that scleral penetration appears to be the preferred route of ocular entry to access the trabecular meshwork and ciliary body.\textsuperscript{21,22} Although other studies have supported corneal entry as well, as noted earlier.\textsuperscript{23,24}

Bimatoprost ophthalmic solution is a clear, colorless, isotonic solution that uses benzalkonium chloride as the preservative. Bimatoprost after systemic absorption resides mainly in the plasma, with no identified systemic accumulation after achieving steady-state concentrations. Storage of bimatoprost does not require refrigeration, and it can be stored in the original container at 15°C–25°C.\textsuperscript{27}

**Clinical effectiveness**

The prostaglandin class is considered first-line medical therapy in the management of OHT and glaucoma. The lower side-effect profile and high clinical efficacy with once-daily dosing enabled this class of medication to quickly supplant beta-blocker class from this previously held position. The mechanism of action through enhanced uveoscleral and trabecular outflow, although not fully elucidated, complements the other available classes of medicine that
predominantly decrease aqueous formation. Bimatoprost ophthalmic solution 0.03% has been available for use since 2001 in the US.

Many clinical trials have demonstrated the efficacy of bimatoprost in lowering IOP. In the Phase II/III studies, and in the post marketing surveillance studies, the once-daily dosing of bimatoprost lowered IOP from 7.2 to 8.1 mmHg.\textsuperscript{15,28–32} Bimatoprost demonstrated greater efficacy given both once or twice daily when compared to 0.5% timolol maleate in two randomized, controlled, double-blinded trials. These trials showed an ~8.1 mmHg reduction in IOP with bimatoprost compared to 5.6 mmHg with timolol 0.5% twice daily. Furthermore, significantly greater proportions of patients reached the predetermined target IOP lowering in the bimatoprost groups versus the timolol 0.5% groups.\textsuperscript{15,28–32} Once-daily evening dosing was determined to be the most effective dosing schedule – with greater effectiveness in reducing IOP compared to AM dosing or twice-daily dosing.

While many studies demonstrate similar IOP lowering among the members of the prostaglandin class, a 6-month randomized comparison\textsuperscript{33} and a meta-analysis of 4 randomized controlled studies\textsuperscript{34} suggest a slightly greater mean IOP reduction with bimatoprost in glaucoma. Similar results were demonstrated in normal tension glaucoma.\textsuperscript{35} In another study, while bimatoprost and latanoprost achieved statistically significant IOP lowering, greater diurnal efficacy with bimatoprost was observed over a 30-day period.\textsuperscript{29} When used as a replacement therapy for latanoprost in those patients not achieving their target IOP, bimatoprost has been demonstrated to reduce IOP 2.8–4.4 mmHg.\textsuperscript{36}

In a comparison study, bimatoprost 0.01% was equivalent to bimatoprost 0.03% in lowering IOP throughout 12 months of treatment.\textsuperscript{37} Differences in IOP remained <0.9 mmHg through all time points. In addition, reported adverse ocular events were significantly less frequent and severe with the 0.01% concentration. Due to the superior benefit-to-risk ratio seen in the lower concentration formula, bimatoprost 0.01% was approved and is the primary concentration available for commercial use currently in the US.\textsuperscript{38}

Bimatoprost 0.03% is also available outside the US in a fixed-combination formulation with 0.5% timolol maleate (Ganfort; Allergan Inc.). The superior effectiveness of a fixed combination bimatoprost/timolol compared to the individual components has been demonstrated with a safety profile similar to the individual agents.\textsuperscript{39} The fixed combination theoretically offers advantages of complementary mechanisms of action with reduced preservative burden. Improved medication adherence and cost-effectiveness may result from less complicated dosing when patients require multiple medications to achieve target pressures.\textsuperscript{40} Bimatoprost 0.03% in a fixed combination with timolol maleate 0.5% is also available in a preservative-free formulation outside the US. The preservative-free formulation demonstrated equivalence in IOP lowering with no differences in safety and tolerability and may have a role in those patients with known benzalkonium chloride intolerance or ocular surface disease.\textsuperscript{41}

**Common side effects**

Once-daily dosing of bimatoprost has been shown to have a favorable safety profile and is a well-tolerated eyedrop.\textsuperscript{32} However, it is not without its adverse effects. Though most of these effects tend to be mild and short-lived, it is important to be aware of potential adverse effects.

