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REVIEW

Bimatoprost in the treatment of eyelash hypotrichosis

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Abstract: Eyelashes hypotrichosis is a condition indicated by an inadequate amount of eyelashes. Hypertrichosis of eyelashes, characterized by excessive eyelash growth, is a regular phenomenon associated with ophthalmic prostaglandin and prostamide analogs. Recently, the US Food and Drug Administration approved Latisse® (bimatoprost 0.03% solution), identical to the ophthalmic solution for glaucoma treatment, for increasing eyelash length, thickness and darkness in patients with hypotrichosis of the eyelashes. When prostaglandin and prostamide analogs interact with the prostanoid receptors in the hair follicle, this most likely stimulates the resting follicles (telogen phase) to growing follicles (anagen phase). Prostaglandin and prostamide analogs may also prolong the anagen phase of eyelashes, leading to an increase of eyelash length. Although bimatoprost is effective in promoting increased growth of healthy eyelashes and adnexal hairs, its effectiveness in patients with eyelash alopecia areata is debatable and its protective effect is not yet studied in patients with eyelash loss secondary to radiation or chemotherapy. Bimatoprost is generally safe when applied to the base of the eyelashes at the lid margin with minimum side effects. However, other ocular or systemic side effects associated with ophthalmic prostaglandin and prostamide analogs may occur when instilled on the surface of the eye, and patients must be informed and monitored.

Keywords: bimatoprost, Latisse, prostaglandin, prostamide, eyelash, hypotrichosis

Introduction

Hypotrichosis is characterized by a less than normal amount of hair, and eyelashes hypotrichosis is the term for an inadequate amount of eyelashes. Eyelashes provide a natural protective barrier for the eyes from sunshine, wind, foreign bodies, and perspiration. They perform a similar function to the whiskers on a cat or a mouse. They are sensitive to the touch and provide a warning when an object is near the eye, which in turn prompts the eye to close reflexively.[1]

In addition to the protective purpose of the eyelash, a more contemporary goal for eyelash length and thickness in modern humans is cosmetic attraction. Eyelashes frame the eyes together with the eyebrows, hairline, cheekbones, nose, lips and chin to create a facial appearance that is unique to every individual. The absence of eyelashes removes one of the salient anatomical features associated with a normal facial appearance.[1] Long eyelashes are also considered a sign of femininity and beauty in most if not all cultures.

Causes of eyelashes hypotrichosis are many, including hereditary, aging, chemotherapy, other medical treatment and unknown causes. Physical trauma involving the face, eye surgery and trichotillomania may also cause thin or absent lash growth.[2,3]

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Since the introduction of latanoprost in 1996 as an ocular hypotensive agent for the treatment of glaucoma, hypertrichosis of eyelashes has been reported as a regular phenomenon associated with ophthalmic prostaglandin and prostamide analogs.[4,5] When compared to latanoprost in clinical study, ophthalmic bimatoprost 0.03% was found to have an even higher occurrence of eyelash growth.[6–9] Recently, Latisse® (Allergan Inc. Irvine, CA) which is bimatoprost 0.03% solution and identical to the ophthalmic solution for glaucoma treatment, was approved by the US Food and Drug Administration (FDA) for increasing eyelash length, thickness and darkness in patients with hypotrichosis of the eyelashes. In this article, bimatoprost is reviewed in terms of its pharmacology, efficacy, and safety in the treatment of eyelash hypotrichosis. Although this review primarily focuses on bimatoprost, it is necessary to discuss the effects of other prostaglandin analogs on eyelashes, particularly latanoprost, which has been more extensively studied in hypertrichosis of eyelashes. Latanoprost and bimatoprost also share many similarities both structurally and pharmacologically.

