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# The effects of finasteride on scalp skin and serum androgen levels in men with androgenetic alopecia

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**Background:** Data suggest that androgenetic alopecia is a process dependent on dihydrotestosterone (DHT) and type 2 5 $\alpha$ -reductase. Finasteride is a type 2 5 $\alpha$ -reductase inhibitor that has been shown to slow further hair loss and improve hair growth in men with androgenetic alopecia.

**Objective:** We attempted to determine the effect of finasteride on scalp skin and serum androgens.

**Methods:** Men with androgenetic alopecia (N = 249) underwent scalp biopsies before and after receiving 0.01, 0.05, 0.2, 1, or 5 mg daily of finasteride or placebo for 42 days.

**Results:** Scalp skin DHT levels declined significantly by 13.0% with placebo and by 14.9%, 61.6%, 56.5%, 64.1%, and 69.4% with 0.01, 0.05, 0.2, 1, and 5 mg doses of finasteride, respectively. Serum DHT levels declined significantly ( $P < .001$ ) by 49.5%, 68.6%, 71.4%, and 72.2% in the 0.05, 0.2, 1, and 5 mg finasteride treatment groups, respectively.

**Conclusion:** In this study, doses of finasteride as low as 0.2 mg per day maximally decreased both scalp skin and serum DHT levels. These data support the rationale used to conduct clinical trials in men with male pattern hair loss at doses of finasteride between 0.2 and 5 mg. (J Am Acad Dermatol 1999;41:550-4.)

Body hair growth in scalp, pubic, axillary, and facial areas is an androgen-dependent process. Many androgen target tissues in men, including the prostate and scalp hair follicles,

are more responsive to dihydrotestosterone (DHT) than testosterone (T). Two types of 5 $\alpha$ -reductase (5 $\alpha$ R) enzymes, which convert T to DHT, are present in humans.<sup>1-3</sup> Scalp skin contains type 1 5 $\alpha$ R in the

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sebaceous glands and type 2 5 $\alpha$ R in the connective tissue sheaths and dermal papillae of hair follicles.<sup>4</sup> Men with inherited type 2 5 $\alpha$ R enzyme deficiency do not experience benign prostatic hyperplasia or androgenetic alopecia despite the presence of type 1 5 $\alpha$ R.<sup>5</sup> These data suggest that androgenetic alopecia is a DHT- and type 2 5 $\alpha$ R-dependent process. In clinical trials, inhibition of the type 2 5 $\alpha$ R enzyme with finasteride was shown to slow further hair loss and improve hair growth in men with male pattern hair.<sup>6</sup> This study was designed to assess the biochemical dose-response effects of finasteride in the circulation as well as the target organ, scalp skin.

Previous studies with finasteride have demonstrated that administration of doses of finasteride ranging from 0.2 to 100 mg daily for 11 days in healthy male volunteers produced suppression of serum DHT levels.<sup>7,8</sup> In addition, during a preliminary biochemical study, finasteride 5 mg was shown to significantly decrease scalp skin DHT levels.<sup>9</sup> The purpose of this 42-day study was to determine the lowest dose of finasteride that maximally suppresses both scalp and serum DHT levels.

## PATIENTS AND METHODS

### Patient population

This double-blind, randomized, placebo-controlled study was conducted at 16 centers in the United States and Canada and approved by each institutional review board. All participants provided written informed consent. Patients with male pattern hair loss who were in good health, between the ages of 18 and 50 years, and candidates for hair transplantation or willing to undergo scalp biopsies of balding skin were eligible for enrollment. During the 3 months before study start and during the study, patients could not use drugs with androgenic or antiandrogenic properties, topical scalp medications, or drugs with the potential to affect hair growth.

### Study protocol

After an initial screening visit, which included a complete medical history, physical examination, hematology, serum chemistry, and urinalysis, patients were randomized to receive placebo or 0.01, 0.05, 0.2, 1, or 5 mg finasteride orally once daily in the morning for 42 days. On days 0 (baseline) and 42, scalp skin samples (500 mg) were obtained for measurement of DHT and T levels. Serum for assay of DHT, T, and 3-alpha-diol-glucuronide (5 $\alpha$ -androstan-3 $\alpha$ ,17 $\beta$ -diol glucuronide) levels were obtained on days -7, 0, and after discontinuation of medication.

