The importance of dual 5α-reductase inhibition in the treatment of male pattern hair loss: Results of a randomized placebo-controlled study of dutasteride versus finasteride

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Background: Male pattern hair loss (MPHL) is a potentially reversible condition in which dihydrotestosterone is an important etiologic factor.

Objective: Our aim was to evaluate the efficacy of the type 1 and 2 5α-reductase inhibitor dutasteride in men with MPHL.

Methods: Four hundred sixteen men, 21 to 45 years old, were randomized to receive dutasteride 0.05, 0.1, 0.5 or 2.5 mg, finasteride 5 mg, or placebo daily for 24 weeks.

Results: Dutasteride increased target area hair count versus placebo in a dose-dependent fashion and dutasteride 2.5 mg was superior to finasteride at 12 and 24 weeks. Expert panel photographic review and investigator assessment of hair growth confirmed these results. Scalp and serum dihydrotestosterone levels decreased, and testosterone levels increased, in a dose-dependent fashion with dutasteride.

Limitations: The study was limited to 24 weeks.

Conclusion: Dutasteride increases scalp hair growth in men with MPHL. Type 1 and type 2 5α-reductase may be important in the pathogenesis and treatment of MPHL. (J Am Acad Dermatol 2006;55:1014-23.)

Pattern hair loss (PHL) is a genetically determined, potentially reversible type of hair loss. It is limited largely to the top of the scalp and is characterized by recognizable patterns of hair loss in men and in some women. Miniaturization of the hair follicles and shortening of the anagen phase of hair growth occurs in involved hairs.[1-3] Although testosterone is the major circulating androgen, to be maximally active in scalp hair follicles it must first be converted to dihydrotestosterone (DHT) by the enzyme 5α-reductase. The importance of DHT as an etiologic factor in male pattern hair loss (MPHL) is shown by the absence of this condition in men with a congenital deficiency of type 2 5α-reductase,[4] and by varying amounts of hair regrowth in men with MPHL treated with finasteride, a selective type 2 5α-reductase inhibitor.[5] A type 1 5α-reductase, which also metabolizes testosterone to DHT, is

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Abbreviations used:

BPH: benign prostatic hyperplasia
DHT: dihydrotestosterone
MPHL: male pattern hair loss
PHL: pattern hair loss

distinguished from the type 2 enzyme by its optimal pH range in vitro and its location and amount in different tissues.[6] In the skin, type 1 5α-reductase is the principal isoenzyme in sebaceous and sweat glands.[7,8] The mRNA and protein for both isoenzymes have been found in hair follicles, although this is not a universal finding.[9-12] There is no recognized genetic deficiency of type 1 5α-reductase in humans to assess its role in MPHL, and a type 1 5α-reductase inhibitor has not previously been evaluated for its effect on MPHL.

Dutasteride (Avodart) inhibits both type 1 and type 2 5α-reductase[13] and is approved at the 0.5-mg dose for treatment of symptomatic benign prostatic hyperplasia (BPH). It is approximately 3 times as potent as finasteride at inhibiting type 2 5α-reductase and more than 100 times as potent at inhibiting the type 1 enzyme.[14] The objective of this study was to evaluate, in a dose-response manner, whether dual 5α-reductase inhibition leads to improved efficacy in the treatment of MPHL. This randomized, multicenter study compared 4 doses of dutasteride with finasteride and placebo. Outcome measures included scalp hair growth and scalp androgen (testosterone and DHT) concentrations.

MATERIALS AND METHODS

Subject selection

Men 21 to 45 years of age were eligible for this study (GSK study ARIA2004) if they had mild-to-moderate MPHL (IIIv, IV [including IVa] or V Hamilton-Norwood patterns[15]). They must never have used a 5α-reductase inhibitor or have used any medication for alopecia during the previous 6 months. They must have had no significant health problems and must not have taken any androgenic or antiandrogenic drugs during the previous 6 months. All men provided written consent, and the protocol and consent form were approved by local institutional review boards. The study was carried out at 21 centers in the United States.

