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Title page

Title: Topical finasteride for the treatment of male androgenetic alopecia and female pattern hair loss: a review of the current literature

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Topical finasteride for the treatment of male androgenetic alopecia and female pattern hair loss: a review of the current literature

ABSTRACT

Background: Androgenetic alopecia (AGA) is a frequently encountered dermatological concern that impacts a patient's self-esteem and quality of life. Finasteride is a selective 5-alpha reductase inhibitor that has been approved for the treatment of male AGA and the off-label use in female pattern hair loss (FPHL); however, its adverse effects may limit its use. Topical finasteride is a new formulation that aims to decrease complications caused by oral administration.

Objective: This review assesses the pharmacology, current therapeutic use, and safety of topical finasteride for the treatment of AGA and FPHL.

Methods: A PubMed search was conducted to include all English language articles on topical finasteride from January 1992 to January 2020.

Results: A total of 33 articles including 28 topical finasteride related articles and 5 AGA related articles were included in this review. Multiple studies on topical finasteride as the treatment for male AGA and FPHL showed positive results with a favorable safety profile.

Conclusions: Topical finasteride is a promising therapeutic option. We emphasize the importance of continued research for the establishment of a novel therapeutic agent.

Keywords: androgen, 5-alpha reductase inhibitor, dihydrotestosterone, hair disorder, testosterone

Introduction

Androgenetic alopecia (AGA) is one of the common causes of hair loss characterized by progressive thinning of terminal scalp hair with a characteristic pattern distribution in genetically predisposed patients. Clinically, men present with hair thinning on the vertex of the scalp and anterior hairline recession while women present with diffused hair thinning, mostly on the mid-scalp with preservation of the frontal hairline (1,2). Dihydrotestosterone (DHT) is largely responsible for the miniaturization of hair follicles and is considered the most potent etiological factor for the condition. However, the role of androgens in the pathogenesis of hair loss in female patients remains unclear. Therefore, the term 'female pattern hair loss (FPHL)' is preferred over female AGA (3). The current US Food and Drug Administration (FDA)-approved medications for the treatment of male AGA are topical minoxidil and oral finasteride; however, topical minoxidil is the only approved treatment for FPHL (4-6), other therapeutic options include low-level laser therapy, fractional laser therapy, and hair transplantation (7,8).

Finasteride, a selective and competitive type II 5-alpha reductase inhibitor that is primarily indicated for benign prostate hyperplasia, has been widely used in the treatment of AGA (4). It functions by binding to the androgen receptor of the dermal papillae in the hair follicles and blocking the conversion of testosterone to DHT resulting in a significant reduction of scalp and serum DHT concentration (9). To sustain the therapeutic effect, oral finasteride is frequently prescribed for a longer duration; daily use of this drug is considered a drawback. Long-term use of finasteride may lead to undesirable side effects including a decrease in libido, gynecomastia, and erectile dysfunction (10). Moreover, systemic finasteride has a potential teratogenic effect involving abnormal development of the external genitalia in a male fetus, thereby limiting its use in women (11).

The topical formulation of finasteride has been developed as a new therapeutic option to reduce the systemic side effects of oral administration (10,11). As it has not yet been approved by the FDA or the European Medicines Agency, studies on topical finasteride in the treatment of hair conditions are sparse. However, available studies have shown promising and efficacious outcomes. Herein, we review and summarize the pharmacology, therapeutic efficacy, and safety of topical finasteride in the treatment of male AGA and FPHL.

Methods of the literature search

Using PubMed as a primary literature search tool, a literature search was performed to find published articles investigating the use of topical finasteride in AGA and FPHL. The search terms included ‘topical’ and ‘finasteride’. The articles published between January 1992 and January 2020 were screened. Studies examining the pharmacology, drug-delivery system, and clinical use of topical finasteride were included in the review. The efficacy of topical finasteride for the treatment of AGA or FPHL was based on prospective studies, retrospective studies, systematic review, and case reports/series. Non-English publications, studies without full text, and articles irrelevant to topical formulation of finasteride were excluded. Figure 1 shows the flowchart of study selection for review of topical finasteride.

