ORIGINAL ARTICLE

Latanoprost in treatment of alopecia areata and androgenic alopecia: A comprehensive review

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ABSTRACT

Background: Alopecia is a common condition among males and females in all age groups. There are many treatment options with their own benefits and side effects. In some cases, the current treatments lack sufficient efficacy. Therefore, there is a need to probe for alternative treatments. Recently, latanoprost has been suggested as an effective therapeutic option for managing scalp baldness.

Objectives : To review latanoprost effects in different types of scalp alopecia.

Data sources: Scopus and Pubmed data-base

Eligibility criteria and Methods: In this review, we included the studies evaluating effects of latanoprost in different types of scalp alopecia including androgenic alopecia and alopecia areata in the English literature.

Results: There were promising results for latanoprost application in animal models of androgenic alopecia. Effects of latanoprost on human scalp alopecia were satisfying in mostof the studies. In alopecia areata of the eyelash, some studies observed remarkable improvement, while others didn't notice significant changes. One study suggested that latanoprost could be used as an effective adjuvant therapy with corticosteroids in alopecia areata of the scalp.

Conclusion : It seems that latanoprost can be an efficient agent in the treatment of alopecia areata of scalp.

Key words: Prostaglandin F, Latanoprost, Alopecia areata, Androgenic alopecia, Prostaglandin analog, Bimatoprost, Alopecia, Review

INTRODUCTION

Latanoprost is a new synthetic and long-acting prostaglandin F2α analog (PGF2α) which has been widely used to decrease intraocular pressure in patients with glaucoma. Latanoprost increases uveoscleral aqueous flow as its primary mechanism of action. Other clinical manifestations of latanoprost include additional lash rows, greater length and thickness of lashes, conversion of vellus to terminal hairs in canthal areas, as well as in regions adjacent to lash rows (1).

The first attempts to investigate PGF2α agents, dates back to the late 1980s, when de Asua et al. suggested stimulatory effects of PGF2α on DNA synthesis and mitosis on Swiss mouse 3T3 cells (2). Later, reports of latanoprost on eyelash hyperpigmentation and hypertrichosis were published (3-7). In a study by Sasaki S et al. effects of PGF2α effects on hair follicles of a murine model were investigated. They concluded that latanoprost has stimulatory effects on telogen and anagen phases, and mediates telogen to anagen phase conversion through acting on dermal papilla (8).

In addition, prostaglandin D2 has recently been identified as a factor which is elevated in the bald scalp of men with androgenetic alopecia (AGA) and has the capacity to decrease hair lengthening. An enzyme which synthesizes it, prostaglandin D2 synthase (PTGDS or lipocalin-PGDS), is hormone responsive in multiple other organs. PGD2 has two known receptors, GPR44 and PTGDR. GPR44 was found to be necessary for the decrease in hair growth by PGD2. This creates an exciting opportunity to perhaps create novel treatments for AGA, which inhibit the activity of PTGDS, PGD2 or GPR44 (9).

Interesting effects of latanoprost on growth, encouraged clinicians to study its effects on scalp baldness. In this study, we aimed to report effects of latanoprost in scalp alopecia, including, androgenic alopecia and alopecia areata.

METHODS

In this review, we performed a Scopus and Pubmed data-base survey with the keywords of "Scalp", "Alopecia" and "latanoprost OR F2α agonist" in English literature. We included papers evaluating the effects of latanoprost in different types of alopecia including androgenic alopecia and alopecia areata. Exclusion criteria of the reviewed articles were as following: scalp atrophy, cicatricial alopecia, any other skin scalp disorders (infections, severe psoriasis and seborrheic dermatitis), any ophthalmic pathology; allergy or hypersensitivity to any colorant, medicinal product, or component of the investigational product, history of skin cancer, acute or chronic illness interfering with the trial conduct, physical treatments on the head within the last 6 months, using depigmenting or pigmenting products on the scalp or head during the last 3 months, planned ultraviolet sessions or sun exposure of the head during the study period, using topical or systemic drugs or cosmetics that could interfere with the study assessments in the last months, pregnancy or

breastfeeding; candidates with renal, cardiac or liver transplant, immunodeficiencies, retinoids, previous hair transplant or surgery for scalp reduction; use of minoxidil or finasteride (oral or topical) within 6 months before the study, treatments with low energy light, infrared or laser within 6 months before the study, solar erythema on the area to be studied or predicted intense exposure to sun light or UV lamps during the study and use of hair extensions, wig or hair straightening during the 3 months prior to the study, diagnosis of systemic diseases such as hypothyroidism, PCOS (polycystic ovary syndrome) and trichotillomania.