Protocol

After an initial screening evaluation, which included a medical history, physical examination, and laboratory evaluation, eligible men were randomized to receive dutasteride (0.05, 0.1, 0.5, or 2.5 mg), finasteride (5 mg), or placebo daily for 24 weeks. To ensure 45 evaluable subjects per treatment arm (a total of 270 evaluable subjects), 416 eligible subjects were enrolled and randomized to treatment. Subjects were assigned to study treatment in accordance with a predetermined randomization schedule, with a block size of 6, generated by the Medical Data Sciences Department, GSK. During the trial the code was held by GSK, and both investigators and patients were blinded to dutasteride, finasteride, and placebo treatments. The 5-mg finasteride dose was used, rather than the 1-mg dose that has been approved for treatment of MPHL, because the 1-mg dose was not commercially available at the time of study initiation. Furthermore, the 5-mg dose of finasteride had previously been shown to have efficacy in MPHL at least as great as the 1-mg dose.[16]

Assessments

The primary efficacy measure was hair regrowth based on hair counts, determined by means of a macrophotographic technique. The secondary efficacy measures were exploratory assessment of hair count, panel assessment of improvement from baseline, investigators' assessment of improvement, subjects' global assessment of improvement, and stage of MPHL using the modified Hamilton-Norwood classification.

For determination of target area hair counts, the hair in a 1-inch diameter (0.79 square inch) circle at the leading edge of the vertex bald spot was clipped to a length of about 1 mm. Reproducibility of this area was assured by placing a central tattoo and using a plastic target area template. Macrophotographs of the target area were taken with a camera system developed by Canfield Scientific Inc (Fairfield, NJ).[17] Using a validated method to count hair, a technician manually converted the photographs into a dot map of the hairs in the target areas, which was then converted to hair counts using a computer imaging system. Hair counts were measured at baseline and at 12 and 24 weeks.

For expert panel assessment of global changes in the amount of hair, photographs were taken of both the vertex and frontal scalp. A panel of experts (Drs Olsen, Savin and Whiting), blinded as to treatment, was shown pairs of photographs from baseline and either 12 or 24 weeks of treatment from each view. The panel graded the changes in hair growth on a 7-point rating scale: greatly, moderately, or slightly decreased; no change; slightly, moderately or greatly increased; ratings were converted to numbers (−3 to +3) for statistical analysis.

Investigator and subject assessments were done at baseline and at 12 and 24 weeks. For the investigator assessments, baseline photographs were provided

for comparative purposes and the investigators used the same 7-point rating scale as already described for the expert photographic panel. The subjects were asked to rate changes in the size of the vertex spot, hair loss on top of the scalp, bitemporal recession, the amount of hair shedding, hair quality, and overall satisfaction with hair growth on a 3-point rating scale (improved, no change, or worse).

Serum testosterone and DHT levels were measured at baseline and at 6, 12, and 24 weeks during the treatment phase, at 36 weeks (12 weeks after treatment was stopped), and thereafter at follow-up visits approximately every 2 months until DHT levels rose to within 25% of baseline. Serum testosterone was measured by Covance Laboratories (Indianapolis, Ind) using a standard radioimmunoassay. Serum DHT was measured by PPD Pharmaco (Richmond, Va) using a combination of gas chromatography and mass spectrophotometry in order to measure the very low serum DHT levels in subjects treated with dutasteride.

Scalp testosterone and DHT concentrations were determined in 4-mm biopsy specimens taken at baseline and again at 24 weeks. The biopsy specimens were taken anterolateral to the leading edge of the vertex bald spot, adjacent to the target area for hair counts. Scalp testosterone and DHT were measured after tissue homogenization and ether extraction, using the same assay as for serum measurements.

Statistical methods

Descriptive statistics are expressed as the mean (or mean change from baseline) with one standard deviation or median percentage change from baseline. The primary population of subjects to be statistically analyzed was the intention-to-treat population. Analysis of the hair count change from baseline was performed using a general linear model with effects for treatment, investigator cluster, and baseline hair count. Analyses of the panel and investigator assessments of improvement (on the 7-point scale) were performed using a general linear model with effects for treatment and investigator cluster. Analysis of the panel assessment was based on the average of the ratings of the 3 experts. Analyses of the percentage change from baseline in serum and scalp DHT and testosterone were performed using the following general linear model: log (postbaseline/baseline) = log (baseline) + treatment. For summary and analysis purposes, concentrations reported as below the limit of quantification were set to the lower limit of detection of the assay.