**Conjunctival hyperemia**

By far, the most common adverse event seen with bimatoprost is conjunctival hyperemia, affecting up to 50% of patients.\textsuperscript{42} Several studies have reported its incidence to be the highest in bimatoprost 0.03% compared to other prostaglandin analogs.\textsuperscript{35,44} However, the hyperemia is typically mild, transient and infrequently cited as a cause of drop discontinuation, which was seen in 3%.\textsuperscript{17} In one study, hyperemia peaked 1 day after commencing bimatoprost, and severity progressively declined at each visit during the 6-week study.\textsuperscript{45} Patients already on prostaglandin therapy were less likely to experience an increase in hyperemia when switched to bimatoprost, further demonstrating the transient nature and potentially shared mechanism of hyperemia associated with prostaglandin analogs.\textsuperscript{42,46} Bimatoprost 0.01% demonstrated a reduced incidence (28.6% vs 37.4%) and severity of hyperemia compared to the 0.03% solution, resulting in a lower discontinuation rate with similar effectiveness in IOP reduction.\textsuperscript{37}

The mechanism by which bimatoprost produces conjunctival hyperemia is not fully understood. Due to the pro-inflammatory nature of prostaglandins, ocular inflammation is often thought to be the cause of conjunctival hyperemia. However, no associations have been made between signs of inflammation and bimatoprost-induced hyperemia. Histopathologic evidence of inflammation was infrequent in conjunctival specimens from bimatoprost-treated eyes (22%) and no more frequent compared to untreated controls (33%).\textsuperscript{47} One study showed an induction in nitrous oxide (NO) synthase and NO-induced vasodilation as a potential cause of prostaglandin-related hyperemia.\textsuperscript{48}
Eyelash growth
Prostaglandins have long been known to be associated with increasing the length, number, thickness and pigmentation of eyelashes. This finding was especially pronounced in bimatoproct in one study comparing several prostaglandin analogs and their effect on eyelash growth in rabbits. Hypertrichosis is the most common non-ocular side effect of bimatoprost and is observed in 42.6%–53.6% of patients. Although the actual molecular mechanism is yet unclear, bimatoprost has been shown to significantly extend the duration of anagen (growth phase) in mouse eyelashes. This benign side effect has been leveraged to commercially market bimatoprost as a cosmetic product for lash growth (Latisse; Allergan Inc.).

Iris pigmentation
Bimatoprost, along with the other prostaglandin analogs, has been reported to cause increased iris pigmentation. This finding was observed in 1.9% of eyes after 1 year of bimatoprost. By comparison, 12% of US patients on latanoprost experienced iris color changes. The same study found that homogeneously blue or dark brown irides were seldom affected while eyes with heterogeneously pigmented eyes were more frequently affected. Histopathologic studies showed an increase in melanosomes rather than an increase in melanocytes. This is mediated by a prostaglandin-induced upregulation of tyrosinase, a key enzyme in melanogenesis. Iris color changes have not been shown to improve following drop cessation. Therefore, patients should be properly counseled of potential permanent iris color changes, especially those who have hazel, green or heterogeneously pigmented irides.

Periocular skin pigmentation
Increased periocular skin pigmentation has also been reported with prolongued use of bimatoprost. A total of 6% of patients treated with bimatoprost 0.03% experienced increased eyelid skin pigmentation after 1 year compared to 1% with latanoprost. Like the iris, the increase in pigmentation is a result of an increase in melanosomes in dermal melanocytes. The pigmentary changes are typically mild and reversible after the drug is discontinued and were less frequently observed with the 0.01% preparation.

Structural eyelid and peri orbital changes
Chronic use of bimatoprost can result in deepening of upper eyelid sulcus (DUES), relative enophthalmos, loss of lower eyelid fullness and involution of dermatochalasis. The conglomeration of these findings was later termed prostaglandin-associated peri orbital syndrome (PAPS). Lipodystrophy characterized by fat atrophy and decreased adipocyte density has been described as a potential mechanism. Although the abovementioned periorbitopathies have been observed in all prostaglandin analogs, it tends to be more frequent and severe in bimatoprost users. The presence of DUES was observed in 60% of patients 6 months after replacing latanoprost with bimatoprost. Symptoms were mild and were noticed by 53% of those with documented changes with only one dropping from the study due to DUES. Conversely, 85% of those switching from bimatoprost to latanoprost experienced a reduction or resolution of DUES after 6 months. While periorbitopathy implies pathology, bimatoprost-associated peri orbital changes have been leveraged to improve cosmesis for those with dermatochalasis, a concept termed “chemical blepharoplasty.” In patients undergoing unilateral therapy, this potential side effect should be considered given its greater noticeability.