Pharmacology

Human eyelash characteristics

Human have 90 to 160 eyelashes in the upper eyelid and 75 to 80 in the lower eyelid, with great variation of length.[10,11] The lashes typically originate from the anterior lamella of the eyelid where they lie on the tarsal plate. They grow in imperfect rows of 5 to 6 in the upper lid and 3 to 4 in the lower lid in Caucasians.[12,13] An eyelash is terminal hair, which is coarse, medullated, long and pigmented. In comparison, vellus hair, which is often found on a woman's face, is soft, unmedullated, short and non-pigmented. Eyelashes have the widest diameter of body hairs and are the most pigmented of the terminal hairs.[14]

Hair follicles have a unique cyclical behavior pattern and the entire cycle varies in duration depending on the location in the body. Each human eyelash lives an average of 3 to 6 months.[13,15] The growth phase (anagen) of the eyelash hair follicle and eyelash lasts for approximately 30 days. At the end of the eyelash growth period, a brief transition stage (catagen) of 15 days follows, with shortening of the hair follicle. Finally, the follicle enters a resting phase (telogen) of about 100 days, leading to the detachment of the eyelash.[10,13,16–18] The proportion of follicles in telogen is normally higher in eyelashes than scalp hairs. One study estimated 59% to 85% of eyelash follicles are in telogen phase, depending on whether they are on the upper or lower lid.[18]

The length of an eyelash can vary greatly, from 8 to 12 mm in the upper lid and from 6 to 8 mm in the lower lid, and depends on the ethnicity of the individual.[10,11] Eyelash follicle growth rate is also quite variable, with an average of 0.12 to 0.14 mm daily.[11,13] All eyelashes are characterized by a tendency to bend from the bulb to the top of the shaft.[13] The degree of curvature depends on ethnic origin.[11] Interestingly, eyelashes do not turn grey with aging, or only at a very late stage.[10]

Several factors are involved with hair follicle growth and cycling but their effects on eyelash growth are unclear. Androgens are the principal hormones that control sexual hair growth by receptors localized in the dermal papilla, but eyelashes do not seem to be as sensitive.[19,20] Retinoic acid derivatives affect the hair growth cycle in mice by increasing the length of the anagen phase, and insulin-like growth factor-I slows the hair cycle entry in the catagen phase. Growth hormone, insulin, glycocorticoids, and prolactin are also implicated, but there is no evidence to support an involvement of these hormones in eyelash growth.[17]

Prostamides metabolism

Bimatoprost is a synthetic product initially designed pharmacologically to reduce the intraocular pressure (IOP) for the treatment of glaucoma. It is structurally similar to the other prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) analogs, including latanoprost, travoprost and unoprostone, but has an ethyl amide instead of an isopropyl ester at the C-1 carbon of the alpha chain. Bimatoprost has been proposed to be similar to a class of naturally occurring fatty acid amides otherwise known as "prostamides" (prostaglandin ethanolamides).[21,22]

Prostamides are recently identified as a unique class of compounds that are formed from anandamide catalyzed by cyclooxygenase-2 (COX-2). Anandamide is one of the naturally occurring mammalian endogenous cannabis-like ligands (endocannabinoids) derived from arachidonic acid.

The biosynthesis of anandamide consists of two steps of enzymatic reactions: (1) formation of the membrane glycerophospholipid precursor, N-arachidonoylphospharidylethanolamide (NArPE), by the transfer of a fatty acyl chain from the sn-1 position of glycerophospholipids to the amino group of pho sphatidylethanolamine, (2) enzymatic hydrolysis of NArPE catalyzed by a N-acylphophatidylethanolamides selective phospholipase D (NAPE-PLD) to form anandamide.[23] After synthesis, anandamide is rapidly inactivated via a tightly controlled series of events involving sequestration

by cells and enzymatic hydrolysis of its amide bond to arachidonic acid and ethanolamide.[24] With the presence of an arachidonate moiety in their chemical structure, anandamide and another endocannabinoid, 2-arachidonoylglycerol (2-AG) are substrates for enzymes of the arachidonate casade including COX-2, but not COX-1.[25] Similar to the conversion of arachidonic acids to prostaglandins by COX and prostaglandins synthase, COX-2 converts anandamide to the endoperoxide intermediates prostamide G_2 (PMG_2) and prostamide H_2 (PMH_2), which are then converted by specific prostaglandins synthases to the various prostamides.[26] However, unlike anandamide, prostamides do not possess cannabimimetic and related activity, and their physiological actions have not been fully investigated.

