Promising alternative clinical uses of prostaglandin F2α analogs: Beyond the eyelashes

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Prostaglandin F2α analogs, commonly prescribed for glaucoma treatment, have been shown to induce side effects such as cutaneous hypertrichosis and hyperpigmentation. Therefore, these medications have theoretic applications in the treatment of alopecia and disorders of hypopigmentation. We reviewed the literature to find original studies assessing the use of prostaglandin F2α analogs in these settings. Studies and reports were analyzed in regards to androgenic alopecia, alopecia areata, chemotherapy-induced alopecia, vitiligo, and hypopigmented scarring. Based on the results of these studies, and consideration of pathophysiologic mechanism, the most promising applications for prostaglandin F2α analogs include androgenic alopecia, chemotherapy-induced alopecia, and alopecia areata concurrently treated with corticosteroids. (J Am Acad Dermatol 2015;72:712-6.)

Key words: alopecia areata; androgenic alopecia; bimatoprost; glaucoma; latanoprost; prostaglandin; prostaglandin F2α analog; travoprost; vitiligo.

In December 2008, the US Food and Drug Administration approved the use of bimatoprost (an analog of prostaglandin F2α [PGF2α]) 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.1

Initial case reports beginning in 1997 noted trichomegaly and hypertrichosis in patients treated with bimatoprost and latanoprost (another PGF2α analog) for glaucoma, including in 1 patient with alopecia of the eyelashes.2-4 Reports of undesirable hyperpigmentation of the eyelids and irides after use of bimatoprost and other PGF2α analogs for glaucoma followed soon after.5-16

In this review, we will examine the underlying mechanism behind PGF2α analog-induced hypertrichosis and hyperpigmentation, and address potential dermatologic applications, including treatment of alopecia and disorders of hypopigmentation.

METHODS

From March to June 2014, we conducted a systematic search of the PubMed Medline database using the key words: “prostaglandin,” “prostaglandin analogue,” “PGF2alpha,” “hyperpigmentation,” “hypertrichosis,” “trichomegaly,” “bimatoprost,” “latanoprost,” “travoprost,” “alopecia,” “androgenetic alopecia,” “chemotherapy-induced alopecia,” “radiation-induced alopecia,” “hypomelanosis,” “vitiligo,” “post-inflamatory hypopigmentation,” “pityriasis alba,” “idiopathic guttate hypomelanosis,” and “tinea versicolor.” We included original studies and case reports regarding the use of PGF2α analogs for disorders of alopecia or hypopigmentation. Studies addressing the pathophysiology of hypertrichosis or hyperpigmentation with PGF2α analogs were also reviewed.

RESULTS

Hypertrichosis with PGF2α analogs

In a study using a murine model, 10 mice receiving bimatoprost 0.03% ophthalmologic solution once daily for 14 days were compared with mice treated with vehicle control. Every hair follicle of each eyelid was classified into a phase of the hair cycle. 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. Other studies of latanoprost have suggested a mechanism of induction of telogen follicles into anagen phase, with 1 study demonstrating an induction of murine hair follicles into anagen phase within 8 days of treatment. 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. A stimulus from PGF2α analogs may therefore stimulate and prolong the anagen phase, accounting for an increase in the number, thickness, and length of hairs.

**Application to androgenic alopecia**

Androgenic alopecia, also termed “male pattern hair loss” or “female pattern hair loss,” is a progressive, genetically programmed hair loss that affects nearly half of the female population by age 50 years and nearly all the Caucasian male population. Analysis of hair in androgenic alopecia reveals a progressive shortening of the anagen phase and elongation of the telogen phase leading to an overall decrease in the anagen to telogen ratio, and eventual miniaturization and loss of hair follicles. The increase in telogen hairs accounts for hair shedding and a decreased number of scalp hairs.

Unlike scalp hair, eyelashes are not affected by androgens such as scalp hairs. Khidhir et al analyzed the effects of bimatoprost on cultured scalp hair follicles, finding a concentration-dependent increased follicular growth rate, number of anagen follicles, and total amount of hair produced. A PGF2α receptor antagonist negated this effect, confirming a direct receptor-mediated mechanism. Similarly in mice, topically applied bimatoprost at 0.03%, 0.10%, and 0.30% significantly increased the number, thickness, and length of hairs.

Blume-Peytavi et al performed a randomized, double-blind, placebo-controlled pilot study of 16 men with androgenic alopecia, applying topical latanoprost 0.1% daily on the right or left frontotemporal mini-zones. After 24 weeks of treatment, the latanoprost-treated site demonstrated a significant increase in hair density compared with baseline (P < .001) and placebo site (P = .0004). Besides a localized erythematous reaction, no adverse events were reported. Despite these findings, in a case report of a woman with female pattern hair loss treated with injected bimatoprost, a similar response was not seen.