### Androgen measurements

DHT and T were extracted from scalp skin and measured by high-pressure liquid chromatography-radioimmunoassay as described previously.<sup>9</sup> Interassay precision was 5.5% for 1 ng T/g tissue and 12.1% for 1.7 ng DHT/g tissue. The limit of detection was 0.13 ng/g and 0.10 ng/g for

scalp skin DHT and T, respectively. Serum DHT, T, and 3-alpha-diol-glucuronide were assayed by Endocrine Sciences (Calabasas Hills, Calif) as described previously.<sup>10</sup> All analyses were performed by investigators blinded with respect to treatment.

### Statistical methods

All patients who had a baseline and at least 1 posttreatment measurement were included in the analysis. Treatment effects were evaluated by means of the stepwise Tukey trend test,<sup>11,12</sup> adjusted for multiplicity. This approach evaluated the dose-response relationship for the 5 doses of finasteride and provided the comparison with placebo by means of analysis of variance (ANOVA) techniques. If a statistically significant result was observed, then the highest dose group was deleted and the test repeated. This statistical process proceeded in a stepwise fashion until lack of significance was observed, in an effort to determine the minimal detectable dose that was significantly different from placebo. Analysis of variance models were used to assess pairwise differences between treatment groups.

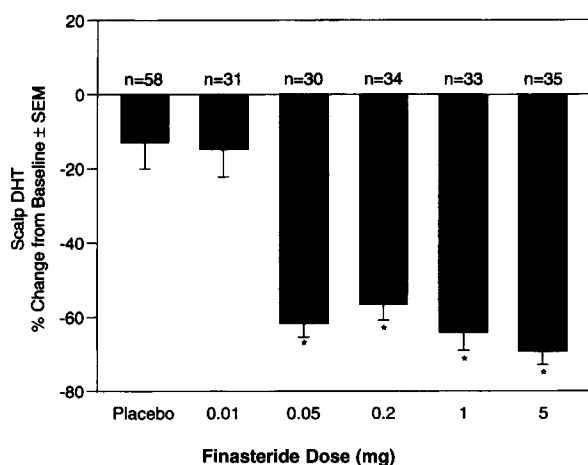
## RESULTS

Of 249 eligible men, 67 were randomized to receive placebo, 37 received 0.01 mg, 34 received 0.05 mg, 36 received 0.2 mg, 37 received 1 mg, and 38 received 5 mg of finasteride. The mean age of the patients enrolled was 37 years, and 93% were white (Table I). Mean baseline scalp skin DHT levels ranged from 2.0 to 2.4 ng/g across treatment groups, and mean baseline serum DHT levels ranged from 41.1 to 51.5 ng/dL. Mean baseline T levels ranged from 1.6 to 2.3 ng/g in scalp skin and from 437.6 to 528.5 ng/dL in serum. Mean baseline serum 3-alpha-diol-glucuronide levels ranged from 472.0 to 699.5 ng/dL. There were no clinically meaningful differences between treatment groups in baseline demographics.

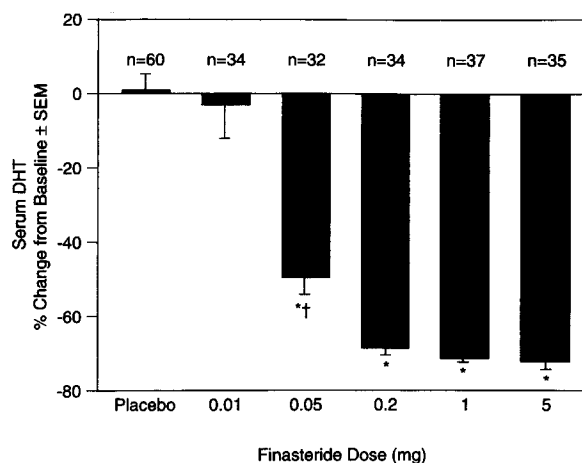
A total of 230 patients completed the study. Two placebo-treated patients withdrew because of a clinical adverse event, 11 patients refused to undergo a second biopsy, and 6 patients withdrew for other reasons. The treatment groups were similar with respect to the proportion of patients who withdrew from the study.