Synthetic prostamide analog, bimatoprost, and prostaglandin $F_{2\alpha}$ analogs, such as latanoprost, travoprost and unoprostone are effective ocular hypotensive agents. The mechanism of IOP reduction involves secretion of metalloproteinases by ciliary smooth muscle cells and remodeling of the extracellular matrix, the resulting widening of intermuscular spaces, and ultimately an increase of uveoscleral outflow of aqueous. Although prostamides are structurally similar to prostaglandins, they exhibit no meaningful activity at prostanoid receptors.[26] Experimental evidence suggests that prostamides may act as endogenous ligands at their own receptors (prostamide receptors). Nevertheless, prostamide activity has not been demonstrated in the absence of prostanoid receptor activity.[26]

In a recent study, Liang at al identified 6 splicing variants of prostanoid FP receptor mRNA in human ocular tissues.[27] Immunoprecipitation analysis further confirmed that the FP receptor is dimerized with FP receptor variant-4 (altFP4). It appears that the FP-altFP4 heterodimer maintains responsiveness to $PGF_{2\alpha}$ and its analogs and acquires sensitivity to bimatoprost. It was also found that $PGF_{2\alpha}$ and bimatoprost has a different calcium mobilization profile. $PGF_{2\alpha}$ elicited a rapid increase in intracellular calcium followed by a steady state phase. In contrast, bimatoprost elicited an immediate increase in intracellular calcium followed by a second phase, and the prostamide antagonist, AGN211335, selectively and dose-dependently inhibited the bimatoprost-initiated second phase, but did not block the action of $PGF_{2\alpha}$. Novel ligand-recognition sites may have emerged as a result of prostanoid-prostanoid receptor hererodimerization, and FP-altFP complexes may represent the underlying basis of bimatoprost pharmacology on IOP.[27] It remains to be proven if this receptor heterodimerization is also responsible for the action of bimatoprost on eyelash growth.

Hair growth induced by prostaglandins and prostamides

Prostaglandins are probably involved in a specific and complex network in hair growth and differentiation control. Most of the hair cell types are endowed with prostaglandin metabolism machinery and are able to produce PGE_2 and/or $PGF_{2\alpha}$; and all prostaglandin receptors are present in hair follicle.[28–30] The epithelial part of the hair bulb was identified by immunohistology and enzyme-linked immunosorbent assays as the main source of prostaglandin synthesis and interconversion.[28] Both the F series and E series prostaglandins may have an effect on hair growth.[31] Inhibitors of prostaglandin endoperoxide synthase such as indomathacin, ibuprofen, and aspirin were shown to block prostaglandin synthesis and inhibit hair growth.[32,33] Minoxidil, a known hair growth agent, was reported to activate activity of purified COX-1, suggesting a positive role of prostaglandin in hair growth onset.[34] Latanoprost, a $PGF_{2\alpha}$ analog, was found to be able to promote hair regrowth in C57/B16 mouse model.[35] $PGF_{2\alpha}$ and PGE_2 were reported to have hypertrichotic effects on mice.[36] $PGF_{2\alpha}$ and prostaglandin F receptor analogs were able to induce telogen to anagen transition. Similar effects were found on stump-tailed macaque.[37]

Although prostaglandin metabolism machinery and prostaglandin receptors are present in hair follicle, the mechanisms by which prostaglandins and prostamides trigger eyelash growth are not clear. So far, this area of research is limited to prostaglandin analogs, or specifically, latanoprost. It is suggested that hypertrichosis following administration of prostaglandin analogs is probably a result of the induction of the anagen phase in telogen phase follicles of eyelashes.[15] Prostaglandin analogs may also prolong the anagen phase of eyelashes, leading to an increase of eyelash length.[38] The increased anagen duration has been hypothesized to be determined at the initiation of the anagen phase and is probably controlled by the dermal papilla.[39] In a study to determine the minimum interval of latanoprost exposure necessary to cause hypertrichosis of eyelashes, brief exposure to latanoprost (<22 days) was associated with hypertrichosis similar to those following sustained exposure. The effect persisted to some degree throughout the duration of a follow-up interval of 14 months.[15] The author suggested that a program is initiated to trigger the anagen phase of the hair cycle in the follicles of eyelashes

and that this program is able to proceed in the absence of an ongoing stimulus.[15]

