Bimatoprost in Dermatology

Abstract

Bimatoprost is a prostamide analogue used for treatment of glaucoma in ophthalmology. Surprisingly, the side effects such as increased pigmentation of eyelids and hypertrichosis in patients being treated with prostaglandin analogues for glaucoma have opened new areas of application in various dermatological disorders such as alopecia mainly affecting eyelashes, eyebrows, and vitiligo.

Keywords: *Alopecia areata, bimatoprost, vitiligo*

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Introduction

Bimatoprost is a synthetic prostamide F2a analog.[1] The prostamides and their structural analogs are structurally, pharmacologically, and functionally distinct from prostaglandins and prostaglandin analogs.[1-3] The free acid of bimatoprost is identical to that of latanoprost, the only exception being a double, instead of single, bond at the carbon 13–14 positions.[4] Bimatoprost exerts its effects by stimulating the prostamide receptor, which is pharmacologically distinct from F prostanoid (FP) receptors.[1,5] Prostaglandin receptors involved in the development and regrowth of the hair follicle have been identified throughout the hair follicle, particularly in the dermal papilla and outer root sheath.[6,7] Although there is no therapeutic approach toincreasefollicle numbers, changes in the hair cycle, induced physiologically or pharmacologically, can affect the number and quality of hair visible to clinicians and patients.[8] Unlike their effects on scalp hair, androgens have no effect on eyelash growth.[9] Clinical studies related to the efficacy, safety, and mechanisms of action of bimatoprost in various dermatological disorders are presented.Cochrane database was searched using keywords bimatoprost, dermatology, eyebrow and eyelash hypotrichosis, alopecia, and vitiligo.

Mechanism of Action

The mechanism by which bimatoprost 0.03% ophthalmic solution affects eyelash growth is yet to be fully elucidated. In a study using a murine model, the bimatoprost-treated group demonstrated a significantly greater proportion of anagen follicles and a decrease in telogen and late catagen follicles, suggesting that bimatoprost extends the duration of anagen phase.[10] Bimatoprost 0.03% may influence the growth cycle of eyelashes by stimulating follicles to enter anagen earlier and remain there longer.[11,12] Eyelash hair follicles, in particular, are known to be proportionally higher in the telogen phase, which supports the effectiveness of bimatoprost for hypotrichosis of the eyelashes.[11] Bimatoprost-induced periocular hyperpigmentation is caused by increased melanogenesis without concomitant proliferation of melanocytes, cellular atypia, or evidence of an inflammatory reaction.[13]

Indications of Bimatoprost

FDA approved:

1. Eyelash hypotrichosis

Other off label uses:

2. Eyebrow hypotrichosis
3. Androgenetic alopecia
4. Alopecia areata (AA)

Others with minimal evidence:

5. Vitiligo

What is the Evidence

Cochrane database was searched using keywords bimatoprost, eyebrow, eyelash, and hypotrichosis. The studies on safety and efficacy of bimatoprost in eyebrow and

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eyelash hypotrichosis due to various etiologies have been summarized in Table 1.

Alopecia involving eyelashes and eyebrows:

In December 2008, the US Food and Drug Administration approved the use of bimatoprost (an analog of prostaglandin F2a [PGF2a]) ophthalmic solution, 0.03% (Latisse, Allergan Inc, Irvine, CA), for hypotrichosis of the eyelashes, after reports of trichomegaly (increased eyelash growth) in patients with glaucoma receiving prostaglandin analog treatment.[14]

In a 3-month bimatoprost versus latanoprost trial for reducing intraocular pressure, the side effects profile for hyperemia and eyelash growth were more common in the bimatoprost group thanlatanoprost.[4] Roseborough *et al*.[15] analyzed the use of

Table 1: Studies showing effect of bimatoprost in various dermatological disorders