### Efficacy

**Dihydrotestosterone levels.** Scalp skin DHT levels declined significantly ( $P < .05$ ) from baseline in all treatment groups, including placebo. Median decreases from baseline in scalp skin DHT levels were 13.0% in the placebo group, and 14.9%, 61.6%, 56.5%, 64.1%, and 69.4% in the finasteride 0.01, 0.05, 0.2, 1, and 5 mg groups, respectively. The higher doses of finasteride provided greater reductions



**Fig 1.** Median percent change from baseline in scalp skin DHT levels in men treated with placebo or 0.01, 0.05, 0.2, 1, or 5 mg finasteride daily for 42 days. \* $P < .001$  versus placebo and 0.01 mg.



**Fig 2.** Median percent change from baseline in serum DHT levels in men treated with placebo or 0.01, 0.05, 0.2, 1, or 5 mg finasteride daily for 42 days. \* $P < .001$  versus baseline and placebo. † $P < .001$  versus 0.2, 1, and 5 mg.

**Table I.** Baseline demographics of patients randomized to 42 days of treatment with finasteride or placebo

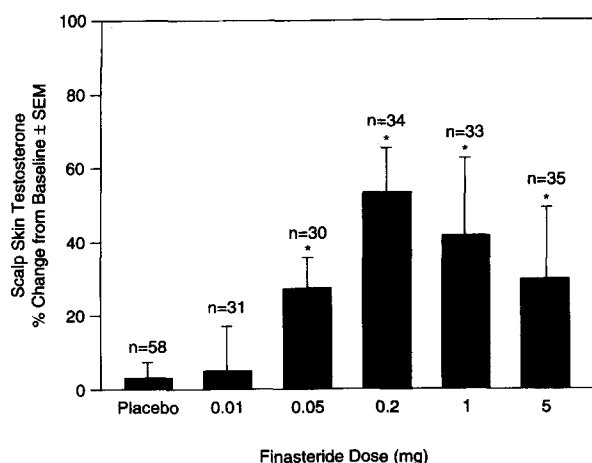
Parameters	Placebo (n = 67)	Finasteride				
		0.01 mg (n = 37)	0.05 mg (n = 34)	0.2 mg (n = 36)	1 mg (n = 37)	5 mg (n = 38)
Age (y)						
Mean	38	36	39	38	36	37
Range	19-49	20-48	25-51	22-51	21-50	22-46
Race (%)						
White	87	100	94	92	97	95
Hispanic	9	0	3	3	3	0
Black	3	0	3	3	0	3
Asian	2	0	0	3	0	3
Mean scalp skin DHT ± SD (ng/g)	2.0 ± 0.8	2.1 ± 0.8	2.4 ± 1.1	2.4 ± 1.0	2.1 ± 1.1	2.0 ± 0.8
Mean serum DHT ± SD (ng/dL)	40.1 ± 16.8	44.5 ± 20.7	43.0 ± 15.4	51.5 ± 18.1	45.6 ± 19.0	48.2 ± 26.7
Mean scalp skin T ± SD (ng/g)	1.7 ± 0.8	1.9 ± 0.8	2.3 ± 1.4	1.6 ± 0.8	1.6 ± 0.8	1.7 ± 0.8
Mean serum T ± SD (ng/dL)	437.6 ± 136.4	449.1 ± 145.3	455.4 ± 135.1	528.5 ± 133.8	441.4 ± 151.1	509.3 ± 208.4
Mean serum 3-alpha-diol- glucuronide ± SD (ng/dL)	564.8 ± 332.3	560.7 ± 386.3	616.9 ± 378.0	576.7 ± 474.3	699.5 ± 415.4	472.0 ± 237.7

DHT, Dihydrotestosterone; SD, standard deviation; T, testosterone.