Efficacy

Hair growth associated with prostaglandin and prostamide analogs

Increase of hair growth is regularly associated with ophthalmic application of different prostaglandin and prostamide analogs in patients of different ethnicities and age groups. In a series of 317 patients, Demitsu et al reported latanoprost-induced hypertrichosis in 77% of patients.[40] In Japanese patients receiving ophthalmic latanoprost treatment for its ocular hypotensive effect, increased vellus hair of the lid was noted in 37.6% and hypertrichosis of eyelashes was noted in 50.5% of patients.[41] In a study to compare the eyelash lengthening effect of latanoprost in adults and children with glaucoma, Elgin et al found that the mean difference in eyelash lengths at baseline and the sixth month was 0.67 ± 0.09 mm in adults and 0.75 ± 0.25 mm in children.[42] After taking travoprost 0.004% for 12 months, changes in eyelashes, including increased length, thickness, density, and color, were reported in 57% of patients.[43] Eyelash growth has been reported in 12.6% to 35.7% of patients during clinical trials of bimatoprost 0.03%.[6,44,45]

In a 3-month bimatoprost versus latanoprost trial, eyelash growth was more common in the bimatoprost group (13% bimatoprost vs. 4% latanoprost).[6] Hypertrichosis appears to occur earlier during bimatoprost treatment as compared to latanoprost. This may be because of the possibility that bimatoprost, unlike latanoprost, does not need to be converted into an active metabolite in order to extend potent pharmacological activity. Another possible explanation is that bimatoprost sensitivity may be conferred by interacting with FP-altFP heterodimer receptor instead, and the additional secondary calcium signaling pathway elicited by bimatoprost may translate into a stronger response of hair growth.

Bimatoprost seems to be able to increase the length of the eyelash more than latanoprost. In an unpublished randomized vehicle-controlled, multicenter, clinical trial, 278 patients were assigned to apply either one drop of bimatoprost (n = 137) or vehicle only (n = 141) to the upper eyelid margin at the base of the eyelashes once nightly for 16 weeks.[46] Eyelash prominence, measured primarily by length but also by thickness and darkness, was rated using a 4-point Global Eyelash Assessment scale developed by the manufacturer. An increase in the scale occurred in 78% (≥1 grade) and 32.8% (≥2 grades) on bimatoprost compared to 18% and 1.4% in the vehicle group, respectively. In the bimatoprost group, eyelash length increased an average of 1.4 mm (25%) compared to 0.1 mm (2%) in the vehicle group after 16 weeks of treatment.[46] In a prospective study assessing the effect of eyelash growth in the ipsilateral eyelids of patients treated with unilateral ophthalmic latanoprost for glaucoma, Johnstone documented an average increase of 19.5% in eyelash length with mean treatment duration of 20 weeks.[4]

The FDA has approved bimatoprost in a 0.03% solution for increasing eyelash length, thickness and darkness in patients with hypotrichosis of the eyelashes. For eyelash enhancement, one drop of bimatoprost 0.03% solution is placed on a single-use applicator and applied to the upper eyelid margin along the roots of the eyelashes once nightly; a new applicator should be used for each eye.

Characteristics of eyelashes in the presence of prostaglandin and prostamide analogs

Hypertrichosis is a regular seen side effect in eyes treated with ophthalmic prostaglandin and prostamide analogs. In a prospective study of 43 patients who were unilaterally treated with latanoprost, researchers identified a number of characteristics of eyelashes treated with latanoprost.[4] After treatment, eyelashes increased in length, thickness, and pigmentation. The number of eyelashes also increased in preexisting lash rows and in areas of transition between the terminal lashes along the lash line and the vellus hairs of the skin. These hairs had a more robust appearance, were longer, thicker, and more heavily pigmented, and arose at a more acute angle from the skin than in the control eye. The vellus and intermediate hairs had transformed into terminal hairs, and produced the appearance of new rows of terminal eyelashes in the lid margin. The changes in the appearance of the eyelashes were not limited to the lashes along the lid margin, but also affected the hairs in the medical and lateral canthal areas.[4] It is reasonable to expect that all these changes may be more prominent and obvious in bimatoprost treatment. The clinically observable eyelashes hypertrichosis resolved following discontinuation of latanoprost or bimatoprost.[4,46]