Authors	Indication	Sample size	Study design	Method	Result
Smith *et al*.[14]	Eyelash hypotrichosis	*n*=278	Phase III multicentre, randomized, double masked, vehicle-controlled study (duration 5 months)	Patientswere randomized to receive once-daily bimatoprost 0.03% (*n*=137) or vehicle (*n*=141)	78.1%increasein grade 1 global eyelash assessment score inbimatoprost group
Vila *et al*.[16]	Eyelash AA Universalis	*n*=41	One-year retrospective, nonblinded study	Thirty-seven patients with AA universalis without ocular disease applied 0.03% bimatoprost to the eyelid margin once a day	24.32% achieved complete eyelash regrowth
Morris *et al*.[17]	Chemotherapy induced madarosis	*n*=20	Randomized, single-blinded, prospective, internally controlled trial (duration 3 months)	Chemotherapy-treated breast cancer patientswith madarosis were randomized to treatment or control (fellow eyelid) to evaluate effectivenes so fb imatoprost gels in improving eyelash appearance at baseline and monthly intervals	Increase in bimatoprost-treated eyelash length (*P*=0.02)
Ahluwalia[18]	Chemotherapy induced eyelash loss	*n*=130	One-year multicenter, double-masked, randomized, parallelgroup study	Post chemotherapy patientswith significant eyelash loss were randomized to receive bimatoprost or vehicle treatment in 3:1 ratio	Global Eyelash Assessment (GEA) scale demonstrateda statistically significant increase ineyelash growth, thickness andpigmentation
Beer *et al*.[19]	Eyebrow hypotrichosis	*n*=20	Randomized, double-blind, vehicle-controlled pilot study (duration 9 months)	Patients with mild to moderate eyebrow hypotrichosis were enrolled. One groupapplied bimatoprost to each eyebrow for 9months, and another group applied for 5months, and thenappliedbimatoprost or vehicle daily for 4months	Improvement from baseline to 6 (*P*=0.002) and 7 (*P*=0.005) for the eyebrows treated with bimatoprost
Wirta *et al*.[20]	Post chemotherapy eyelash hypotrichosis	*n*=130	One-year double masked, parallel group study	Study randomized (3:1) patients to bimatoprost 0.03% or vehicle applied to upper eyelid margins for six months. Vehicleparticipantswereswitchedto bimatoprost for the next six months	Responder rates reached 61.5% in12th month for patientscontinuing bimatoprost
Jha and Sinha[25]	Vitiligo	*n*=1	Case report	One patient had applied bimatoprost 0.03% ophthalmic solution for periorbital vitiligo	Slight repigmentation along with hypertrichosis
Jha and Sinha[26]	Vitiligo	*n*=1	Case report		Repigmentation along with slight improvement in leukotrichia
Grimes[27]	Nonfacialvitiligo	*n*=32	Randomized, double-blind, controlled study (duration 20 weeks)	Patients randomized to three groups, bimatoprost monotherapy (*n*=11), bimatoprost plus mometasone (*n*=10), and mometasone plus placebo (*n*=11)	Bimatoprost plus mometasone group had the maximum repigmentation

latanoprost and bimatoprost for eyelash alopecia areata. After 16 weeks of treatment, no appreciable eyelash regrowth was observed.Vila *et al.*[16] evaluated patients'eyelash growth every 4 months in patients with alopecia a reata universalis without ocular disease. Patients were given 0.03% bimatoprost to be applied tothe eyelid margin once a day over the course of 1 year. They observed complete growth in 24.32%, moderate growth in 18.91%, slight growth in 27.02%, and no response in 29.72%; 43.23% of the patients had an acceptable cosmetic response (total and moderate growth). Morris *et al.*[17] performed study to assess the use of a topical PGF2a analog for chemotherapy-induced madarosis. They created a gel base instead of ophthalmic solution. After 3 months of treatment, there was a significant increase in eyelash length ($P = 0.02$) and thickness ($P = 0.01$). There was one double-masked, randomized, and placebo-controlled study as safety and efficacy of bimatoprost solution 0.03% topical application in patients with chemotherapy-induced eyelash loss.[18] The other study was a randomized double-blind vehicle controlled pilot study on treatment of eyebrow hypotrichosis using bimatoprost: A randomized, double-blind, vehicle-controlled pilot study by Beer *et al.*[19] Wirta *et al.* showed that the responder rate was significantly higher with bimatoprost versus vehicle at month 4 and month 6. Significant improvements favoring bimatoprost occurred in eyelash length ($P = 0.008$), thickness ($P < 0.001$), or darkness ($P = 0.029$) at month 4, with similar results at month 6.[20]

Androgenetic Alopecia

Khidhir *et al.*[21] analyzed the effects of bimatoprost on cultured scalp hair follicles, and found concentration-dependent increased follicular growth rate, increased number of anagen follicles.[21] A PGF2a receptor antagonist negated this effect, confirming a direct receptor-medicated mechanism.