Pairwise comparisons between the dutasteride and placebo groups were performed using *t* tests from the general linear model in a step-down manner through the following hierarchical dose hypotheses at the two-sided 0.05 level of significance: dutasteride 2.5 mg versus placebo, dutasteride 0.5 mg versus placebo, dutasteride 0.1 mg versus placebo, dutasteride 0.05 mg versus placebo. Pairwise comparisons between the dutasteride and finasteride groups were performed in a similar manner. The pairwise comparison between the placebo and finasteride groups was performed and interpreted at the two-sided .05 level of significance. Correlations between efficacy and scalp androgen concentrations were evaluated across treatment groups using Spearman's rank correlation statistics. Statistical analyses were performed using both LOCF—last observation carried forward—and 'at visit' analyses, with similar results for both. The 'at visit' analyses are reported in this article.

RESULTS

Demography

The randomization of 416 subjects from 21 centers began in December 1997 and ended in June 1998. A total of 416 subjects entered the study, with 390 completing 12 weeks and 374 completing 24 weeks of the study. Demographics are summarized in Table I. The mean age was 36.40 ± 6.05 years (range 21-45 years). Ninety-one percent of subjects were Caucasian, 2% were black, 2% were Asian, and 5% were American Hispanic. The stage of baldness was as follows: IIIv 41%, IV 31%, IVa 5%, and V 23%.*

Target areas were located at similar areas anterior to the vertex balding. The mean and range of baseline hair counts for patterns IIIv, IV, IVa, and V was 939 (range 219-1723). There were no significant differences in the groups with respect to age, race or degree of baldness. Reasons for dropout included the following: withdrawal of consent (n = 20), adverse events (n = 11), lost to follow-up (n = 6), protocol violations and other reasons (n = 5). There were no significant differences in dropout rates among the treatment groups. The average compliance among the groups, as assessed by pill counts, was 94% to 99%.

Hair counts

Mean baseline hair counts in the 1-inch target area circle varied from 902.1 to 1000.6 hairs and were not significantly different between groups. During the 24 weeks of the study, mean hair counts in the placebo

*Three patients were initially labeled by the principal investigator as having Hamilton-Norwood pattern VII, but the mean target area hair count of the vertex, 1021 (range 473-1562) indicated that this pattern was incorrect. The first author reviewed the representative scalp photographs and reassigned all 3 as Hamilton-Norwood pattern V.

Table I. Demographics

	Placebo	Dutasteride (mg) 0.05	0.1	0.5	2.5	Finasteride (5.0 mg)	Total
No. of subjects	64	71	72	68	71	70	416
Age (y)							
Mean	35.8	35.5	36.4	36.1	35.8	38.5	36.4
SD	6.15	5.83	6.48	6.31	5.89	5.34	6.05
Min:Max	23:45	21:45	22:45	21:45	23:45	22:45	21:45
Baseline hair count							
Mean	920.3	1000.6	907.8	927.5	971.5	902.1	938.5
SD	236.36	302.12	224.27	219.84	247.32	262.86	251.7
Min:Max	432:1471	262:1723	317:1371	462:1377	449:1562	219:1712	219:1723
No.	64	70	72	67	70	70	413
Age at first balding (y)							
Mean	25.5	25.3	26.0	27.3	25.8	26.9	26.1
SD	5.62	5.03	6.94	6.22	5.88	6.26	6.04
Min:Max	15:40	18:40	15:42	12:41	14:44	15:41	12:44
No.	64	69	72	68	71	70	414
Stage of MPHL, No. (%)							
III vertex	26 (41)	26 (37)	31 (43)	29 (43)	28 (39)	29 (41)	169 (41)
IV	20 (31)	29 (41)	19 (26)	21 (31)	24 (34)	18 (26)	131 (31)
IVa	3 (5)	3 (4)	4 (6)	3 (4)	1 (1)	5 (7)	19 (5)
V	15 (23)	13 (18)	18 (25)	15 (22)	18 (25)	18 (26)	97 (23)