Results and discussion

Pharmacology of topical finasteride

The topical finasteride formulation aims to locally inhibit the 5α-reductase enzyme and decrease the production of DHT at the level of the hair follicle with minimal disturbance of the serum

DHT concentration. The finasteride plasma concentration in blood and the extent of absorption with the topical application is lower than that observed with oral administration. A preliminary clinical trial reported that serum finasteride concentrations after topical application of a combined 5% minoxidil and 0.1% finasteride lipid solution twice daily for 14 days was 10-fold lower than oral finasteride at a similar dosage (12). Another exploratory study reported very low concentrations of finasteride detected in 5 of 11 subjects after a single application of 0.25% topical finasteride; however, multiple applications of topical solution (twice daily for 7 days) resulted in small detectable finasteride plasma concentration in most subjects. Compared to oral tablets (1 mg twice daily for 7 days), the mean maximum finasteride concentration (Cmax) and area under curve (AUC) of the topical formulation were 15 and 9 times lower, respectively; these were significantly different (13). The reduction in the scalp DHT levels from baseline was similar for 0.25% topical solution twice daily (47%) and oral finasteride 1 mg daily (51%), and significantly lower for daily application once (71%) (14). The suppression of serum DHT level was noted for both oral and topical administrations after 1-week of treatment. Although these confirm the similar inhibitory effects with multiple-dose treatment, the decline in DHT levels seems to be less pronounced with the use of lower concentration topical formulations. A study with application of 0.005% topical solution for 16 months did not observe any change in the serum DHT level (15), while in another study, applying 0.1% topical solution for 24 weeks resulted in no detection of finasteride in half of the blood samples (16). Notably, all studies did not observe any significant difference in serum testosterone levels with topical application (13).

A topical formulation with high skin penetration and deposition but low systemic absorption is preferable. According to a study, the application of finasteride solution in doses of 100 and 200 μL once daily seems to be more efficacious than applying it twice daily. On the

other hand, increasing the dose up to 300 and 400 μL correlates with higher plasma finasteride concentrations and a possibility of systemic side effects (14). The drug-delivery system plays an important role in the efficacy of topical finasteride. Several compounds have been explored to provide appropriate drug delivery and for biomedical applications including topical solutions, gels, polymersomes, vesicular nanocarriers, vesicular ethosomal carriers, liposomes and niosomes, polymeric nanoparticles, and liquid crystalline nanoparticles (17-24). Among these, finasteride liposomal gel system containing 2% methylcellulose and a gel system containing poloxamer P407 exhibited highest skin penetration at the site of application; these may be the ideal future delivery systems for topical finasteride (17).

Therapeutic efficacy of topical finasteride

The use of topical finasteride in the treatment of AGA was first introduced by Mazzarella et al. who conducted a preliminary placebo-controlled trial of topical finasteride. Twenty-eight males and 24 females with AGA were randomly allocated to receive 0.005% finasteride solution or vehicles (50% ethyl alcohol, 25% propylene glycol, and 25% distilled water) twice daily for 16 months. Hair regrowth was observed among patients treated with topical finasteride in the fourth month and sustained throughout the study. Increased hair density at the periphery of balding patches and progressive thickening of hair texture were reported as the responses to the treatment. By 6 months, the rate of hair loss which was evaluated by hair counts from the wash tests showed a significant decrease compared to those applying vehicles. Finasteride-treated patients continued to show a significant reduction in hair loss until the end of the study. The investigators also noted a large number of dropouts from the placebo group due to a lack of improvement (15).

A subsequent randomized controlled trial (RCT) on the efficacy of 0.1% finasteride solution compared to a placebo in 20 males who had moderate-to-severe AGA demonstrated a greater mean hair count increment from baseline in the finasteride group despite no significant difference in the response rates between the two groups. Clinical improvements graded by the patients and investigators in the topical finasteride group were considerably higher than the placebo group (25). Another 6 months placebo-controlled analysis of 50 AGA males further testified the efficacy of topical finasteride. Patients treated with 0.5% topical solution twice daily demonstrated significantly higher hair counts and greater mean terminal hair changes from baseline than those receiving placebo as early as 3 months of treatment. At the end of the study, global photography also showed sustainability of hair loss in 53.8% and clinical improvement in 46% of the finasteride-treated patients, while 83.3% of the placebo-treated patients demonstrated no change in their hair loss with 16.7% of them reporting a worsening condition (16).

