Medical Hypotheses (2004) **62**, 112–115

ELSEVIER

medical hypotheses

http://intl.elsevierhealth.com/journals/mehy

Ketocazole as an adjunct to finasteride in the treatment of androgenetic alopecia in men

B.S. Hugo Perez

California College of Podiatric Medicine, 371 Columbus Avenue, San Francisco, CA 94133, USA

Received 5 June 2002; accepted 11 November 2002

Summary Dihydrotestosterone (DHT) binding to androgen receptors (AR) in hair follicles is commonly accepted as the first step leading to the miniaturizing of follicles associated with androgenetic alopecia (AGA). Testosterone is converted to DHT by the enzyme 5α-reductase. Finasateride a 5α-reducase inhibitor blocks the production of DHT and is currently used to treat AGA. The inhibition is not complete but a reduction of DHT systemically and in the scalp is accomplished. Ketoconazole has been clinically shown to be effective in the treatment of AGA. In this paper, evidence is presented to support the hypothesis that ketoconazole 2% shampoo has a local disruption of the DHT pathway. It is proposed that using ketoconazole 2% shampoo as an adjunct to finasteride treatment could lead to a more complete inhibition of DHT and thus better treat AGA.

Introduction

Androgenetic alopecia (AGA) is commonly referred to as male pattern hair loss or female pattern hair loss in genetically susceptible men and women [1]. Thinning of hair diameter as well as a miniaturizing of the terminal hair follicle is characteristic of AGA. With time, miniaturized hair follicles produce shorter and thinner hair [2,3]. The onset of AGA in both sexes is between 12 and 40 years of age [1]. Until recently there were few treatment options for thinning hair. Approved treatments by the FDA are promising, but these regimens have their limits. As a result, there is a need for continued research into more efficacious treatments.

The hair cycle

In order to appreciate the pathophysiology of AGA, a basic understanding of the hair cycle is needed. There are three phases to the hair cycle: anagen (growth phase), catagen (involution phase), and telogen (rest phase) [4]. At any given time about 90–95% of hair follicles are in anagen. The remaining 5–10% are in telogen with a small portion of the follicles, about 1% in catagen [5]. When a follicle ends the telogen phase the hair is shed and this initiates the onset of the anagen phase, thus completing the cycle. The different phases of the hair cycle have different time frames; anagen usually lasts 2–6 years, categen lasts 2–3 weeks and telogen last 2–3 months. It is the duration in the anagen phase that determines the hair length and the diameter of the hair bulb determines the thickness of the hair [1]. Thus, a miniaturized hair follicle that has a short anagen phase will produce a short and thin hair. Treatment for AGA is ideally aimed at prolonging anagen phase and preventing miniaturizing thus restoring of hair follicle size.

Androgenetic alopecia

AGA is a result of the effects of androgens in genetically susceptible individuals [6]. The peripheral

E-mail address: Hugop2002@yahoo.com (B.S. Hugo Perez).

0306-9877/$ - see front matter © 2003 Published by Elsevier Ltd.
doi:10.1016/S0306-9877(03)00264-0

conversion of testosterone (T) by the enzyme 5α-reductase (5α-R) to the more potent dihydrotosterone (DHT) has been implicated as the responsible androgen in the progression of AGA [1—6]. Although T and DHT both act at the androgen receptor (AR), DHT has a higher affinity for the receptor. Furthermore, the binding of DHT appears to be necessary in the pathologic activity in tissues like prostate or hair follicles [7]. Men genetically deficient in 5α-R show an absence of AGA, supporting the hypothesis of the role of DHT in AGA [8]. In addition, studies have found an over expression of 5α-R in human hair follicles of patients with AGA [9]. It has been suggested that DHT binds to the AR causing the activation of the genes that are responsible for the miniaturizing of the hair follicles [1,3]. These miniaturized follicles in turn are responsible for the production of the thin hair seen in AGA.

The conversion of T to DHT is accomplished by type I and type II isoenzymes of 5α-R. Biochemical studies have indicated that 5α-RI is the predominant isoform in the human scalp [12,13]. Immunohistochemistry studies performed to determine the exact distribution of the two isoforms have concluded that 5α-RI is found exclusively in the sebaceous gland, whereas the 5α-RII is found within the innermost layer of the outer root sheath of the hair follicle and extends into the inner root sheath into more proximal regions of the follicle [14].