Min:Max, Minimum:maximum; *MPHL,* male pattern hair loss; *SD,* standard deviation.

group decreased by 32.3 ± 59.2 hairs, while hair counts increased in all active treatment groups (Fig 1). Dutasteride 0.1−2.5 mg and finasteride groups were significantly different from placebo for mean change in hair count from baseline at 12 and 24 weeks ($P < .001$) as follows: placebo, −26.5 (n = 56) and −32.3 hairs (n = 50); dutasteride 0.1 mg, 55 (n = 63) and 78.5 hairs (n = 58); dutasteride 0.5 mg, 71.3 (n = 59) and 94.6 hairs (n = 61); dutasteride 2.5 mg, 99.9 (n = 62) and 109.6 hairs (n = 62); and finasteride group, 52.1 (n = 68) and 75.6 hairs (n = 66) (Fig 1). The mean hair count in the 2.5-mg dutasteride group was significantly greater than the finasteride group at both 12 weeks ($P < .001$) and 24 weeks ($P = .009$). At 24 weeks, the percentage of subjects with at least a 10% increase in hair counts was 0%, 17%, 38%, 48%, and 56% for placebo, 0.05, 0.1, 0.5 and 2.5 mg dutasteride, respectively, and 41% for finasteride.

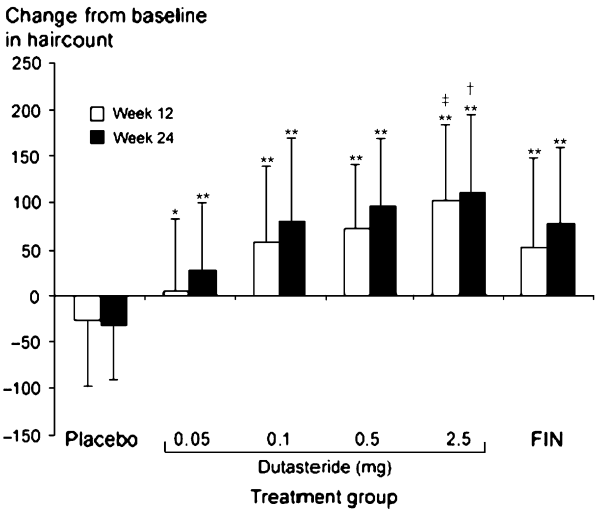

Fig 1. Mean changes in hair counts after 12 and 24 weeks, compared with baseline, for placebo, datasteride (0.05-2.5 mg), and finasteride (*FIN*). *, $P \leq .05$; **, $P \leq .001$ compared with placebo; †, $P \leq .05$; ‡, $P \leq .001$ compared with finasteride.

Expert panel assessment of global photographs

The 3-member panel assessed paired photographs of baseline versus 12 and 24 weeks of treatment in both the vertex (Table II) and frontal (Table III) regions. Their assessments were given numeric values from −3 (greatly decreased compared with baseline) to +3 (greatly increased compared with baseline), in order to permit statistical analysis. In the vertex photographs, dutasteride (0.1, 0.5, and 2.5 mg) and finasteride showed significantly greater

Table II. Expert panel assessment of changes in vertex photographs at 12 and 24 weeks*

	Moderately decreased		Slightly decreased		No change		Slightly increased		Moderately increased		Greatly increased	
	Wk 12	Wk 24	Wk 12	Wk 24	Wk 12	Wk 24	Wk 12	Wk 24	Wk 12	Wk 24	Wk 12	Wk 24
Placebo	0	0	7	8	90	91	3	0	0	2	0	0
0.05 mg Dut	0	0	5	10	83	75	13	12	0	3	0	0
0.1 mg Dut	0	0	0	0	70	61	28	33	2	7	0	0
0.5 mg Dut	0	0	0	0	65	37	31	40	5	21	0	2
2.5 mg Dut	0	0	3	0	46	22	35	48	15	28	1	1
5.0 mg FIN	1	0	3	0	67	43	25	48	4	9	0	0

Dut, Dutasteride; *FIN,* finasteride; *Wk,* week.
*Values denote percentage of patients in each category.