Uncommon adverse events
Serious adverse events, although fortunately rare, have been reported, and the drop should be initiated with appropriate caution in those who are potentially at risk for developing these effects.

Uveitis
The use of prostaglandin analogs in patients with inflammatory glaucoma has been controversial due to the theoretically higher risk of anterior uveitis, cystoid macular degeneration and reactivation of herpes simplex virus (HSV) keratitis. Smith et al published a review of 527 patients treated with latanoprost, and 1% (5/505) of patients without a prior history of uveitis developed ocular inflammation, while 23% (3/13) with a prior history of uveitis experienced a flare up. All patients improved after discontinuing latanoprost. Several cases have been reported in other prostaglandin analogs, including bimatoprost.

In contrast, Fortuna et al published a review of patients on bimatoprost in a uveitis subspecialty clinic that showed no increase in risk of flares compared to non-prostaglandin glaucoma drops. The rate of uveitis flares was 52 per 100 person-years while on non-prostaglandin drops, whereas it was 32.4 per 100 person-years while on bimatoprost. Chang et al published a similar study again showing no increase in flares with prostaglandin analogs compared to non-prostaglandin drops. Of note, both the studies were done at tertiary uveitis subspecialty clinics where many patients were controlled on immunomodulatory therapy.

The use of bimatoprost may be considered for uveitic patients especially in those with quiescent and well-controlled...
disease. Although the rate of developing uveitis is relatively infrequent, the consequences of uncontrolled and unrecognized ocular inflammation can be deleterious. Patients should be properly counseled and monitored for reactivation of inflammation after initiating therapy.

**Macular edema**

Cystoid macular edema (CME) is thought to arise from the release of endogenous inflammatory mediators, including prostaglandins. This raises the possibility of topical prostaglandins inducing CME. The incidence of CME in pseudophakic and aphakic eyes on prostaglandin analogs is ~1%–2%.\(^6^6\) The incidence of CME is significantly higher at 5% in aphakic or pseudophakic eyes with posterior capsular defects.\(^7^0\) Ayyala et al\(^7^1\) reported several cases of CME that occurred shortly after initiation of latanoprost with resolution after discontinuation of the medication. On the other hand, Chang et al reported that 69 patients with uveitis and no prior evidence of CME did not develop CME with prostaglandins.\(^6^3\) Further, a meta-analysis revealed that the incidence of CME associated with bimatoprost was exceedingly rare at 0.3% (1/306).\(^7^2\)

Many of the cases reported to date are confounded by other contributing risk factors that may cause CME alone.\(^7^3\) Although the current evidence of prostaglandins relationship with the development of CME is inconclusive, patients with other contributing risk factors or a previous history of CME should be placed on bimatoprost with caution and proper monitoring.

**No evidence for effect on pigmented tumors**

There is a lack of evidence linking bimatoprost and other topical prostaglandin analogs with malignant melanoma. There is one case of cutaneous melanoma reported with bimatoprost use.\(^7^4\) The same holds true for latanoprost with no cases or ocular melanoma and only three cases of cutaneous melanoma among 19,940 subjects.\(^7^5\) In addition, pigmented iris nevi were not noted to be affected after long-term use of topical prostaglandin agonists.\(^5^1\)

**Potential dermatologic applications**

The tendency of topical bimatoprost to cause increased skin pigmentation and promote hair growth has been harnessed in several dermatologic conditions. It has been used to treat facial and non-facial vitiligo with moderate success.\(^7^6\) Other applications include the treatment of eyebrow hypotrichosis and alopecia areata.\(^7^7\) Early study results are promising; however, larger and long-term trials are pending.

**Sustained-release delivery systems**

Medication adherence remains a very important and complex issue in glaucoma management, prompting the search for new modes of drug delivery. Studies have repeatedly demonstrated poor rates of medication compliance. One study reported that 50% of subjects were not adhering to their medications 75% of the time despite receiving medications free of charge and knowing they were being monitored.\(^7^8\) Sustained delivery systems bring the promise of substantially improved glaucoma care by eliminating the medication adherence problem. Several companies are currently developing sustained-release devices as vehicles for bimatoprost.