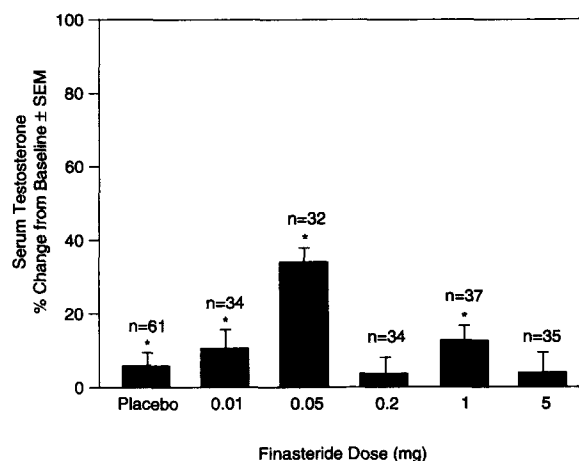
than 0.01 mg (Fig 1), and no significant difference was seen between 0.01 mg finasteride and placebo.

Serum DHT decreased with doses of finasteride of 0.05 mg and higher, but not in the placebo and finasteride 0.01 mg groups (Fig 2). A significant ( $P <$

.001) median percent decrease from baseline in serum DHT levels of 49.5%, 68.6%, 71.4%, and 72.2% occurred in the 0.05, 0.2, 1, and 5 mg finasteride groups, respectively, with a clear dose-response effect observed. The 4 higher finasteride doses



**Fig 3.** Median percent change from baseline in scalp skin testosterone levels in men treated with placebo or 0.01, 0.05, 0.2, 1, or 5 mg finasteride daily for 42 days. \* $P < .01$  versus placebo and 0.01 mg.



**Fig 4.** Median percent change from baseline in serum testosterone levels in men treated with placebo or 0.01, 0.05, 0.2, 1, or 5 mg finasteride daily for 42 days. \* $P \leq .05$  versus baseline.

decreased serum DHT levels significantly more than the 0.01 mg dose. Additionally, the 0.05 mg dose was suboptimal and caused significantly less of a decrease in serum DHT levels than the 3 higher doses.

**Testosterone levels.** The median percent increase from baseline in scalp skin T levels was 3.1% in the placebo group and 5.0%, 27.2%, 53.2%, 41.4%, and 29.7% in the 0.01, 0.05, 0.2, 1, and 5 mg finasteride groups, respectively (Fig 3). The median percent change from baseline was significant ( $P < .001$ ) for all finasteride doses greater than 0.01 mg. There was no significant difference between the 0.01 mg finasteride group and placebo, but each differed significantly from the other 4 finasteride treatment groups ( $P < .01$ ).

No significant dose-response effect was observed on the basis of serum T percent change from baseline. Median serum T levels were variably increased among treatment groups (Fig 4), with significant increases from baseline in the placebo group (5.7%,  $P = .014$ ), and 0.01, 0.05, and 1 mg finasteride groups (10.5%, 33.9%, 12.5%, respectively;  $P < .002$ ), but nonsignificant increases in the 0.2 and 5 mg finasteride groups (3.5%, 3.7%).

**3- $\alpha$ -phadiol-glucuronide levels.** There was a significant ( $P < .002$ ) decrease in median serum 3- $\alpha$ -phadiol-glucuronide levels from baseline, with a clear dose-response effect, in all 5 finasteride groups but not in the placebo group: 0.1% decrease with placebo and 15.2%, 63.3%, 68.1%, 74.8%, and 73.6% with 0.01, 0.05, 0.2, 1, and 5 mg finasteride, respectively. Median serum 3- $\alpha$ -phadiol glucuronide

was decreased to a significantly greater extent in the finasteride treatment groups than in the placebo group.