The mechanism of AGA development does not seem to be limited to DHT levels. The number of AR expressed by an individual may have an effect on AGA as well. It is well established that individuals with AGA have higher levels of AR [9—11]. When compared, higher levels of AR have been found in the hair follicles in thinning regions of the scalp versus non-thinning regions [10].

Finasteride

Finasteride is a competitive inhibitor of 5α-RII, the isoenzyme of 5-R found mainly in the root sheath. Consequently, administration of finasteride prevents the conversion of T to DHT [15]. Reducing the total amount of DHT available lowers the overall binding of DHT to androgen receptors. Since finasteride has no affinity for the AR, it only inhibits the production of DHT, not the binding of DHT to the AR in the hair follicle [2,9]. The optimal dose of finasteride for the treatment of AGA has been determined to be 1 mg/day [6]. Finasteride 1 mg/day reduced serum DHT levels by 71.4% and reduced scalp DHT levels by 64.1%. Finasteride had no statistically significant reduction on the serum concentrations of T but a 41 % increase in scalp T concentrations was noted [16]. The selectivity of finasteride for 5α-RII along with the predominance of 5-RII in the scalp has led researchers to conclude that the efficacy of finasteride in the treatment of AGA is at least in part mediated by local inhibition of 5α-RII in the hair follicle [7].

The efficacy of oral finasteride in the treatment of AGA is well documented. In three randomized, double-blinded, placebo controlled studies, finasteride significantly increased hair counts and improved scalp coverage [17—19]. After two years of treatment with finasteride, about two-thirds of men showed improved scalp coverage, about one-third maintained their coverage, and only 1% showed a decrease in scalp coverage. It is believed that since the miniaturizing of the hair follicle takes years the reversal of the process may also takes years of treatment [1].

Finasteride has been shown to be ineffective for the treatment AGA in women. Clinical trials with postmenopausal women given 1 mg of finasteride a day for one year showed no positive benefit of finasteride [1].

Ketoconazole

Ketoconazole is an imidazole broad-spectrum antifungal and steroid biosynthesis inhibitor [20,21]. Ketoconazole in high doses (400 mg TID) blocks both testicular and adrenal androgen biosynthesis [22—24]. The androgen lowering potential of high doses of ketoconazole has led to its use in the treatment of advanced prostate cancer.

The mechanism of action of high doses of ketoconazole is through the inhibition of cytochrome P450 and 17, 20-lyase, which are involved in the synthesis and degradation of steroids including the precursors of testosterone [22—25]. Recent studies have demonstrated that treatment with high doses of ketoconazole can produce a significant response in a majority of patients with advanced prostate cancer. In the treatment of prostate cancer, ketoconazole is considered to have a reasonable toxicity profile. The most serious potential adverse effects of the drug can be ameliorated by simple measures [24].

Ketoconazole has also been shown to be an effective treatment for AGA. Long-term use of shampoos containing 2% ketoconazole increased the density, size and proportion of anagen follicles in men between the ages of 21—33 [26]. In this study, 27 subjects used 2% ketoconazole shampoo exclusively 2—4 times a week for 21 weeks. The remaining 12 in the control group used an unmedicated

shampoo. Pilary index (PI) was used to measure AGA. PI is calculated by multiplying the follicles in anagen (A) with average diameter (D) of the hair shafts ($PI = A \times D$). The unmedicated group showed a linear decrease in PI ($r = 0.56$, $p < 0.05$) with time. The ketoconazole group yielded progressive PI increase ($r = 0.69$, $p < 0.01$).

Although the effects of ketoconazole on 5α-R have been documented, the authors of the study concluded that the benefits were attributed to its effects on fungal scalp infections in genetically predisposed individuals. They argued that AGA has a multifactorial pathogenesis with an inflammatory reaction caused by a Malassezia fungal infection. It was concluded that ketoconazole was therapeutic by reducing inflammation through its anti-inflammatory properties and by clearing the adjacent fungal infection. Exploration of the inflammatory aspect of AGA was in great part based on the results of a biopsy study by Jaworsky et al. [27], showing that AGA patients had signs of T-cell infiltration of follicular stem cell epithelium. However, limited conclusions should be drawn from the Jaworsky study because it only included 4 subjects and only 3 of them were men.