**Application to alopecia areata**

Alopecia areata is an autoimmune disorder characterized by a T-cell-mediated atrophy of hair follicles. Androgen hair follicles are normally a site of immune privilege, where the presentation of surface autoantigens and major histocompatibility complex class I are suppressed. In alopecia areata, there is thought to be a collapse of immune privilege, causing exposure of immunogenic surface antigens and T-cell targeting of pigment-producing anagen hair follicles.

Ross et al performed a randomized, investigator-blinded study of 8 patients with severe eyebrow alopecia areata who were assigned to treat 1 eyebrow with topical latanoprost daily. After 12 weeks of treatment, 7 patients did not display any significant regrowth, and 1 patient demonstrated a positive response that was likely a result of concomitant prednisone use. In a similar study of 26 patients with eyelash and eyebrow alopecia areata, Faghihi et al demonstrated that topical latanoprost treatment for 4 months also did not display significant regrowth.

Roseborough et al analyzed the use of latanoprost and bimatoprost for eyelash alopecia areata. Eleven patients were randomized to receive topical latanoprost or bimatoprost to 1 eyelid daily, with the contralateral eyelid serving as control. After 16 weeks of treatment, no appreciable eyelash regrowth was observed.

Ochoa et al used instilled bimatoprost ophthalmic solution daily to 7 patients with alopecia areata of their eyelashes. After 16 weeks of treatment, 5 patients who had a baseline of 95% or greater eyelash loss showed no appreciable regrowth, whereas 2 patients with 60% and 70% baseline eyelash loss experienced a 10% and 15% eyelash regrowth, respectively. This study suggests that less extensive cases of alopecia areata may benefit from instilled PGF2α analog treatment. Yet, without an adequate control, it is possible that these results stem

**CAPSULE SUMMARY**

- Patients with glaucoma treated with prostaglandin F2α analogs have experienced side effects of hypertrichosis and hyperpigmentation.
- Prostaglandin F2α analogs can induce the anagen phase in hair follicles and stimulate melanogenesis in the skin.
- There are potential applications for topical prostaglandin F2α analogs in the treatment of alopecia and hypopigmentary disorders.
from self-resolving alopecia areata in less extensive cases.

In a larger retrospective study by Vila and Camacho Martinez,30 37 patients with alopecia areata universalis applied topical bimatoprost to their eyelid margins nightly for a period of 1 year. All patients were also treated with concomitant triamcinolone acetonide 0.125% injections of the scalp and eyebrows every 3 months. Results demonstrated that 24.32% achieved complete eyelash regrowth, 18.91% achieved moderate regrowth, 27.02% achieved slight growth, and 29.72% achieved no growth. Three patients initially enrolled were withdrawn because of conjunctivitis, but treatment was otherwise well tolerated. This study was limited by absence of blinding or controls, but suggests that topical PGF2α analogs for alopecia areata of the eyelashes may be useful.

Coronel-Pérez et al31 performed a similar study in 40 patients with alopecia areata universalis. Ten patients received triamcinolone acetonide injections of their eyebrows and scalp every 3 months whereas 44 patients received the same corticosteroid regimen along with topical latanoprost ophthalmic solution to their eyelids every day. After a 2-year treatment period, 17.5% of treated patients experienced total eyelash regrowth, 27.5% experienced moderate regrowth, 30% experienced slight regrowth, and 25% experienced no regrowth. Patients in the control group did not demonstrate any eyelash growth. These results also support the possible benefit of topical PGF2α analogs for alopecia areata and eyelid involvement.

Application to chemotherapy-induced alopecia

Alopecia caused by chemotherapy is a common adverse effect. Chemotherapeutic agents selectively target rapidly proliferating cancer cells, leading to DNA damage, which ultimately signals a pro-apoptotic pathway.32 Other areas of normally proliferating cells are susceptible to this consequence as well. The proliferating matrix cells of anagen hair follicles are the primary sites at which chemotherapeutic agents cause alopecia. Although permanent destruction of hair follicles can occur in some cases, hair regrowth is usually seen after cessation of therapy.32

Morris et al33 performed the only study to date assessing the use of a topical PGF2α analog for chemotherapy-induced madarosis (loss of eyelashes or eyebrows). In a randomized controlled single-blinded study, 20 patients with breast cancer and chemotherapy-induced madarosis were treated with topical bimatoprost 0.03% to 1 assigned eyelid. Instead of bimatoprost solution, the study investigators created a gel form of bimatoprost in an attempt to increase delivery to eyelash hair follicles. After 3 months of treatment, there was a significant increase in eyelash length (P = .02) and thickness (P = .01), and an overall increase in patient satisfaction at last follow-up (P = .002).