RESULTS

Androgenetic Alopecia (Male & Female pattern): Androgenic alopecia is the most prevalent type of hair loss affecting both sexes. It presents itself with recession of the hairline and vertex balding. In this condition terminal hair follicles gradually transform into vellus-like follicles known as Follicle miniaturization. In 2002, Uno et al, studied the effects of latanoprost on macaque model of androgenic alopecia. They observed 5-10% hair growth and conversion of vellus hairs to intermediary, or terminal hairs in monkeys receiving 500 µg/ ml of topical latanoprost per day over 3 months (10).

In 2012, Blume- Peytavi et al., compared the effects of latanoprost in males with mild androgenetic alopecia (Hamilton II- III) in two mini-zones of the scalp. Latanoprost 0.1% and placebo were applied daily for 24 weeks on two minizones on the scalp. After 24 weeks of treatment with latanoprost 0.1 %, there was a significant increase in hair density (terminal and vellus hairs) compared to the baseline ($P< 0.001$) and placebo group ($P< 0.0004$) (11).

In 2018, Bloch et al. studied the effects of latanoprost in patients with androgenic alopecia in a comparative double-blind study within 24 weeks. Patients were divided into six groups (G1 - placebo, G2 - 5% minoxidil, G3 - 5% minoxidil + 0.005% latanoprost, G4 - 0.005% latanoprost, G5 - 5% minoxidil + 0.01% latanoprost, G6 - 0.01% latanoprost) and the total count of hair strands were evaluated using a phototrichogram. The groups who received latanoprost 0.005 % (G4) and a combination of minoxidil 5% + latanoprost 0.01% (G5) acheived a significant improvement in the total number of hair strands and anagen follicles. However, the group who applied latanoprost 0.01 % alone, did not show significant difference compared to the placebo group (12). This original study did not available in English, so we did not any access to discussion of the authors about why they did not see any efficacy by latanoprost 0.01% but did with 0.005 % that may be related to some probable bias in sampling which we can not discuss more.

Alopecia areata: Alopecia areata is an immune-mediated and polygenic disease that involves both adults and children. The presentation varies from transient circle-shaped alopecia patches on scalp to persistent complete hair loss (13). Scalp is the most common affected site, though any hair covered area can be involved (14). In 2009, Coronel-P'erez et al. observed satisfying results in 45% of their patients with alopecia areata of the eyelash after a 24-month-treatment trial (14). In contrast, some studies reported a lack of efficacy of topical latanoprost in alopecia areata of the eyebrow and eyelash (15-17). In 2018 El-Ashmawy et al. compared the effects of topical latanoprost with a combination of dexamethasone and minoxidilin 100 patients with alopecia areata. They divided the patients into 5 groups receiving different regimens. (Group I: patients were applying topical latanoprost 0.1% lotion twice daily. Latanoprost 0.1% weight/volume was prepared in a solvent system comprising of ethanol, propylene glycol and distilled water which were mixed at a volume ratio of 50%:20%:30%. Freshly prepared formulation was given to each patient every 2 weeks. Group II: patients were applying topical 5% minoxidil lotion twice daily. Group III: patients were applying topical betamethasone valerate 0.1% solution twice daily. Group IV: patients applying topical betamethasone valerate 0.1% solution once daily in the morning and topical latanoprost 0.1% lotion once daily at night. Group V (control group): patients applying placebo (drug free formula) lotion twice daily.) After a 20-week follow-up, scalp hair growth in the group which received latanoprost 0.1 % alone had a statistically significant improvement ($p= 0.044$). Meanwhile, the patients who received a combination of latanoprost 0.1% and betamethasone valerate 0.1%, showed up a remarkable change in hair growth ($p= 0.004$). According to their results, latanoprost could be used as an efficient topical adjunctive therapy for alopecia areata (18). In 2020, Dr. Ahmed Abdulhussein Kawen evaluated the effects of topical latanoprost 0.005% vs latanoprost 0.005%+ minoxidil 5% on alopecia areata of scalp of 95 patients. Their results indicated both treatments to be effective with a superiority in minoxil application alone ($p= 0.002$ vs $p= 0.0001$) (19).The outcomes of latanoprost on Androgenic alopecia and alopecia areata of the scalp is summarized in Table 1. Some of the important outcomes were increased hair density, improvement in the total number of hair strands and anagen follicles, conversion from telogen to the anagen phase and hypertrichosis and trichomegaly with melanogenesis.