A bimatoprost sustained-release implant (bimatoprost SR), a depot implant injected into the anterior chamber, is currently undergoing Phase III trials. Phase II trials of the implant showed a mean IOP reduction of –7.2 to –9.5 mmHg from baseline in 75 eyes 16 weeks following injection. The fellow eyes received once-daily topical bimatoprost 0.03% and experienced an IOP reduction of –8.4 mmHg. Rescue treatment was not required in 91% and 71% at months 4 and 6, respectively. Conjunctival hyperemia was less frequently seen with the depot bimatoprost affecting 6.7% of eyes compared to 17.3% receiving topical therapy.\(^7^9\)

A topical ocular ring impregnated with bimatoprost has also been developed and recently completed Phase II trials. The ring is positioned under the upper and lower eyelids and rests in the conjunctival fornices. There was a mean reduction from baseline IOP of –3.2 to –6.4 mmHg for the bimatoprost implant group compared with –4.2 to –6.4 mmHg for the timolol 0.5% group over 6 months. The study did not meet the non-inferiority definition for the majority of time points. The retention rate of the ocular ring was 88.5% at 6 months.\(^8^0\)

**Conclusion**

Since its introduction in 2001, bimatoprost has been well established as a potent ocular hypotensive agent. Numerous studies have demonstrated that bimatoprost effectively and sustainably decreases IOP. This is achieved by improved outflow through the trabecular and uveoscleral pathways. This dual mechanism is unique to bimatoprost, making it an especially potent compound for the pharmacotherapy of glaucoma and OHT. Comparative studies have demonstrated a superior IOP-lowering effect compared to other prostaglandin analogs and fixed-combination agents. Bimatoprost is well tolerated, and adverse events are generally mild and self-limiting. The release of the 0.01% formulation has further improved tolerability compared to the original 0.03%.
Conjunctival hyperemia, eyelash growth and periocular pigmentation have been reported to occur more frequently with bimatoprost compared with other prostaglandins. These effects are generally mild and transient. Cases of increased iris pigmentation are likely permanent and will not resolve despite cessation of therapy. Although these adverse effects do not have significant consequences to visual functioning and are cosmetic in nature, patients should be properly counseled and educated regarding these potential effects prior to initiating therapy. Bimatoprost should be used with caution in eyes with active or previous macular edema, uveitis and herpetic keratitis. These events are fortunately rare, and their direct relationship with bimatoprost use is yet to be established.

Topical agents are effective, but high rates of patient non-adherence have limited therapeutic success. Bimatoprost is currently being investigated in sustained-release delivery systems. Although these novel delivery systems may reduce the problem of medication adherence and the incidence of side effects, addressing adverse effects may prove to be difficult after the administration of a depot. It is yet unclear how these novel delivery systems will be accepted among patients and physicians, and their place in the growing spectrum of ocular hypotensive therapies is yet to be determined.