Even brief exposure to an ophthalmic prostaglandin analog appears to be associated with eyelash change. Johnstone reported that a very brief exposure to latanoprost could produce a similar effect of eyelash growth as compared to chronic exposure.[15] However, the hypertrichosis had a marked irregular pattern of lash curling. The author postulated

that the differences in appearance of eyelashes and pattern of eyelash growth between brief exposure and sustained exposure to prostaglandin analogs may be secondary to a lack of uniform penetration into the hair follicle leading to asymmetric development of the follicle and inner root sheath. Some patients were also found to have persistent trichomegaly up to 14 months following a brief exposure to latanoprost.[15] It is uncertain if similar characteristics of eyelash growth after brief exposure may happen to bimatoprost applied to upper eyelid margin along the roots of the eyelashes.

The hypertrichosis of eyelashes associated with prostaglandin and prostamide analogs usually occurs together with darkening of the eyelashes. However, some patients developed bilateral poliosis after using different ophthalmic prostaglandin $F_{2\alpha}$ analogs for treating primary open angle glaucoma.[47]

Eyelash regrowth in alopecia areata

There are case reports of the successful use of prostaglandin analogs including latanoprost and bimatoprost in the treatment of eyelash alopecia areata.[48–51] In an 11-year-old patient who had alopecia areata with bilateral loss of eyelashes, Mehta et al reported a successful regrowth of the eyelashes after cutaneous treatment with latanoprost.[51] Minimal lash growth was noted on all four lids 4 weeks after application of latanoprost once daily, and pronounced lash growth was noted in 8 weeks. Treatment was then altered to once a week and the number of eyelashes was maintained over the next 6 months.[51]

However, lack of efficacy of topical latanoprost and bimatoprost ophthalmic solutions in promoting eyelash growth in patients with alopecia areata has also been reported.[52] In a 16-week, randomized, investigator masked, controlled study, 11 patients with alopecia areata and greater than 50% bilateral eyelash loss were randomized to receive an application of either latanoprost or bimatoprost to the upper and lower eyelid margins of one eye only. No appreciable eyelash regrowth was noted on clinical assessment of eyelid margins or on review of digital photographs after 16 weeks. Authors questioned whether ocular instillation of prostaglandin analogs used in glaucoma treatment may be more effective in stimulating eyelash growth.[52] In patients without eyelashes, it may be difficult to keep the cutaneously applied medication on the lid margin for adequate penetration into the hair follicles. It is also possible that irreparable damage to the follicle stem cells in some patients may have led to irreversible hair loss.

In another prospective study of similar design with bimatoprost 0.03% solution instilled on the eye, 7 patients (11 patients enrolled, 7 completed the study) with eyelash alopecia areata with greater than 50% bilateral eyelash loss received bimatoprost solution once daily to one eye, while the untreated eye served as the control.[49] Bimatorpost was found to be ineffective in promoting eyelash growth in 5 patients with 95% or greater eyelash loss caused by alopecia areata. However, in 2 patients with 30% and 40% eyelashes present at baseline, some bilateral eyelash growth was noted.[49] Another prostaglandin analog, travoprost, has also been studied in eyelash alopecia areata. Growth of eyelashes was observed in only 1 out of 3 patients, whereas all three developed increased pigmentation of the eyelid skin.[53] It seems that prostaglandin or prostamide analogs are only effective in promoting eyelash regrowth in patients with a mild form of eyelash alopecia areata.