DISCUSSION

This study aims to shed light on latanoprost as an alternative therapeutic strategy for managing androgenic alopecia and scalp alopecia areata. There are different mechanisms explaining how PGF2αs influence hair growth (Table 2). In a study by doctor Johnstone in 2002, effects of intra-ocular latanoprost in patients with glaucoma were mentioned. It was suggested that the route of administration, penetration rate and systemic absorption may explain the inconsistency in the results of different studies of latanoprost application (1). Androgen gene receptor expression is associated with levels of dehydrotestosterone and consequently the rate of therapeutic response. Ghassemi et al, studied the effects of gene polymorphism and response to finasteride therapy in men with hereditary androgenic alopecia. They concluded that gene polymorphism and pattern of inheritance play an important role in determining a treatment plan, dose of medications and duration of therapy (20). In the study by Uno et al. in 2002, effects of latanoprost on bald scalp of primate model of human androgenic alopecia macaques, suggested to be dose dependent; at a dose of 500 µg/ml (0.05 %) induced remarkable hair growth comparing to the dose of 50 µg/ml (0.005 %) (10).

Blume Peytavi et al. implied that latanoprost increases both anagen and telogen phases of hair growth and induced new hairs into growth phase. One of the limitations of their study was a relatively small sample size and narrow and young age range (23 to 35 years) (11). In 2019, Villarreal et al, analyzed transcripts of prostaglandin D2 synthase (PTGDS), prostaglandin D2 receptor (PTGDR2) and prostaglandin E synthase (PTGDE) in biopsies of bald scalps of males and females with androgenic alopecia. They investigated over-expression of PTGDS and PTGES in males but no difference in PTGDR2 expression comparing to their controls (21). Their findings were in agreement with a previous study by Garza et al in 2012 (22). Prostaglandin D2 (PGD2) is the product of PTGDS which induces testosterone synthesis and initiates catagen phase, while PTGDR2 mediates its effect (1, 22, 23). Villarreal et al. suggested that high levels of PGD2 may increase testosterone levels and lead to scalp baldness (21). Setipiprant is an investigational drug that antagonizes PTGDR2s. Its effects are being evaluated in a clinical trial (ClinicalTrials.gov Identifier: NCT02781311). Along with the studies investigating the effects of latanoprost, other prostaglandin analogues such as bimatoprost, with a more prominent focus on eyelash and eyebrow regrowth have also been studied (24-28). Some possible reasons for the inconsistent results of latanoprost on eyelashes and eyebrows compared to the scalp hair, is their different growth patterns. These differences consist of androgen sensitivity, hair cycle duration, number of follicles, average growth rate, and anagen or telogen duration (29-33). Chemotherapy induced alopecia is also a major problem, and poses a great burden in cancer patients, with approximate incidence of 65% which represents a challenge especially in women and children. Moreover, chemotherapy side effects induce madarosis (loss of eyelashes) for which to date, there is no effective treatment (1). In 2011, Morris et al evaluated bimatoprost eyelash gel in relation to eyelash enhancement of madarosis patients. There was a significant improvement in patient satisfaction scale (p=0.002), eyelash length (p=0.02), thickness (p=0.01) and pigmentation (p=0.06) after 3 months of follow up (34). Side effects of latanoprost

Latanoprost is widely applied in ophthalmology. Intraocular side effects include hyperpigmentation of the eyelids after regular application within a period of 1-2 years, mild conjunctival hyperemia, reactivation of herpes-keratitis/-dermatitis and cystoid macular edema and anterior uveitis (35). Poliosis (eyelash depigmentation) and hyportrichosis on latanoprost withdrawal were also reported (1, 5, 36). Scalp latanoprost application induced allergic contact dermatitis on scalp, face and neck of a female patient with alopecia areata (1).Bimatoprost *and other types of prostaglandin F (PG-F) analogues* One recent product to stimulate hair growth has been bimatoprost (Latisse). Bimatoprost is a prostaglandin analogue of Prostaglandin F2a and is prescribed to augment the growth of eyelash hair, with extensive efforts to extend this for the treatment of scalp alopecias (37, 38). Latanoprost and bimatoprost were both used to decrease ocular pressure in glaucoma and were incidentally noted to cause hair lengthening (1, 39, 40). There exists a precedence for suspecting the importance of lipids in hair follicle function (41, 42), particularly in the context of the sebaceous gland and scarring alopecias (43-45). However, the discovery of the potency for latanoprost and bimatoprost to induce human hair lengthening requires some of the strongest evidence to implicate prostaglandins in hair follicle function.In this comprehensive review, we focused on therapeutic roles of these drugs, mainly Latanoprost, in 3 forms of alopecia; Androgenic, Areata as the main categories and Chemotherapy-induced alopecia as the newest topic needed to be more evaluated. It seems that Latanoprost is an efficient agent in treatment of different types of alopecia which appears to be more effective when it is applied in combination with corticosteroids especially in the case of alopecia Areata. It seems that Latanoprost can be an efficient agent in treatment of different types of scalp alopecia. Bimatoprost and Travoprost have been approved to be more beneficial in the treatment of scalp and eyelash alopecia (12, 13-17, 37-40), although in this review we focused mainly on Latanaoprost since it is more accessible, cost-effective and available in some commercial medications forms that may be used in that form for dermatologic disorders too. The authors of this study have worked on various forms of alopecia and the novel and most recent proposed therapies in this regard (46-49) and now in this comprehensive review we focused on prostaglandin F analogues as a hot topic in dermatology in the field of alopecia.