**Disclosure**

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**References**

1. Parrish RK 2nd, Feuer WJ, Schiffman JC, Lichter PR, Musch DC; CIGTS Optic Disc Study Group. Five-year follow-up optic disc findings of the Collaborative Initial Glaucoma Treatment Study. *Am J Ophthalmol.* 2009;147(4):717.e1–724.e1.
2. Heijl A, Leske MC, Bengtsson B, et al. Reduction of intraocular pressure and glaucoma progression: results from the Early Manifest Glaucoma Trial. *Arch Ophthalmol.* 2002;120(10):1268–1279.
3. Kass MA, Heuer DK, Higginbotham EJ, et al. The Ocular Hypertension Treatment Study: a randomized trial determines that topical ocular hypotensive medication delays or prevents the onset of primary open-angle glaucoma. *Arch Ophthalmol.* 2002;120(6):701–713. Discussion 829–830.
4. Quigley HA, Broman AT. The number of people with glaucoma worldwide in 2010 and 2020. *Br J Ophthalmol.* 2006;90(3):262–267.
5. Leske MC, Connell AM, Wu SY, Hyman L, Schachat AP. Distribution of intraocular pressure. The Barbados Eye Study. *Arch Ophthalmol.* 1997;115(8):1051–1057.
6. Quigley HA, Enger C, Katz J, Sommer A, Scott R, Gilbert D. Risk factors for the development of glaucomatous visual field loss in ocular hypertension. *Arch Ophthalmol.* 1994;112(5):644–649.
7. Tham YC, Li X, Wong TY, Quigley HA, Aung T, Cheng CY. Global prevalence of glaucoma and projections of glaucoma burden through 2040: a systematic review and meta-analysis. *Ophthalmology.* 2014;121(11):2081–2090.
8. [No authors listed] Comparison of glaucomatous progression between untreated patients with normal-tension glaucoma and patients with therapeutically reduced intraocular pressures. Collaborative Normal-Tension Glaucoma Study Group. *Am J Ophthalmol.* 1998;126(4):487–497.
9. Anderson DR; Normal Tension Glaucoma Study. Collaborative normal tension glaucoma study. *Curr Opin Ophthalmol.* 2003;14(2):86–90.
10. Musch DC, Gillespie BW, Lichter PR, Niziol LM, Janz NK; CIGTS Study Investigators. Visual field progression in the Collaborative Initial Glaucoma Treatment Study the impact of treatment and other baseline factors. *Ophthalmology.* 2009;116(2):200–207.
11. [No authors listed] The Advanced Glaucoma Intervention Study (AGIS): 7. The relationship between control of intraocular pressure and visual field deterioration. The AGIS Investigators. *Am J Ophthalmol.* 2000;130(4):429–440.
12. Prum BE Jr, Rosenberg LF, Gedde SJ, et al. Primary open-angle glaucoma preferred practice pattern(R) guidelines. *Ophthalmology.* 2016;123(1):P41–P111.
13. Weinreb RN, Aung T, Medeiros FA. The pathophysiology and treatment of glaucoma: a review. *JAMA.* 2014;311(18):1901–1911.
14. Alexander CL, Miller SJ, Abel SR. Prostaglandin analog treatment of glaucoma and ocular hypertension. *Ann Pharmacother.* 2002;36(3):504–511.
15. Patil AV, Vajaranant TS, Edward DP. Bimatoprost – a review. *Expert Opin Pharmacother.* 2009;10(16):2759–2768.
16. Davies SS, Ju WK, Neufeld AH, Abaran D, Chemtob S, Roberts LJ 2nd. Hydrolysis of bimatoprost (Lumigan) to its free acid by ocular tissue in vitro. *J Ocul Pharmacol Ther.* 2003;19(1):45–54.
17. Eisenberg DL, Toris CB, Camras CB. Bimatoprost and travoprost: a review of recent reviews of two new glaucoma drugs. *Surv Ophthalmol.* 2002;47(suppl 1):S105–S115.
18. Hellberg MR, Ke TL, Haggard K, Klimko PG, Dean TR, Graff G. The hydrolysis of the prostaglandin analog prodrug bimatoprost to 17-phenyl-trinor PGF2alpha by human and rabbit ocular tissue. *J Ocul Pharmacol Ther.* 2003;19(2):97–103.
19. Maxey KM, Johnson JL, LaBreque J. The hydrolysis of bimatoprost in corneal tissue generates a potent prostanoid FP receptor agonist. *Surv Ophthalmol.* 2002;47(suppl 1):S34–S40.
20. Woodward DF, Krauss AH, Wang JW, et al. Identification of an antagonist that selectively blocks the activity of prostamides (prostaglandin-ethanolamides) in the feline iris. *Br J Pharmacol.* 2007;150(3):342–352.
21. Krauss AH, Woodward DF. Update on the mechanism of action of bimatoprost: a review and discussion of new evidence. *Surv Ophthalmol.* 2004;49(suppl 1):S5–S11.
22. Woodward DF, Krauss AH, Chen J, et al. Pharmacological characterization of a novel antiglaucoma agent, Bimatoprost (AGN 192024). *J Pharmacol Exp Ther.* 2003;305(2):772–785.
23. Camras CB, Toris CB, Sjoquist B, et al. Detection of the free acid of bimatoprost before cataract surgery. *Ophthalmology.* 2003;111(12):2193–2198.
24. Cantor LB, Hoop J, Wudunn D, et al. Levels of bimatoprost acid in the aqueous humour after bimatoprost treatment of patients with cataract. *Br J Ophthalmol.* 2007;91(5):629–632.
25. Christiansen GA, Nau CB, McLaren JW, Johnson DH. Mechanism of ocular hypotensive action of bimatoprost (Lumigan) in patients with ocular hypertension or glaucoma. *Ophthalmology.* 2004;111(9):1658–1662.
26. Brubaker RF, Schoff EO, Nau CB, Carpenter SP, Chen K, Vandenburgh AM. Effects of AGN 192024, a new ocular hypotensive agent, on aqueous dynamics. *Am J Ophthalmol.* 2001;131(1):19–24.
27. Johnson TV, Gupta PK, Vudathala DK, Blair IA, Tanna AP. Thermal stability of bimatoprost, latanoprost, and travoprost under simulated daily use. *J Ocul Pharmacol Ther.* 2011;27(1):51–59.
28. Brandt JD, VanDenburgh AM, Chen K, Whitcup SM; Bimatoprost Study Group. Comparison of once- or twice-daily bimatoprost with twice-daily timolol in patients with elevated IOP: a 3-month clinical trial. *Ophthalmology*. 2001;108(6):1023–1031. Discussion 1032.