To compare the clinical outcomes between the topical and oral formulations, Hajheydari et al. carried out a double-blind controlled trial in 45 males who had AGA and randomly assigned them into 2 groups: 1% finasteride gel twice daily with placebo tablets daily and vehicle gel twice daily plus 1 mg oral finasteride tablet daily for 6 months. Both the groups revealed comparable results in terms of changes in hair counts from baseline and an increase in the terminal hair counts after 6 months of treatment. Although patients taking oral tablets showed a faster improvement, the therapeutic response was not statistically different between the two groups (26).

Since topical minoxidil is at present the first choice of treatment for AGA, novel combination therapy of finasteride with minoxidil has been investigated to enhance the therapeutic efficacy. In 2012, a pilot RCT compared the efficacy and safety between 3%

minoxidil lotion and a combination of 3% minoxidil and 0.1% finasteride lotion in 40 men with AGA. After 24 weeks of application, the increase in hair counts from baseline was significantly different only in patients treated with the combined treatment (58.09 ± 13.39 vs 62.91 ± 13.34, p = 0.044). Additionally, the global assessment scores graded by three blinded physicians were significantly greater in the combination group (1.84 ± 0.79 vs 1.02 ± 0.69, p = 0.003) (27). A retrospective study with 5% topical minoxidil fortified with 0.1% finasteride following prior use of 5% topical minoxidil combined with 1 mg oral finasteride proved that topical combination therapy could maintain good hair density after discontinuation of oral finasteride and may serve as a maintenance medication after treatment. The study also included five patients who stopped the treatment for 8-12 months. Of these, 80% demonstrated excellent improvement after resuming the treatment with a combination of topical minoxidil and finasteride (28). Further, Sheikh et al. conducted an RCT with the same concentration as the previous study for 48 weeks in 104 patients. The combined topical solution showed better hair growth and scalp coverage, smaller balding area, a slower rate of hair loss, and greater patient satisfaction with regards to the frontal hairline than minoxidil alone (12).

A subsequent randomized comparative study in 300 Indian men reported similar effectiveness between 5% topical minoxidil solution with and without 0.1% topical finasteride for the treatment of AGA. Both treatments showed equally good clinical responses in terms of changes in hair counts from baseline after 6 months of treatment (29). Another study randomly assigned 50 men with AGA to receive 5% topical minoxidil as a combination therapy with 1 mg oral finasteride or with 0.1% topical finasteride. After 12 months of administration, the group that received topical finasteride showed more favorable outcomes as determined by digital photography and trichoscopy (30).

Most recently, two RCTs were performed by Suchonwanit et al. who further examined the synergistic effect of topical finasteride admixed with minoxidil solution in both male and female patients (31,32). Both studies determined the clinical efficacy of a topical formulation of 0.25% finasteride in combination with 3% minoxidil (FMX) twice daily compared to 3% minoxidil solution twice daily for 24 weeks. The study in 40 men with AGA exhibited significant superiority of FMX over 3% minoxidil in increasing hair density after 16 and 24 weeks of treatment and in increasing the hair density after 24 weeks of treatment. The mean change from baseline in total hair density (61.84 ± 15.65 hairs/cm^2 vs 34.88 ± 10.24 hairs/cm^2, p = 0.003) and in hair diameter (17 ± 5.24 μm vs 13 ± 4.15 μm, p = 0.034) at week 24 was significantly greater in FMX group than the minoxidil group. Global photographic assessment graded by both patients and physicians displayed a significantly higher improvement in hair growth for the FMX group at 24 weeks (31). Similarly, females with FPHL also demonstrated the superior effect of FMX solution. Another RCT in 30 postmenopausal women demonstrated superior increment in the hair diameter for the FMX-treated patients compared to the minoxidil-treated patients after 24 weeks (11.9 μm vs 7 μm, p = 0.039); however, it did not show a statistically significant difference between the two groups for increased hair counts over time (102.55 ± 22.7 hairs/cm^2 vs 98.1 ± 19.0 hairs/cm^2, p = 0.66). Global photography showed equivocal changes from the baseline rated by the patients and physicians in both groups. The authors observed that at 24 weeks, the serum DHT levels were significantly lower than the baseline in the FMX group compared to the minoxidil group only in the study on females with FPHL (p = 0.016) (32). However, serum DHT concentrations in both the studies remained in the normal physiological ranges throughout the study period (31,32).