Limitations: There are not many studies available in the literature evaluating the application of latanoprost in scalp alopecia and the results of the available studies are sometimes controversial. There is a need to perform more studies with a greater sample size on the subject.

CONCLUSIONS

There are many evidences of the efficacy and safety of prostaglandin F analogues for cosmetic therapies like hair hyperpigmentation or hair growth, re-growth even overgrowth in dermatology especially for eye-lash and eyebrow enlargement and hyperpigmentation. These characteristics of mentioned drugs caused to be used for other non-cosmetic dermatologic disorders like vitiligo and different types of alopecia especially alopecia areata. In this comprehensive review, we focused on the therapeutic roles of these drugs, mainly latanoprost in forms of alopecia areata and androgenic alopecia. It seems that latanoprost is an efficient agent in treatment of different types of alopecia, which appears to be more effective when it is applied in combination with corticosteroids, especially in the case of alopecia areata.

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Table 1. Effect of latanoprost on scalp androgenic alopecia and alopecia areata

Year	Model	Alopecia type	Duration of treatment	Dosage	Route of administration	Outcome	Side effects
2002 Hideo Uno et al. (10)	Primate macaque model	Androgenic	Once daily, 5 times a week for 3 months	0.5 ml of latanoprost at 500 µg/ml (0.05 %),	Topical solution	5- 10 % hair growth and conversion of vellus hairs to intermediary or terminal hairs	-
2012 by Blume-Peytavi et al. (11)	16 males 23- 35 years	Mild Androgenetic alopecia (Hamilton II- III)	Once daily for 24 weeks	50 µl of latanoprost 0.1 % on two symmetric minizones 3 cm^2 of scalp	Topical solution	a significant increased hair density (terminal and vellus hairs) (P< 0.001)	Erythema, n= 5 Folliculitis, n= 1 Burning sensation n=1, Erysipelas N=1
2018 Bloch et al. (12)	123 males and females 20- 55 years	Telogen effluvium or androgenic alopecia	Once daily for 24 weeks	G1 - placebo, G2 - 5% minoxidil, G3 - 5% minoxidil + 0.005% latanoprost, G4 - 0.005% latanoprost, G5 - 5% minoxidil + 0.010% latanoprost, G6 - 0.010% latanoprost.	Topical solution	1 & 2 : improvement in the total number of hair strands and anagen follicles 3- no significant difference	No significant signs of discomfort, pruritus, scaling or erythema
2018 El-Ashmawy et al. (18)	100 males and females 3-81 years	Alopecia areata	20 weeks	1- latanoprost 0.1 % alone 2- latanoprost 0.1% + betamethasone valerate 0.1%	Topical solution	1- significant improvement (p= 0.044) 2- remarkable change in hair growth (p= 0.004)	-
2020 Ahmed Abdulhussein Kawen (19)	95 males and females 4- 45 years	Alopecia areata	4- 10 weeks	1- minoxidil 5% 2- minoxidil 5%+ latanoprost 0.005%	Topical solution	1- significant improvement (p= 0.0001) 1- significant improvement (p= 0.002)	mild pruritic erythema (no systemic adverse effects)
2005 Sasaki S et al. (8)	33seven week-old female C57BL/6 mice	-	Once Daily for 3 weeks	1- PGF2a 2- latanoprost eye drops 3- Unoprostone eye drops 4- PGE2	Topical solution	- Stimulatory effects on the murine hair follicles and the follicular melanocytes in both the telogen and anagen stages - Stimulating conversion from the telogen to the anagen phase -Hypertrichosis and trichomegaly with melanogenesis	-

Table 2. Mechanism of action of Prostaglandin F2α

1.	Cell surface receptors linked by a G protein to phosphorylase C are activated by prostaglandin F2α which subsequently activates protein kinase families and the cascade of cell growth.
2.	Prostaglandin F2α analogues modulate extracellular matrix components which inhibits apoptosis and evokes gene expression and/or cell division potentials.
3.	Some in vitro studies confirmed the ability of prostaglandin F2α to directly induce DNA replication, cell division and growth in cultured fibroblasts.
4.	Latanoprost as a synthetic prostaglandin F2α analog has the highest ability to stimulate DNA synthesis in a number of cell types. The analysis of structure and activity of prostaglandins revealed that there might be a specific receptor for prostaglandin F2α which initiates mitogenic response (2, 3, 50).