29. Dubiner H, Cooke D, Dirks M, Stewart WC, VanDenburgh AM, Felix C. Efficacy and safety of bimatoprost in patients with elevated intraocular pressure: a 30-day comparison with latanoprost. *Surv Ophthalmol*. 2001;45(suppl 4):S53–S360.

30. Gandolfi S, Simmons ST, Sturm R, Chen K, VanDenburgh AM; Bimatoprost Study Group. Three-month comparison of bimatoprost and latanoprost in patients with glaucoma and ocular hypertension. *Adv Ther*. 2001;18(3):110–121.

31. Laibovitz RA, VanDenburgh AM, Felix C, et al. Comparison of the ocular hypertensive lipid AGN 192024 with timolol: dosing, efficacy, and safety evaluation of a novel compound for glaucoma management. *Arch Ophthalmol*. 2001;119(7):994–1000.

32. Sherwood M, Brandt J; Bimatoprost Study Group. Six-month comparison of bimatoprost once-daily and twice-daily with timolol twice-daily in patients with elevated intraocular pressure. *Surv Ophthalmol*. 2001;45(suppl 4):S361–S368.

33. Noecker RS, Dirks MS, Cholin NT, et al. A six-month randomized clinical trial comparing the intraocular pressure-lowering efficacy of bimatoprost and latanoprost in patients with ocular hypertension or glaucoma. *Am J Ophthalmol*. 2003;135(5):55–63.

34. Simmons ST, Dirks MS, Noecker RJ. Bimatoprost versus latanoprost in lowering intraocular pressure in glaucoma and ocular hypertension: results from parallel-group comparison trials. *Adv Ther*. 2004;21(4):247–262.

35. Dirks MS, Noecker RJ, Earl M, Roh S, Silverstein SM, Williams RD. A 3-month clinical trial comparing the IOP-lowering efficacy of bimatoprost and latanoprost in patients with normal-tension glaucoma. *Adv Ther*. 2006;23(3):385–394.

36. Myers JS, Vold S, Zaman F, Williams JM, Hollander DA. Bimatoprost 0.01% or 0.03% in patients with glaucoma or ocular hypertension previously treated with latanoprost: two randomized 12-week trials. *Clin Ophthalmol*. 2014;8:643–652.

37. Katz LJ, Cohen JS, Batoosingh AL, Felix C, Shu V, Schiffman RM. Twelve-month, randomized, controlled trial of bimatoprost 0.1%, 0.0125%, and 0.03% in patients with glaucoma or ocular hypertension. *Am J Ophthalmol*. 2010;149(4):661,666–671,661.

38. U.S. Food and Drug Administration CDEAR. *Lumigan NDA 22–184*. Available from: http://www.accessdata.fda.gov/drugsatfda/docs/nda/2010/022184Orig1s000SumR.pdf. Accessed February 11, 2017.

39. Brandt JD, Cantor LB, Katz LJ, et al. Bimatoprost/timolol fixed combination: a 3-month double-masked, randomized parallel comparison to its individual components in patients with glaucoma or ocular hypertension. *J Glaucoma*. 2008;17(3):211–216.

40. Gehle M, Mayer JR, Siam GA, Monteiro de Barros DS, Thomas TL, Katz LJ. Managing refractory glaucoma with a fixed combination of bimatoprost (0.03%) and timolol (0.5%). *Clin Ophthalmol*. 2008;2(1):15–20.

41. Goldberg I, Gil Pina R, Lanzagorta-Asle A, Schiffman RM, Liu C, Bejanian M. Bimatoprost 0.03%/timolol 0.5% preservative-free ophthalmic solution versus bimatoprost 0.03%/timolol 0.5% ophthalmic solution (Ganfort) for glaucoma or ocular hypertension: a 12-week randomised controlled trial. *Br J Ophthalmol*. 2014;98(7):926–931.