Eyelashes regrowth in other causes of hypotrichiasis

Prostaglandin analogs, not prostamide, have been studied in animal model of hair injury associated with radiation therapy and chemotherapy. Prostaglandin E_2 (PGE_2) analog was shown to have a significant degree of protection against radiation-induced or doxorubicin-induced alopecia in mice.[54–56] This protective effect has yet to be studied in human undergoing radiation therapy or chemotherapy.

Safety

Side effects of ophthalmic prostaglandin and prostamide analogs

Prostaglandin and prostamide analogs have been associated with similar systemic and local side effects when administered topically on the surface of the eye as an ocular hypotensive agent for glaucoma. When bimatoprost is applied to the eyelashes and lid margins in very close proximity to the surface of the eye to promote growth of the eyelash, potential side effects may occur if the medication is administered inappropriately on the surface of the eye.

Ophthalmic use of prostaglandin analogs and bimatoprost is known to be associated with increase iris pigmentation. Iris darkening may be due to increase of melanin granule size secondary to an induced heightened melanogenesis.[57,58] Older patients may have more iris color change when topical prostaglandin is used.[59] Patients with hazel irises that have mixed coloring are at higher risk of iris darkening, whereas homogenous blue or brown irises have relatively little likelihood of getting induced iris darkening.[60]

Conjunctival hyperemia is associated with ophthalmic prostaglandin analogs and bimatoprost. It is the most

common adverse event associated with bimatoprost 0.03% as ophthalmic therapy for glaucoma, which occurred in 42% to 46% of patients.[6,44,45] Approximately 1% to 4% of patients discontinued treatment with bimatoprost 0.03% because of conjunctival hyperemia.[44,45] Comparing with latanoprost, bimatoprost has significantly more conjunctival hyperemia and increased eyelash growth reported, but headaches were more commonly reported with latanoprost.[6–8,61,62]

Increase of pigmentation of the periocular skin is seen with ophthalmic prostaglandin analogs or bimatoprost therapy. The increase of pigmentation is caused by increased melanogenesis without melanocyte proliferation or inflammation.[63] This side effect occurs more frequently with bimatoprost than latanoprost. Wiping the lid was found to help decrease the hyperpigmentation when a topical drop is used.[64] Patients are advised to blot off any solution that drips from the treated area.

Deepening of the eyelid sulcus, periorbital fat atrophy, and relative enophthalmos have been reported with ophthalmic travoprost and bimatoprost used in treatment of glaucoma.[65–68] In some patients the disparity of periorbital appearance between the treated eye and the fellow eye returned to normal after discontinuation of the ophthalmic prostaglandin analogs or prostamide for a relatively long interval.[66,68] The exact mechanism is uncertain, but fatty degeneration and reduced collagen fibers in the levator complex caused by the prostaglandin or prostamide analogs have been proposed as a possible mechanism.[66,68]

Anterior uveitis has been reported in patients using ophthalmic prostaglandin or prostamide analogs.[69,70] Anterior uveitis has been observed in approximately 1% of patients receiving latanoprost, which resolves with corticosteroid therapy.[71] Association of latanoprost and uveitis has been confirmed with a dechallenge and rechallenge method in two studies.[72,73] Because of the similar efficacy and safety profile between prostaglandin analogs and bimatoprost, use of these agents is generally avoided in eyes with active inflammation.

The association of herpetic simplex viral infection and prostaglandin analogs and bimatoprost has been documented.[74,75] Herpes simplex keratitis has been reported to develop after initiation of latanoprost therapy with dechallenge and rechallenge method.[76] In another case report, 2 patients developed HSV dermatitis of the periocular skin after using latanoprost.[77] Latanoprost has been shown to worsen acute herpetic keratitis in the rabbit eye (New Zealand white (NZW) rabbit) and increase the risk of recurrences in latently infected animals.[78] However, in the Induced Reactivation and Spontaneous Shedding HSV-1/NZW rabbit latency models, latanoprost was not found to promote ocular shedding of HSV-1.[79] Use of any topical prostaglandin and prostamide analogs in patients with a history of ocular herpetic viral infection should be avoided.

Patients with active or at risk of ocular inflammation or infection should avoid using bimatoprost to promote eyelash growth.