### Safety and tolerability

Of the 249 patients who entered the study, only 2 drug-related adverse experiences were reported in more than 1 patient in any treatment group: headache (placebo 3%, 1 mg 2.7%, none on 5, 0.2, 0.05, or 0.01 mg) and decreased libido (placebo 4.5%, 0.01 mg 2.7%, 0.05 mg 2.9%, 0.2 mg 8.3%, 1 mg 0%, and 5 mg 2.6%).

### DISCUSSION

This double-blind, randomized, placebo-controlled trial provides evidence of the exquisite sensitivity of finasteride in suppressing scalp skin DHT levels. Even at low doses, finasteride decreased scalp skin DHT levels by approximately 60% within 42 days of beginning treatment. Because DHT is implicated in the pathogenesis of male pattern hair loss,<sup>5,13,14</sup> it was hypothesized that suppression of DHT with finasteride would lead to improvement in androgenetic alopecia.<sup>6,15</sup> A small preliminary biochemical study that evaluated the effects of finasteride on scalp skin DHT levels in balding versus nonbalding areas of scalp skin demonstrated that DHT levels are higher in balding skin.<sup>9</sup> The results of that study also indicated that daily use of 5 mg of finasteride for 4 weeks reduced balding scalp skin DHT levels by 34%. Subsequent clinical trials have confirmed that treatment with finasteride does improve androgenetic alopecia in men.<sup>6</sup>

Although the type 2 5 $\alpha$ R enzyme has been found in the scalp hair follicle,<sup>4,16,17</sup> the predominant enzyme in scalp skin is type 1 5 $\alpha$ R,<sup>1</sup> largely because of type 1 enzyme localized to the sebaceous glands.<sup>17,18</sup> However, finasteride, a specific type 2 5 $\alpha$ R inhibitor, decreases scalp skin DHT levels by more than 60%. Therefore it seems likely that a significant amount of DHT found in scalp skin is derived from both local DHT production and circulating DHT. Consequently, the effect of finasteride on scalp DHT is likely because of its effect on both local follicular DHT levels as well as serum DHT levels. Further studies with clinically relevant end points were required to arrive at the definitive therapeutic dose.

This study was conducted to determine the pharmacologic effects of doses of 5 mg or less of finasteride on balding scalp skin and serum androgen levels. Patients treated with 0.05 mg or more of finasteride had greater median reductions in scalp skin DHT than patients in the placebo or 0.01 mg finasteride groups. However, the 0.05 mg dose was sub-optimal in terms of serum DHT suppression. Doses of at least 0.2 mg were needed to maximally suppress both scalp skin and serum DHT levels. These data support the rationale used to conduct clinical trials in men with hair loss at doses between 0.2 and 5 mg<sup>6,19,20</sup> because local scalp and serum DHT appear to contribute to total scalp DHT levels, and both may be important in the pathophysiology of male pattern hair loss in men.