Topical application of finasteride is an upcoming and promising modality in the treatment of AGA and FPHL with excellent therapeutic outcomes. Clinical studies on topical formulation have been summarized in Table 1. Furthermore, combination therapy with topical finasteride exhibited an additional effect over topical minoxidil as a monotherapy. These new solutions may be alternative treatment options for individuals who would like to avoid complications from the oral administration. However, as several different concentrations and vehicles for topical finasteride have been used, further studies are required in the future to establish the most effective drug-delivery system, compositions, formulations, regimens, and concentrations of topical finasteride as monotherapy and as a combination therapy with topical minoxidil.

Safety of topical finasteride

Adverse effects of oral finasteride including gynecomastia, erectile dysfunction, a decrease of libido, and breast cancer are believed to be the consequences of DHT reduction in serum and other tissues in the sexual organs (e.g. prostate, seminal vesicles, and epididymis) (33). Topical finasteride has been developed as an alternative to minimize these systemic complications. An animal toxicity study using topical finasteride at different concentrations ranging from 0.2% to 1% observed no signs of skin or systemic toxicity during the 28 days of the study period. Further, there were no histopathological changes in the tissues taken from the rat's liver, kidney, heart, and spleen (12). Concerning clinical studies, no serious side effects or sexual dysfunction have been reported. Although alterations in the serum DHT levels were observed, no one developed unwanted sexual complications caused by the changes in DHT levels (12-15,31,32). Side effects with respect to topical formulation in humans are mainly local and insignificant. Scalp pruritus, irritation, burning sensation, contact dermatitis, and erythema have been reported

with good tolerability (15,26,27,30-32). Other side effects include mild dry and flaky scalp and heaviness on the topical sites (30,32). As the studies on topical finasteride are still limited, further long-term clinical trials in a larger number of subjects are needed to determine the safety of topical finasteride in the treatment of AGA.

Conclusion

This review summarizes the pharmacology, clinical efficacy, and side effects of a topical formulation of finasteride in the treatment of AGA and FPHL. Current data support the therapeutic potential of topical finasteride in increasing hair density and hair diameter while decreasing the systemic adverse effects associated with oral administration. The combination of topical finasteride and minoxidil provides an additional benefit over minoxidil monotherapy and may be a promising treatment option in the future. Despite its proven efficacy, the use of topical finasteride is limited due to a smaller number of studies. Further studies are warranted to determine the most efficacious formulations and to investigate the consequences following the long-term use of topical finasteride.

Disclosure statement

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Table 1. Clinical studies of topical finasteride for the treatment of androgenetic alopecia and female pattern hair loss**.**

Authors	Study design	N	Finasteride regimen	Duration of treatment	Population	Results	Side effects
Mozzarella et al.,1997[15]	Retrospective	52	0.005% finasteride solution twice daily	16 months	18-38 years; men & pre-menopausal women, Hamilton-Norwood scale I-III in men, Ludwig scores I-II in women	• Progressively lower hair counts from wash test from 49.8 ± 5.9 to 45.2 ± 7.5 at 6 months & 36.8 ± 8.1 at 16 months • Clinically improved hair density & increased hair regrowth	None
Charuwichitratana et al., 2003[25]	RCT	12	0.1% finasteride solution vs placebo twice daily	12 months	39.3 years (finasteride), 46.2 years (placebo); men; Hamilton-Norwood scale III-VI	• Higher proportions of improved patients in finasteride group (100%) than placebo group (40%) • 28.6% of finasteride-treated patients & 20% placebo-treated patients had increase in hair counts	Folliculitis (placebo group)
Sittichareoenchai, 2006[16]	RCT	50	0.5% finasteride vs placebo twice daily	6 months	18-60 years; men; Hamilton-Norwood scale III-V	• Increased terminal hair counts of 34.2 & 80.9 in finasteride group at 3 months & 6 months respectively • 46.2% of patients in finasteride group showed improved GPA % & 53.8% remained unchanged • 83.3% of patients in placebo group remained unchanged & 16.7% had	None