Table III. Expert panel assessment of changes in frontal photographs at 12 and 24 weeks*

	Moderately decreased		Slightly decreased		No change		Slightly increased		Moderately increased		Greatly increased	
	Wk 12	Wk 24	Wk 12	Wk 24	Wk 12	Wk 24	Wk 12	Wk 24	Wk 12	Wk 24	Wk 12	Wk 24
Placebo	0	0	0	2	95	87	5	12	0	0	0	0
0.05 mg Dut	0	0	13	5	81	73	6	20	0	2	0	0
0.1 mg Dut	0	0	0	0	81	67	17	30	2	3	0	0
0.5 mg Dut	0	0	0	0	77	52	21	30	2	18	0	0
2.5 mg Dut	0	0	1	1	68	37	29	36	1	25	0	0
5.0 mg FIN	1	1	3	1	87	52	9	36	0	9	0	0

Dut, Dutasteride; *FIN,* finasteride; *Wk,* week.
*Values denote percentage of patients in each category.

improvement than placebo ($P < .001$) at both 12 and 24 weeks (Fig 2, *A*). Dutasteride 0.5 mg showed a significantly greater improvement than finasteride at 24 weeks ($P = .026$), whereas dutasteride 2.5 mg showed significantly greater improvements than finasteride at both 12 and 24 weeks ($P < .001$). At 24 weeks, the mean expert panel score was −0.04, 0.19, 0.47, 0.84 and 1.01 points for placebo, 0.05-, 0.1-, 0.5-, and 2.5-mg dutasteride groups, respectively, and 0.62 points for finasteride (Fig 2, *A*). The percentages of patients judged to have improved hair growth (slightly to greatly increased) at 24 weeks in the vertex photographs were 2%, 15%, 39%, 63%, and 78% for placebo, 0.05-, 0.1-, 0.5 and 2.5-mg dutasteride groups, respectively, and 57% for finasteride (Table II). The panel assessments of the vertex photographs correlated with changes in hair counts assessed by macrophotography ($r = 0.41$, $P < .001$).

In the frontal region, the dutasteride 0.1, 0.5, and 2.5 mg groups improved significantly more than placebo at both 12 and 24 weeks (Fig 2, *B*). Finasteride was not significantly different from placebo at 12 weeks ($P = .69$) but was at 24 weeks ($P < .001$). At 12 weeks, the improvement in the 0.5-mg dutasteride group (0.28 ± 0.40) and in the 2.5-mg dutasteride group (0.37 ± 0.46) was significantly greater than the finasteride group (0.09 ± 0.39, $P = .009$ and $P < .001$, respectively). At 24 weeks, the improvement in the 2.5-mg dutasteride group (0.85 ± 0.79) was also significantly greater than the finasteride group (0.51 ± 0.66, $P = .002$). The proportions of patients judged to have improved hair growth (slightly to greatly increased) at 24 weeks in the frontal photographs were 12%, 22%, 33%, 48%, and 61% for placebo, 0.05, 0.1, 0.5 and 2.5 mg dutasteride, respectively, and 45% for finasteride (Table III). The proportion of patients with moderate or greater increases was higher with dutasteride 0.5 and 2.5 mg than with finasteride for both vertex and frontal photographs.

Investigators' global assessment

As for the expert panel assessment, the investigator assessments of hair growth were given numerical values from −3 (greatly decreased compared with baseline) to +3 (greatly increased compared with baseline). At the vertex, mean investigator ratings showed improvement in hair growth for the placebo group compared with baseline (0.44 ± 0.73 and 0.52 ± 0.86 at 12 and 24 weeks, respectively) (Fig 3, *A*). At 12 weeks, only the 2.5-mg dutasteride group (1.14 ± 0.85) showed a significant increase in investigator rating compared with placebo ($P < .001$), and this group was also significantly more improved than the finasteride group (0.66 ± 0.87) ($P = .001$). For vertex hair growth at 24 weeks, investigator ratings of 1.23, 1.34, and 1.85 points were given for 0.1-, 0.5-, and 2.5-mg dutasteride