**Hyperpigmentation with PGF2α analogs**

The untoward effect of hyperpigmentation with PGF2α analogs may offer a potential therapy for hypopigmentary disorders. A study of cultured human skin melanocytes demonstrated the presence of surface prostaglandin F receptors, which are the target of PGF2α and its analogs. It was shown that activation of the prostaglandin F receptors were potent stimulators of human melanocyte dendricity.34 In another study, cultured human skin melanocytes were treated daily for 5 days with fluprostenol, a potent PGF2α analog. Melanocytes treated with fluprostenol at 5, 10, and 100 nmol/L demonstrated a 1.6-, 1.95-, and 2.2-fold increase in tyrosinase activity, respectively (P < .05 for all). Furthermore, fluprostenol-treated melanocytes did not have a significant increase in cell number from untreated cells.35 These findings provide strong evidence that hyperpigmentation with PGF2α analogs is a result of increased melanogenesis rather than melanocyte proliferation, an important finding for concerns about an increased risk of melanoma.

**Application to vitiligo**

Vitiligo, a common disorder of depigmentation, is thought to be caused by a complex interplay of genetics, autoimmunity, and resulting toxic injury to melanocytes. Histopathology reveals loss of melanocytes in the basal layer of the epidermis, thought to be a result of melanocyte destruction.36

We did not find any controlled studies to date on the use of PGF2α analogs in the treatment of vitiligo. However, 1 case series in the Korean literature presented 3 patients with periorbital vitiligo treated with topical latanoprost. After 2 months of therapy, patients experienced 20%, 50%, and greater than 90% repigmentation of their vitiligo lesions.37

**Application to other hypopigmentary conditions**

Other common hypopigmentary conditions of the skin include postinflammatory hypopigmentation, tinea versicolor, and pityriasis alba.38 We did not find any specific studies assessing the use of PGF2α analogs in the treatment of these diseases. One study by Massaki et al39 did study the use of bimatoprost in combination with fractionated laser and topical retinoids for the treatment of hypopigmented scars.
Fourteen patients with hypopigmented scarring were treated with fractionated 1550-nm erbium-doped laser (mean 4.5 sessions every 4-8 weeks), topical bimatoprost 0.03% twice daily, and topical tretinoin 0.05% or pimecrolimus 1% daily to their lesions. Most patients demonstrated significant improvement in their hypopigmentation, but the isolated effect of topical bimatoprost was not evaluated.

**DISCUSSION**

PF2α analogs have proven to be an effective treatment for glaucoma with well-documented side effects of hypertrichosis2-4 and periorcular hyperpigmentation.5-10 Periorbital fat atrophy, another commonly reported side effect of PGF2α analogs, is not addressed in this review, as potential dermatologic applications of this interesting side effect have not yet been systematically studied.40-42

Given their otherwise favorable side-effect profile, PGF2α analogs have been investigated for applications in the treatment of alopecia and hypopigmentary disorders. With the exception of alopecia areata, sufficient controlled studies are lacking and limited conclusions can be drawn from the few case reports and small studies available.

From a pathophysiologic standpoint, PGF2α analogs are well suited to target androgenic alopecia by lengthening the phase of anagen follicles and stimulating resting follicles into anagen, and increased hair density has been demonstrated in a small number of patients. Not surprisingly, there are currently 4 registered clinical trials (3 completed, 1 recruiting) on the use of bimatoprost in male and female patients with androgenic alopecia.43-46

The use of PGF2α analogs has been more thoroughly investigated in alopecia areata, primarily of the eyebrows and eyelashes in cases of alopecia areata universalis, but results of topical latanoprost and bimatoprost in these cases were unremarkable, possibly because of the immune-mediated nature of the disease, rather than an alteration in anagen function or duration.

The nonimmune-mediated apoptosis of anagen-phase hair follicles from chemotherapy does appear to respond favorably to PGF2α analogs, and the promising use is being pursued in 2 registered ongoing clinical trials assessing the use of topical bimatoprost in such patients.47,48

Regarding application of PGF2α analogs in hypopigmentary disorders, there is a paucity of clinical studies in the treatment of conditions such as vitiligo, postinflammatory hypopigmentation, pityriasis alba, and tinea versicolor. As vitiligo is a disease caused by melanocyte destruction, the stimulation of melanogenesis by PGF2α analogs may be ineffective as a treatment modality, however, case reports have shown potential. Blinded studies evaluating topical PGF2α analogs for this common condition should be relatively easy to conduct, and would be a welcome alternative to the side effects of corticosteroids and ultraviolet treatments.

**Conclusion**

PF2α analogs have been investigated for the treatment of alopecia and disorders of hypopigmentation. Studies have shown potential benefit for the treatment of androgenic alopecia, chemotherapy-induced alopecia, and alopecia areata. The application of PGF2α analogs in hypopigmentary conditions has not been adequately investigated at this time, but is a logical direction of future research.

**REFERENCES**