Specific safety concerns of bimatoprost used in treating hypotrichiasis

The most common local side effects reported by subjects in the clinical trial using bimatoprost as treatment of hypotrichosis were essentially consistent with those experienced by patients using bimatoprost as a treatment in glaucoma. The most common side effects in the clinical trial were eye pruritus, conjunctival hyperemia, eye irritation, dry eye symptoms, and erythema and hyperpigmentation of the eyelids.[46]

Although increase of the length, thickness and darkness of eyelashes are desirable effects of bimatoprost in treatment of hypotrichosis, excessive growth and thickness of the eyelashes has been reported after using the ophthalmic solution of bimatoprost 0.03% once daily after 1 to 3 months.[80–82] Patients were reported to have increased hair growth in the malar regions and external canthal area, excessive growth of eyelashes and eyebrows, and eyelid hyperpigmentation. In one patient, whose eyelash and eyebrow growth returned to normal within 2 months of stopping the ophthalmic bimatoprost treatment, the medication was restarted with instruction to thoroughly clean the ophthalmic solution drippings from her eyes. Nevertheless, after one month of reinstating the treatment, excessive growth and thickness of the eyelashes and eyebrow was again observed along with malar hypertrichosis and eyelid hyperpigmentation.[81] In addition, lash ptosis and trichiasis secondary to misdirected eyelash growth have also been reported in association with latanoprost and travoprost use.[83,84]

Ophthalmic bimatoprost 0.03% has been reported to cause changes in the pigmentation of tissues, including pigmentation of the periocular skin. Bimatoprost-induced periocular hyperpigmentation appears between 3 to 6 months, with hyperpigmentation resolving between 3 to 12 months upon discontinuation of the drug.[85,86]

Increased iris pigmentation has been cited as a side effect of ophthalmic bimatoprost when used in glaucoma treatment. However, iris pigmentation changes were not noted in the clinical trial of bimatoprost used for promoting eyelash growth. This is probably because the drug was

applied at the lid margin and the root of the eyelashes and intraocular penetration was therefore minimized.[46] Since iris pigmentation change, associated with use of ophthalmic prostaglandin analog, can be permanent, patients who desire to use bimatoprost to promote eyelash growth must be informed of this possible side effect.

As mentioned above, there are patients reported to develop poliosis together with hypertrichosis when ophthalmic prostaglandin analog is used in treating glaucoma. Chen et al reported a series of 7 patients, aged 59 to 78, who developed poliosis after prostaglandin analogs were used; including 4 patients on latanoprost, 2 patients on bimatoprost, and 1 patient on travaprost. Poliosis was noted as earlier as 6 weeks after starting treatment.[47] The affected lashes were typically interspersed with normally pigmented lashes. The authors observed on several occasions that the white lashes were new, implying that the side effect may result from failure of pigmentation in newly stimulated eyelash growth or a stimulated growth of previously inconspicuous white lashes.[47] A possible explanation proposed by the authors is that during the anagen phase of the hair follicle cell cycle, genetically predetermined differences in follicular response results in some dermal papillae secreting mitogens, whereas others synthesize inhibitory factors and result in varying response of hair follicles to prostaglandin analogs.[15,47]

The commercially available bimatoprost products (both Latisse® and Lumigan® [also marketed by Allergan Inc.]) contain benzalkonium chloride as preservative. Ocular exposure to benzalkonium chloride may have a cytotoxic effect on human cornea in some patients, and clinically present as erosion of epithelium, irritation, foreign body sensation, and other dry eye symptoms.[87]

Cystoid macular edema has been reported when ophthalmic bimatoprost was used in high-risk patients (aphakia, pseudophakia with ruptured posterior capsule during surgery, history of uveitis, or retinal inflammatory or vascular disease). Cystoid macular edema developed in a patient with glaucoma therapy switched from latanoprost to bimatoprost 9 months after cataract surgery.[88]