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## REFERENCES

- Harris G, Azzolina B, Baginsky W, Cimisi G, Rasmuson GH, Tolman RL, et al. Identification and selective inhibition of an isozyme of steroid 5 $\alpha$ -reductase in human scalp. *Proc Natl Acad Sci U S A* 1992;89:10787-91.
- Thigpen AE, Silver RI, Guileyardo JM, Casey ML, McConnell JD, Russell DW. Tissue distribution and ontogeny of steroid 5 $\alpha$ -reductase isozyme expression. *J Clin Invest* 1993;92:903-10.
- Jenkins EP, Andersson S, Imperato-McGinley J, Wilson JD, Russell DW. Genetic and pharmacological evidence for more than one human steroid 5 $\alpha$ -reductase. *J Clin Invest* 1992;89:292-300.
- Hoffmann R. Localisation of steroid-5 $\alpha$ -reductase-isoenzymes within the human hair follicle. Programme and book of abstracts, clinical dermatology, Singapore '98. June 18-20, 1998; Singapore. Abstract 239.
- Imperato-McGinley J, Guerrero L, Gautier T, Peterson RE. Steroid 5 $\alpha$ -reductase deficiency in man: an inherited form of male pseudohermaphroditism. *Science* 1974;186:1213-5.
- Kaufman KD. Clinical studies on effects of oral finasteride, a type 2 5 $\alpha$ -reductase inhibitor, on scalp hair in men with male pattern baldness. In: Van Neste D, Randall VA, editors. *Hair research for the next millennium. Proceedings of the First Tricontinental Meeting of Hair Research Societies*, Oct 8-10, 1995, Brussels, Belgium. Amsterdam (Netherlands): Elsevier Science BV, 1996. p. 363-5.
- Gormley GJ, Stoner E, Rittmaster RS, Gregg H, Thompson DL, Lasseter KC, et al. Effects of finasteride (MK-906), a 5 $\alpha$ -reductase inhibitor, on circulating androgens in male volunteers. *J Clin Endocrinol Metab* 1990;70:1136-41.
- Stoner E. The clinical development of 5 $\alpha$ -reductase inhibitor, finasteride. *J Steroid Biochem Mol Biol* 1990;37:375-8.
- Dallob AL, Sadick NS, Unger W, Lipert S, Geissler LA, Gregoire SL, et al. The effect of finasteride, a 5 $\alpha$ -reductase inhibitor, on scalp skin testosterone and dihydrotestosterone concentrations in patients with male pattern baldness. *J Clin Endocrinol Metab* 1994;79:703-6.
- Schwartz JJ, Tanaka WK, Wang DZ, Ebel DL, Geissler LA, Dallob A, et al. MK-386, an inhibitor of 5 $\alpha$ -reductase (5 $\alpha$ R) type 1, reduces DHT concentration in serum and sebum without affecting DHT concentrations in semen. *J Clin Endocrinol Metab* 1997;82:1373-7.
- Tukey JW, Ciminera JL, Heyse JF. Testing the statistical certainty of a response to increasing doses of a drug. *Biometrics* 1985;41:295-301.
- Capizzi T, Surville TT, Heyse JF, Malani H. An empirical and simulated comparison of some tests for detecting progressiveness of response with increasing doses of a compound. *Biometrics* 1992;48:275-89.
- Bingham KD, Shaw DA. The metabolism of testosterone by human male scalp skin. *J Endocrinol* 1973;57:111-21.
- Schweikert HU, Wilson JD. Regulation of human hair growth by steroid hormones: I. Testosterone metabolism in isolated hairs. *J Clin Endocrinol Metab* 1974;38:811-9.
- Diani AR, Mulholland MJ, Shull KL, Kubicek MF, Johnson GA, Schostarez HJ, et al. Hair growth effects of oral administration of finasteride, a steroid 5 $\alpha$ -reductase inhibitor, alone and in combination with topical minoxidil in the balding stump-tail macaque. *J Clin Endocrinol Metab* 1992;74:345-50.
- Bayne CW, Donnelly F, Chapman K, Bollina P, Buck C, Habib FK. A novel coculture model for benign prostatic hyperplasia expressing both isoforms of 5 $\alpha$ -reductase. *J Clin Endocrinol Metab* 1998;83:206-13.
- Eicheler W, Dreher M, Hoffmann R, Happle R, Aumüller G. Immunohistochemical evidence for differential distribution of 5 $\alpha$ -reductase isoenzymes in human skin. *Br J Dermatol* 1995;133:371-6.
- Thiboutot D, Harris G, Iles V, Cimisi G, Gilliland K, Nagari S. Activity of the type 1 5 $\alpha$ -reductase exhibits regional differences in isolated sebaceous glands + whole skin. *J Invest Dermatol* 1995;105:209-14.
- Kaufman KD, Olsen EA, Whiting D, Savin R, DeVillez R, Bergfeld W, et al. Finasteride in the treatment of men with androgenetic alopecia. *J Am Acad Dermatol* 1998;39:578-89.
- Leyden J, Dunlap F, Miller B, Winters P, Lebwohl M, Hecker D, et al. Finasteride in the treatment of men with frontal male pattern hair loss. *J Am Acad Dermatol* 1999;40:930-7.