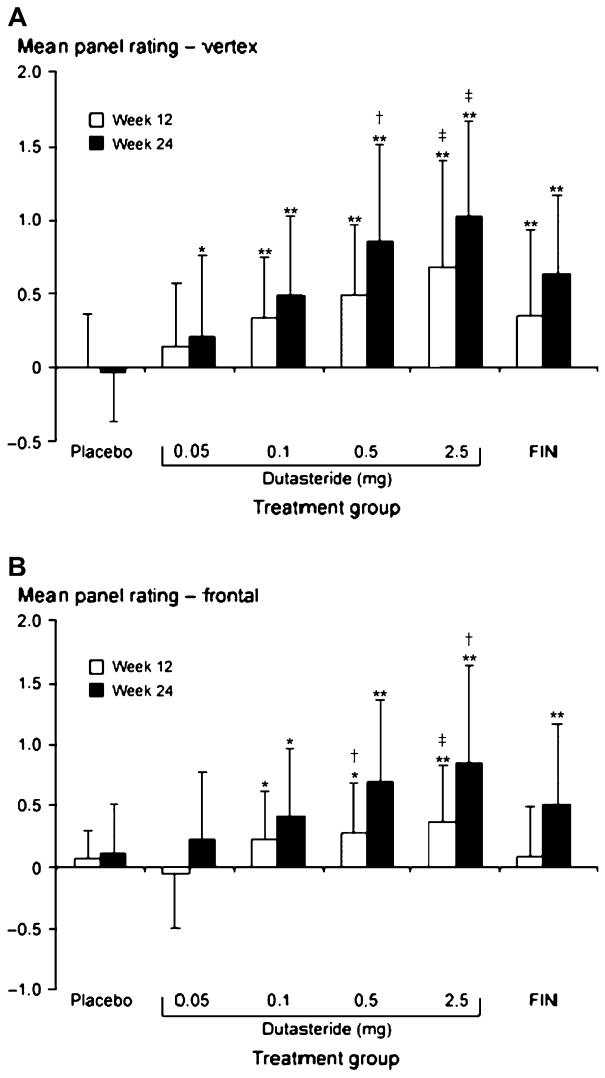

Fig 2. Mean expert panel ratings of photographs after 12 and 24 weeks, compared with baseline, for placebo, dutasteride (0.05-2.5 mg) and finasteride (*FIN*). Assessments were made of photographs of the vertex (**A**) and frontal (**B**) regions on a 7-point scale from −3 (greatly decreased) to +3 (greatly increased). *, $P \leq .05$; **, $P \leq .001$ compared with placebo; †, $P \leq .05$; ‡, $P \leq .001$ compared with finasteride.