Discussion

The development of AGA in genetically susceptible individuals has been linked to an overproduction of 5α-R and an over expression of AR. Thus, a treatment that addresses both components while maintaining a favorable side effect profile would be most beneficial.

It can reasonably be concluded that the clinical efficacy of ketoconazole shampoo in the treatment of AGA is primarily a function of DHT pathway disruption rather than an anti-inflammatory effect. In rat studies ketoconazole caused 5α-R inhibition [28]. Furthermore, in humans ketoconazole has also been shown to inhibit the binding of 5α-R to sex hormone globulins [29]. These clinical studies suggest that ketoconazole like finasteride may inhibit the production of DHT. Unlike finasteride ketoconazole has been shown to bind to human AR [30]. Thus, the effect of ketoconazole on the DHT pathway may be two-fold: inhibition of DHT and/or inhibition of DHT binding to AR. Either or both of these properties would result in reduced incidence of DHT binding to AR and inhibiting the pathway that leads to the miniaturizing of hair follicles.

Although finasteride is a competitive inhibitor of 5α-R, increasing the dose of finasteride to further inhibit DHT is unlikely to be beneficial in the treatment of AGA. Scalp DHT levels were reduced by 64.1% and 69.4% while serum DHT levels were reduced by 71.4% and 72.2% with 1 and 5 mg of finasteride, respectively [14]. Investigators found a 75% and 68% improvement in rating of AGA in patients taking 1 and 5 mg of finasteride, respectively [6]. Clinically, 5 mg doses of finasteride have not been superior over 1 mg in the treatment of AGA [6,16]. Consequently, reducing the effects of DHT in the hair follicle might also require inhibiting the binding of DHT to the AR.

One possible argument against the use of ketoconazole for AGA is that the high concentrations required for ketoconazole to affect binding are higher than safely possible through oral means [30]. However, for purposes of AGA treatment, the only tissue that requires a relative high concentration of ketoconazole is the hair follicles. Therefore, a local application of ketoconazole in the form of a shampoo would be most appropriate. In this way systemic toxicity can be avoided and the ketoconazole can be directly delivered to the area of concern. A review of the literature did not turn up any studies determining the systemic concentration of ketoconazole when using ketoconazole 2% shampoo.

Clinical trials are needed to evaluate the effectiveness of ketoconazole shampoo in the treatment of AGA. These trials should attempt to elucidate the method of action responsible for the results. Both the inflammation and the DHT pathway need to be addressed.

Conclusion

Finasteride is effective at reducing scalp DHT level, but it does nothing to stop the remaining DHT from binding to the abundant AR found in AGA patients. Local ketoconazole 2% can potentially inhibit DHT production and/or DHT binding to AR. Finasteride therapy adjunct with ketoconazole shampoo could potentially block the DHT pathway more completely; however, further clinical trials are warranted.

References

[1] Price VH. Treatment of hair loss. N Engl J Med 1999; 341(13):964–73.
[2] Kaufman KD. Androgen metabolism as it affects hair growth in androgenetic alopecia. Dermatol Clin 1996; 14(4):697–711.
[3] Price VH. Testosterone metabolism in the skin. A review of its function in androgenetic alopecia, acne vulgaris, and idiopathic hirsutism including recent studies with antiandrogens. Arch Dermatol 1975;111(11):1496–502.