42. Kurtz S, Mann O. Incidence of hyperemia associated with bimatoprost treatment in naive subjects and in subjects previously treated with latanoprost. *Eur J Ophthalmol*. 2009;19(3):400–403.

43. Honrubia F, Garcia-Sanchez J, Polo V, de la Casa JM, Soto J. Conjunctival hyperaemia with the use of latanoprost versus other prostaglandin analogues in patients with ocular hypertension or glaucoma: a meta-analysis of randomised clinical trials. *Br J Ophthalmol*. 2009;93(3):316–321.

44. Parrish RK, Palmberg P, Shue WP, XLT Study Group. A comparison of latanoprost, bimatoprost, and travoprost in patients with elevated intraocular pressure: a 12-week, randomized, masked-evaluator multicenter study. *Am J Ophthalmol*. 2003;135(5):688–703.

45. Trattler W, Noecker RJ, Earl ML. A multicentre evaluation of the effect of patient education on acceptance of hyperaemia associated with bimatoprost therapy for glaucoma or ocular hypertension. *Adv Ther*. 2008;25(3):179–189.

46. Craven ER, Liu CC, Batoosingh A, Schiffman RM, Whitcup SM. A randomized, controlled comparison of macroscopic conjunctival hyperemia in patients treated with bimatoprost 0.01% or vehicle who were previously controlled on latanoprost. *Clin Ophthalmol*. 2010;4:1433–1440.

47. Leal BC, Medeiros FA, Medeiros FW, Santo RM, Susanna R Jr. Conjunctival hyperemia associated with bimatoprost use: a histopathologic study. *Am J Ophthalmol*. 2004;138(2):310–313.

48. Astin M, Stjernschantz J, Selen G. Role of nitric oxide in PGF2α-induced ocular hyperemia. *Exp Eye Res*. 1994;59(4):401–407.

49. Johnstone MA. Hypertrichosis and increased pigmentation of eyelashes and adjacent hair in the region of the ipsilateral eyelids of patients treated with unilateral topical latanoprost. *Am J Ophthalmol*. 1997;124(4):544–547.

50. Gianiconi AT, Lima L, Russ HH, Montiani-Ferreira F. Eyelash growth induced by topical prostaglandin analogues, bimatoprost, tafluprost, travoprost, and latanoprost in rabbits. *J Ocul Pharmacol Ther*. 2013;29(9):817–820.

51. Higginbotham EJ, Schuman JS, Goldberg I, et al. One-year, randomised study comparing bimatoprost and timolol in glaucoma and ocular hypertension. *Arch Ophthalmol*. 2002;120(10):1286–1293.

52. Tauchi M, Fuchs TA, Kellenberger AJ, Woodward DF, Paus R, Lutjen-Drecoll E. Characterization of an in vivo model for the study of eyelash biology and trichomegaly: mouse eyelash morphology, development, growth cycle, and anagen prolongation by bimatoprost. *Br J Dermatol*. 2010;162(6):1186–1197.

53. Wistrand PJ, Stjernschantz J, Olsson K. The incidence and time-course of latanoprost-induced iridal pigmentation as a function of eye color. *Surv Ophthalmol*. 1997;41(suppl 2):S129–S138.

54. Stjernschantz JW, Albert DM, Hu DN, Drago F, Wistrand PJ. Mechanism and clinical significance of prostaglandin-induced iris pigmentation. *Surv Ophthalmol*. 2002;47(suppl 1):S162–S175.

55. Sharpe ED, Reynolds AC, Skuta GL, Jenkins JN, Stewart WC. The clinical impact and incidence of periorcular pigmentation associated with either latanoprost or bimatoprost therapy. *Curr Eye Res*. 2007;32(12):1037–1043.

56. Kapur R, Osmanovic S, Toyran S, Edward DP. Bimatoprost-induced periorcular skin hyperpigmentation: histopathological study. *Arch Ophthalmol*. 2005;123(11):1541–1546.

57. Doshi M, Edward DP, Osmanovic S. Clinical course of bimatoprost-induced periorcular skin changes in Caucasians. *Ophthalmology*. 2006;113(11):1961–1967.

58. Filippopoulos T, Pauls JS, Torun N, Hatton MP, Pasquale LR, Grosskreutz CL. Periorbital changes associated with topical bimatoprost, travoprost, and latanoprost. *Jpn J Ophthalmol*. 2011;55(1):22–27.