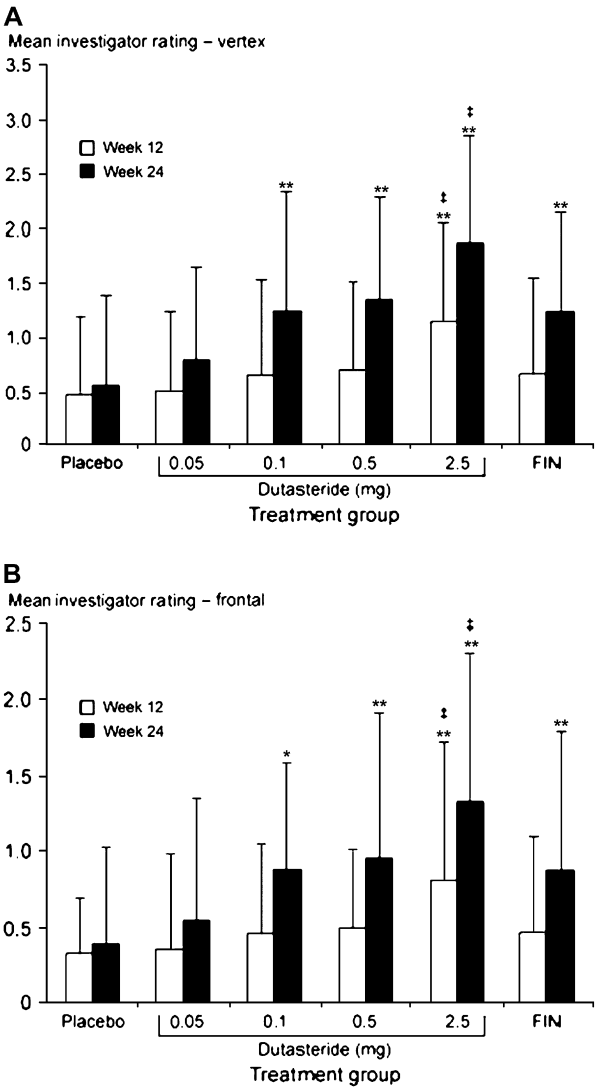

Fig 3. Mean investigator ratings of improvement in vertex (**A**) and frontal (**B**) hair growth after 12 and 24 weeks, compared with baseline, for placebo, dutasteride (0.05-2.5 mg) and finasteride (*FIN*). Assessments were made of changes in hair growth on a 7-point scale from −3 (greatly decreased) to +3 (greatly increased). *, $P \leq .05$; **, $P \leq .001$ compared with placebo; †, $P \leq .05$; ‡, $P \leq .001$ compared with finasteride.

groups, respectively, and 1.21 points for the finasteride group, which were all significantly greater ratings compared with placebo ($P < .001$). In addition, the 2.5-mg dutasteride group (1.85 ± 1.01) was significantly more improved than the finasteride group at 24 weeks (1.21 ± 0.94, $P < .001$). The expert panel assessment of hair growth correlated with investigator assessment at the vertex (r = 0.52, $P < .001$) and at the frontal area (r = 0.42, $P < .001$) for 24-week evaluations.

At the frontal scalp, the investigator rating highlighted a modest improvement in the placebo group compared with baseline (0.18 ± 0.51 at 12 weeks and 0.31 ± 0.70 at 24 weeks) (Fig 3, *B*). At 12 weeks, only the 2.5-mg dutasteride group (0.85 ± 0.87) showed a significant increase in investigator rating compared with placebo ($P < .001$). The 2.5-mg dutasteride group also showed a significant increase compared with finasteride ($P < .001$) at 12 weeks. At 24 weeks, dutasteride 0.1, 0.5, and 2.5 mg and finasteride groups showed significantly more improvement than the placebo group. The 2.5-mg dutasteride group (1.38 ± 0.93) was also significantly more improved than finasteride (0.83 ± 0.95, $P < .001$).

Table IV. Percentage of men with improvement in scalp hair after 24 weeks according to answers to a self-assessment questionnaire

		Dutasteride (mg)				Finasteride
	Placebo	0.05	0.1	0.5	2.5	(5.0 mg)
Size of vertex spot	31	58*	57*	52*	69*	61*
Hair loss on top of scalp	29	55*	52	40	63*	51*
Bitemporal recession	16	28	27	18	31*	39*
Hair shedding	47	67*	63	56	74*	64*
Hair quality	36	47	47	45	60*	57*
Overall satisfaction	42	58	57	56	72*	61*

*$P < .05$ compared with placebo, based on the overall distribution of answers (improved, no change, worse).

Subjects' assessment

In general, the 0.1-, 0.5-, and 2.5-mg dutasteride groups and the finasteride group provided numerically higher self-assessment scores than the placebo group for each parameter on the self-assessment questionnaire at 12 and 24 weeks. Only the 2.5-mg dutasteride and the finasteride groups at 24 weeks were consistently significantly greater than the placebo group for all parameters on the questionnaire ($P < .05$) (Table IV).

Serum and scalp androgen levels

Serum DHT concentrations in all dutasteride groups were suppressed significantly compared with placebo ($P \leq .001$) in a dose-related manner, with the greatest median suppression at 24 weeks occurring in the 0.5-mg (92%) and 2.5-mg (96.4%) dutasteride groups (Fig 4, *A*). The 0.1-mg dutasteride and finasteride groups showed a similar median degree of DHT suppression at 24 weeks (69.8% and 73.0%, respectively). Serum testosterone levels rose significantly in all active treatment groups, increasing by a median of 27.5% in the 2.5-mg dutasteride group, compared with 10.4% in the finasteride group (Fig 4, *B*). In the 0.5-mg dutasteride group, the median increase at 24 weeks was 23.8%, which is similar to previous findings.[14,18] Serum DHT concentration was inversely correlated with target area hair count ($r = -0.49$, $P < .001$), panel assessment of the vertex photographs ($r = -0.50$, $P < .001$), and investigators' assessments of the vertex hair growth ($r = -0.37$, $P < .001$). Twelve weeks after termination of treatment (36 weeks), the mean serum DHT was not significantly different from the baseline value in the placebo, dutasteride 0.05 mg and 0.1 mg groups and the finasteride 5.0 mg group. However, at 36 weeks, serum DHT had not yet returned to baseline for patients receiving dutasteride 0.5 mg and 2.5 mg (−11.03 and −88.4 median difference from baseline,