						decreased GPA	
Hajheydari et al., 2009[26]	RCT	45	1% finasteride gel twice daily vs 1 mg oral finasteride daily	6 months	22.8 ± 3.3 years; men	• Both groups similarly had significantly increased hair counts & increased number of terminal hairs from baseline • The size of alopecia remained indifferent from pre-treatment	Erythema (finasteride group)
Tanglertsampan, 2012[27]	RCT	40	3% MNX with 0.1% finasteride vs 3% MNX lotion twice daily	6 months	34.2 ± 7 years (MNX with finasteride), 34.5 ± 5.2 years; men; Hamilton-Norwood scale III-V	• Increased in hair count from baseline of 4.8 ± 9.1 in finasteride + MNX group & 2.9 ± 6.9 in MNX group at 6 months • GPA showed scores of 1.8 ± 1 in finasteride + MNX group & 1 ± 1 MNX group	Contact dermatitis
Chandrashekar et al., 2015[28]	Retrospective	50	5% MNX fortified with 0.1% finasteride	12 months	20-40 years; men; previously treated with MNX & oral finasteride	• 84.4% maintained a good hair density • 4 of 5 patients who discontinued oral finasteride within 1 years responded to topical MNX-finasteride combination	None
Sheikh et al., 2015[12]	RCT	104	5% MNX with 0.1% finasteride vs 5% MNX solution	6 months	18-45 years; men; Hamilton-Norwood II-V	• Patients in finasteride + MNX group had significantly higher investigator scores (64.7% vs 25.5%) • Significantly higher number of patients with finasteride +	None

						MNX (88.9%) than with MNX (60%) showed greater improvement in GPA • Patients with finasteride + MNX had greater satisfaction related to hair growth, slowing down hair loss & hairline at the front	
Narasimhalu, 2018[29]	RCT	300	0.1% finasteride with 5% MNX vs 5% MNX solution	6 months	18-45 years; men; maximum diameter of bald area < 10 cm	• Comparable response in extent of bald area, hair count & number of terminal hairs	Mild burning sensation & erythema
Rai et al., 2018[30]	RCT	50	5% MNX with 1 mg oral finasteride (group A) vs 5% MNX with 0.1% topical finasteride (group B)	12 months	29.4 ± 3.6 years; men; Hamilton-Norwood scale III-IV	• Mean quality of life was significantly higher in patients of group A (46.3) than patients in group B (40.5) at 12 months ($p < 0.05$) • 65% of patients in group A & 83% of patients in group B had clinical improvement	Pruritus, erythema & heaviness (group B)
Suchonwanit et al., 2018[31]	RCT	40	0.25% topical finasteride with 3% MNX vs 3% MNX solution twice daily	6 months	39.3 ± 11.9 years (finasteride + MNX), 44.4 ± 12.5 years (MNX); men, Hamilton-Norwood scale III-V	• Mean increased hair density of 61.8 ± 15.6 hairs/cm^2 in finasteride + MNX group & 34.9 ± 10.2 hairs/cm^2 in MNX group at 6 months • Mean increased hair diameter of 17 ± 5.2 µm in finasteride + MNX group & 13 ±	Scalp pruritus & dry flaky scalp (both groups), headache (MNX group)

						4.2 µm in MNX group at 6 months • 63.1% & 56.2% of patients in finasteride + MNX group & 22.2% 16.7% of patients in MNX group had marked improvement in GPA by investigators & patients, respectively	
Suchonwanit et al., 2019[32]	RCT	30	0.25% topical finasteride with 3% MNX vs 3% MNX solution twice daily	6 months	56.8 ± 6.6 years (finasteride + MNX) vs 59.8 ± 7.7 years (MNX); post-menopausal women, Ludwig scores I-III	• Mean increased hair diameter of 11.9 µm in finasteride + MNX group & 7 µm in MNX group at 6 months • Mean increased hair density of 24.7 hairs/cm^2 in finasteride + MNX group & 21.9 hairs/cm^2 in MNX group at 6 months • 93% & 93.3% of patients in finasteride + MNX group & 85.7% & 92.9% of patients in MNX group had improvement in GPA by investigators & patients, respectively • Decreased serum DHT level in finasteride + MNX group	Pruritus (both groups), irritation (MNX group)

DHT, dihydrotestorone; **GPA**, global photographic assessment; **MNX**, minoxidil; **RCT**, randomized controlled trial

Figure Legend

Figure 1. Flowchart of study selection for review of topical finasteride**.**