Systemic side effects of bimatoprost

Systemic adverse events reported after treatment with bimatoprost 0.03% have included symptoms of common cold and upper respiratory tract infection, headaches, abnormal liver function tests, asthenia and hirsutism. Bimatoprost 0.03% did not have any clinically significant effect on heart rate or blood pressure in patients with glaucoma or ocular hypertension in clinical trials.[45,89,90]

Since bimatoprost is similar in structure and outcome with the other topical prostaglandin analogs, it is important to be aware of the side effects reported with the other prostaglandin analogs. There is a case report of abdominal cramps associated with travoprost confirmed by dechallenge and rechallenge procedures.[91] Other systemic events, each with an incidence of 1 or 2%, included chest pain/angina, muscle/joint/back pain and rash/allergic skin reaction. Angina, arterial hypertension, and tachycardia have been anecdotally reported following latanoprost use.[92,93] In a randomized study, headache was more frequent in patients receiving latanoprost than in those receiving bimatoprost although this difference did not reach statistical significance.[6] Patients with no prior history of migraine and/or headache have reported migraine after receiving latanoprost treatment.[62]

Bimatoprost is classified as a category C drug according to the use-in-pregnancy ratings of the FDA. Category C denotes that animal reproduction studies have shown an adverse effect on the fetus, with no adequate and well-controlled studies in humans. Potential benefits of the drug, however, may warrant its use in pregnant women despite potential risks. Experience of ophthalmic prostaglandin analogs and prostamide use during human pregnancy is limited. In an observation study of 10 pregnant women exposed to latanoprost during the first trimester, 9 women delivered normal fetuses with no malformations. One pregnancy was complicated by miscarriage, which occurred 2 weeks after treatment was ended in a 46-year-old woman, primi-gravida, who had increased reproductive risk related to her advanced age.[94]

Conclusion

Latisse® is identical to Lumigan® with bimatoprost 0.03% as the active ingredient. Lumigan® is marketed for reduction of elevated IOP in patients with glaucoma, while Latisse® is approved for increasing eyelash length, thickness and darkness in patients with hypotrichosis of the eyelashes. For eyelash enhancement, 1 drop of bimatoprost 0.03% solution is placed on a single-use applicator and applied to the upper eyelid margin along the roots of the eyelashes once nightly; a new applicator should be used for each eye.

Bimatoprost is a synthetic prostaglandin analog. But unlike the prostaglandin $F_{2\alpha}$ analogs such as latanoprost, travoprost and unoprostone, bimatoprost has an ethyl amide rather than an isopropyl ester at the C-1 carbon of the alpha chain, and can be classified as a prostamide. Prostaglandin or prostamide analogs are potent agents in the reduction of elevated IOP and hypertrichosis was found to be a regular side effect. This once perceived side effect is now a desirable outcome for patients

who prefer to have longer, thicker, and darker eyelashes.[2] Clinical trial of bimatoprost for eyelash growth conducted by the manufacturer and other clinical trials using bimatoprost as a glaucoma therapy have shown that it is an effective agent in promoting eyelash growth. Bimatoprost most likely works by interacting with the prostaglandin receptors in the hair follicle and stimulating the resting follicles (telogen phase) to growing follicles (anagen phase). Although bimatoprost is effective in promoting increased growth of healthy eyelashes and adnexal hairs, its effectiveness in patients with eyelash alopecia areata is debatable and its protective effect is not yet studied in patients with eyelash loss secondary to radiation or chemotherapy. Apparently, an intact hair follicle is necessary for exogenous prostaglandin analogs to be effective in the promotion of hair growth.

Bimatoprost is generally safe when applied to the base of the eyelash at the lid margin with minimum side effects including ocular or lid irritation, conjunctiva hyperemia and hyperpigmentaton of the lid. Other ocular or systemic side effects associated with ophthalmic bimatoprost and other prostaglandin analogs when instilled on the surface of the eye should be monitored, and patients must be informed.

Based on the general desire of longer, thicker, and darker eyelashes as a sign of femininity and beauty in most cultures, and the high volume of mascara sales, Latisse® is expected to be a popular alternative for those seeking to augment their lash appearance.

Disclosure

The author has received honoraria from Allergan Inc.

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