59. Kucukcevecioglu M, Bayer A, Uysal Y, Altinsoy HI. Prostaglandin associated periocular pigmentation in patients using bimatoprost, latanoprost and travoprost. *Clin Exp Ophthalmol*. 2014;42(2):126–131.

60. Aihara M, Shirato S, Sakata R. Incidence of deepening of the upper eyelid sulcus after switching from latanoprost to bimatoprost. *Jpn J Ophthalmol*. 2011;55(6):600–604.

61. Sakata R, Shirato S, Miyata K, Aihara M. Recovery from deepening of the upper eyelid sulcus after switching from bimatoprost to latanoprost. *Jpn J Ophthalmol*. 2013;57(2):179–184.

62. Sarnoff DS, Gotkin RH. Bimatoprost-induced chemical blepharoplasty. *J Drugs Dermatol*. 2015;14(5):472–477.

63. Fechtner RD, Khouri AS, Zimmerman TJ, et al. Anterior uveitis associated with latanoprost. *Clin Exp Ophthalmol*. 2005;33(9):853–857.

64. Trattler W. Side effects of prostaglandins in patients treated with bimatoprost. *Arq Bras Oftalmol*. 2002;65(5):469–473.
66. Packer M, Fine IH, Hoffman RS. Bilateral nongranulomatous anterior uveitis associated with bimatoprost. J Cataract Refract Surg. 2003; 29(11):2242–2243.

67. Fortuna E, Cervantes-Castaneda RA, Bhat P, Doctor P, Foster CS. Flare-up rates with bimatoprost therapy in uveitic glaucoma. Am J Ophthalmol. 2008;146(6):876–882.

68. Chang JH, McCluskey P, Missotten T, Ferrante P, Jalaludin B, Lightman S. Use of ocular hypotensive prostaglandin analogues in patients with uveitis: does their use increase anterior uveitis and cystoid macular oedema? Br J Ophthalmol. 2008;92(7):916–921.

69. Schumer RA, Camras CB, Mandahl AK. Latanoprost and cystoid macular edema: is there a causal relation? Curr Opin Ophthalmol. 2000; 11(2):94–100.

70. Wand M, Gaudio AR, Shields MB. Latanoprost and cystoid macular edema in high-risk aphakic or pseudophakic eyes. J Cataract Refract Surg. 2001;27(9):1397–1401.

71. Ayyala RS, Cruz DA, Margo CE, et al. Cystoid macular edema associated with latanoprost in aphakic and pseudophakic eyes. Am J Ophthalmol. 1998;126(4):602–604.

72. Cheng JW, Wei RL. Meta-analysis of 13 randomized controlled trials comparing bimatoprost with latanoprost in patients with elevated intraocular pressure. Clin Ther. 2008;30(4):622–632.

73. Horsley MB, Chen TC. The use of prostaglandin analogs in the uveitic patient. Semin Ophthalmol. 2011;26(4–5):285–289.

74. Sun LL, Welch RT, Vu P. Lower eyelid melanoma during bimatoprost (Lumigan) therapy. Clin Exp Ophthalmol. 2012;40(2):213–214.

75. Tessler CS, Wiseman RL, Dombi TM, et al. Lack of evidence for a link between latanoprost use and malignant melanoma: an analysis of safety databases and a review of the literature. Br J Ophthalmol. 2011;95(11):1490–1495.

76. Grimes PE. Bimatoprost 0.03% solution for the treatment of nonfacial vitiligo. J Drugs Dermatol. 2016;15(6):703–710.

77. Zaher H, Gawdat HI, Hegazy RA, Hassan M. Bimatoprost versus mometasone furoate in the treatment of scalp alopecia areata: a pilot study. Dermatol. 2015;230(4):308–313.

78. Okeke CO, Quigley HA, Jampel HD, et al. Adherence with topical glaucoma medication monitored electronically the Travatan Dosing Aid study. Ophthalmology. 2009;116(2):191–199.

79. Lewis RA, Christie WC, Day DG, et al. Bimatoprost sustained-release implants for glaucoma therapy: 6-month results from a phase I/II clinical trial. Am J Ophthalmol. 2017;175:137–147.

80. Brandt JD, Sall K, DuBiner H, et al. Six-month intraocular pressure reduction with a topical bimatoprost ocular insert: results of a phase II randomized controlled study. Ophthalmology. 2016;123(8):1685–1694.