[4] Jackson EA. Hair disorders. Prim Care 2000;27(2):319—32.
[5] Whiting DA. Chronic telogen effluvium. Dermatol Clin 1996;14(4):723—31.
[6] Roberts JL, Fiedler V, Imperato-McGinley J, et al. Clinical dose ranging studies with finasteride, a type 2 5α-reductase inhibitor, in men with male pattern hair loss. J Am Acad Dermatol 1999;41(4):555—63.
[7] Harris GS, Kozarich JW. Steroid 5α-reductase inhibitors in androgen-dependent disorders. Curr Opin Chem Biol 1997; 1(2):254—9.
[8] Imperato-McGineley J, Guerrero L, Gautier T, Peterson RE. Steroid 5α-reductase deficiency in man: an inherited form of male pseudohermaphroditism. Science 1974;186(4170): 1213—5.
[9] Sawaya ME, Price VH. Different levels of 5α-reductase type I and II, aromatase, and androgen receptor in hair follicles of women and men with androgenetic alopecia. J Invest Dermatol 1997;109(3):296—300.
[10] Pandall VA, Thornton MJ, Messenger AG. Cultured dermal papilla cells from androgen-dependent human hair follicles (e.g. beard) contain more androgen receptors than those from non-balding areas of scalp. J Endocrinol 1992; 133(1):141—7.
[11] Hibberts NA, Howell AE, Randall VA. Balding hair follicle dermal papilla cells contain higher levels of androgen receptors than those from non-balding scalp. J Endocrinol 1998;156(1):59—65.
[12] Thigpen AE, Silver RI, Guileyardo JM, Casey ML, McConnell JD, Russell DW. Tissue distribution and ontogeny of steroid 5α-reductase isozyme expression. J Clin Invest 1993;92(2): 903—10.
[13] Thiboutot D, Harris G, Iles V, Cimis G, Gilliland K, Hagari S. Activity of the type 1 5α-reductase exhibits regional differences in isolated sebaceous glands and whole skin. J Invest Dermatol 1995;105(2):209—14.
[14] Eichler W, Dreher H, Hoffmann R, Happle R, Aumumuller G. Immunohistochemical evidence for differential distribution of 5α-reductase isoenzymes in human skin. Br J Dermatol 1995;133(3):371—6.
[15] Stoner E. The clinical development of a 5α-reductase inhibitor, finasteride. J Steroid Biochem Mol Biol 1990; 37(3):375—8.
[16] Drake L, Hordinsky M, Fiedler V, et al. The effects of finasteride on scalp skin and serum androgen levels in men with androgenetic alopecia. J Am Acad Dermatol 1999; 41(4):550—4.
[17] Kauffman KD et al. Finasteride in the treatment of men with androgenetic alopecia. Finasteride Male Pattern Hair Loss Study Group. J Am Acad Dermatol 1998;39(4 Pt 1):578—89.
[18] Leyden J et al. Finasteride in the treatment of men with frontal male pattern hair loss. J Am Acad Dermatol 1999; 40(6 Pt 1):930—7.
[19] Physician circular for Propecia. West Point, PA: Merck; December 1997.
[20] Marty MS, Crissman JW, Carney EW. Evaluation of the male pubertal onset assay to detect testosterone and steroid biosynthesis inhibitor in cd rats. Toxicol Sci 2001;60(2): 285—95.
[21] Bhasin S, Sikka S, Fielder T, Sod-Moriah U, Levine HB, Swerdloff RS, Rajfer J. Hormonal effects of ketoconazole in vivo in the male rat: mechinism of action. Endocrinology 1986;118(3):1229—32.
[22] Rrachtenberg J, Pont A. Ketoconazole therapy for advaced prostate cancer. Lancet 1984;2(8400):433—5.
[23] Deruyne FM, Witjes FA. Ketoconazole high dose (H.D.) in the management of hormonally pretreated patients with progressive metastatic prostate cancer. Prog Clin Biol Res A 1987;243:301—13.
[24] Bok BA, Small EJ. The treatment of advanced prostate cancer with ketoconazole: safety issues. Drug Saf 1999; 20(5):451—8.
[25] De Coster R, Wouters W, Bruynseels J. P450-dependent enzymes as targets tor prostate cancer therapy. J Steroid Biochem Mol Biol 1996;56(1—6 Spec. No.): 133—43.
[26] Pierard-Frachimont C, De Doncker P, Cauwenbergh G, Pierard GE. Ketoconazole shampoo: effect of long-term use in androgenic alopecia. Dermatology 1998;196(4): 474—7.
[27] Jaworsky C, Kligman AM, Muphy GF. Characterization of inflammatory infiltrates in male pattern alopecia: implications for pathogenesis. Br J Dermatol 1992;127(3): 239—46.
[28] Masubuchi Y, Akaike M, Kumai T, Takanka M, Wantanabe M, Hirai M. Disturbanse or relatively important actions of antihypertensives, antifungal agent and opiate antagonist to the testicular steridogenesis in rats. J Toxicol Sci;17: 41—50.
[29] Ayub M, Levell MJ. The effect of ketoconazole related imidazole drugs and antiandrogens on [^{3}H]R 1881 binding to the prostatic androgen receptor and [^{3}H]5α-dihydrotestosterone and [^{3}H]cortisol binding to plasma proteins. J Steroid Biochem 1989;33(2):251—5.
[30] Eil C. Ketoconazole binds to the human androgen receptor. Horm Metab Res 1992;24(8):367—70.