Alopecia Areata

Zaher *et al.* compared the efficacy and safety of bimatoprost to those of corticosteroid in the treatment of scalp AA. Thirty adult patients with patchy AA were included. Two AA patches were randomly assigned to treatment either by mometasone furoate 0.1% cream once daily (area A) or bimatoprost 0.03% solution twice daily (area B) for 3 months. All responding AA patches showed significant reduction in their severity of alopecia tool score (SALT score) after therapy. Those patches where bimatoprost 0.03% solution (area B) was used demonstrated significantly better results regarding rapidity of response in weeks, percentage of hair re-growth, and side effects compared to other area (area A).[22]

Hypopigmentary Disorders and Vitiligo

Kapur *et al.* investigated light microscopic and ultrastructural changes in bimatoprost-induced skin hyperpigmentation. Eyelid biopsy specimens from bimatoprost-treated patients and matched controls were examined by light microscopy and transmission electron microscopy. Using an image analyzer, melanin granules were counted on Fontana–Masson-stained sections, and melanosomes were counted on electron micrographs. They concluded that bimatoprost-induced periocular hyperpigmentation is caused by increased melanogenesis without concomitant proliferation of melanocytes, cellular atypia, or evidence of an inflammatory reaction.[23] Another study by Anbar *et al.*[24] evaluated the local effect of latanoprost, bimatoprost, and travoprost on skin pigmentation. The role of combination with narrow band UVB (NBUVB) with each of these drugs was also evaluated. Study involved 18 female adult wild guinea pigs with patchy white and red/brown fur. Increased pigmentation was found in all areas with PGF2a analogues with and without NB-UVB. However, the former group had more effect both clinically and histopathologically.In one study, patient had stable periocular vitiligo resistant to topical modalities such as tacrolimus and topical steroids. Patient was prescribed bimatoprost 0.03% ophthalmic solution which was to be applied once daily, after six weeks of follow up there was partial repigmentation of the depigmented area but the treatment was stopped due to localized hypertrichosis.[25] Another study showed that there was partial repigmentation of the area along with some improvement in the leucotrichia.[26] Grimes *et al.* showed bimatoprost alone or with mometasone provided greater repigmentation than treatment with mometasone alone.[27]

Limitations and Safety Profile

Apart from eyelash growth, the most common adverse events reported when bimatoprost is administered as an eyedrop (for the treatment of ocular hypertension) are conjunctival hyperemia, eye pruritus, eye dryness, burning sensation in the eye, eyelid pigmentation, foreign body sensation, eye pain, and visual disturbance.[28-30] Localized unwanted hypertrichosis in aesthetic areas could be an issue in treating patients with vitiligo.[25] Iris pigmentation changes are associated with the ability of the agent to stimulate melanogenesis and are aesthetic in nature and do not appear to present any safety concerns, such as melanocyte proliferation.[31] Few patients had periorbital fat atrophy as a side effect of topical ophthalmic bimatoprost therapy.[32-36] It is possible that less exposure of the ocular tissues to bimatoprost when applied topically accounts for the differences in the safety profile of the drug.[37] Recommended application of bimatoprost 0.03% ophthalmic solution is one drop daily for 16 weeks. The shortcoming of bimatoprost preparation in Indian setting seems to be its cost. Treatment with bimatoprost increases the eyelash and eyebrow hair growth, and has some success in the treatment of alopecia areata.

Conclusion

Bimatoprost seems useful in treating eyelash hypotrichosis. The efficacy of bimatoprost on alopecia areata, androgenetic alopecia, vitiligo, and hypopigmentary disorders is still in infancy phase and needs more evidence.

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Conflicts of interest

There are no conflicts of interest.

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