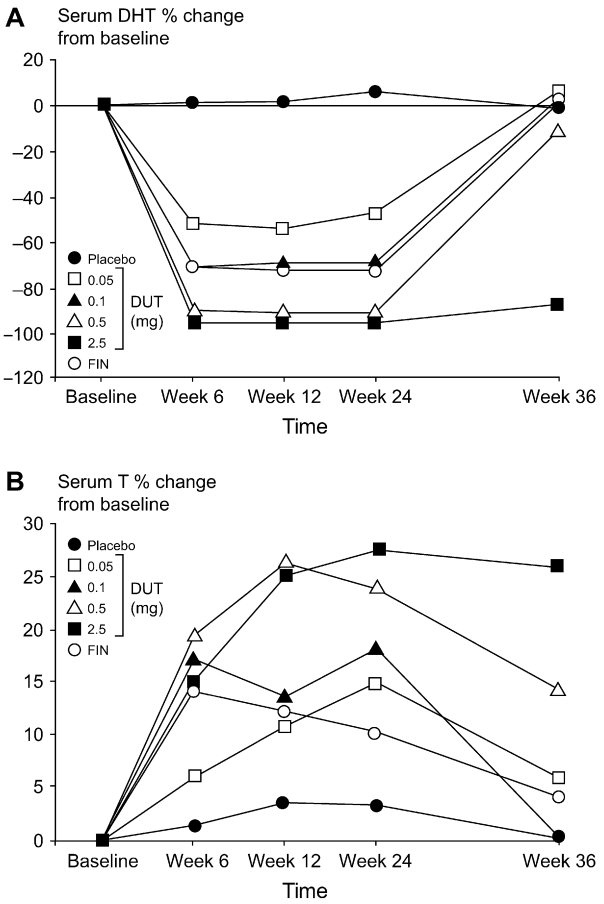

Fig 4. Median percentage changes from baseline in serum dihydrotestosterone (*DHT*) and testosterone (*T*), for placebo, dutasteride (*DUT*) (0.05-2.5 mg), and finasteride (*FIN*). Treatment was stopped after 24 weeks. All active groups were significantly different from placebo for both parameters at 6, 12, and 24 weeks ($P \leq .001$).

respectively). This is summarized in Fig 4, *A*. In subjects whose serum DHT was not within 25% of the baseline value after 36 weeks, serum DHT was measured at approximately 2-month intervals until levels had returned to within 25% of the baseline value. Serum DHT returned to within 25% of baseline in a median of 86 days after treatment (range 71-307 days) for the dutasteride 0.5 mg group and in a median of 155 days (range 72-421 days) for the dutasteride 2.5 mg group.

Scalp DHT concentrations in the dutasteride groups were also significantly suppressed compared with placebo in a dose-related manner. As with serum DHT, the 0.1-mg dutasteride and finasteride groups showed a comparable degree of scalp DHT suppression (32% and 41%, respectively). Scalp DHT decreased by 51% with 0.5-mg dutasteride and by 79% with 2.5-mg dutasteride. Scalp testosterone levels significantly increased in all active treatment

groups compared with placebo, increasing by 23%, 39%, 99%, and 222% with 0.05-, 0.1-, 0.5 and 2.5-mg dutasteride, respectively, and 23% with finasteride. Change in scalp DHT concentration was inversely correlated with change in target area hair count (r = −0.27), panel assessments of the vertex (r = −0.39), and investigators' assessments of the vertex (r = −0.28); the *P* value was less than .001 for all 3 correlations. The relationship between mean percentage change in scalp DHT and mean change in hair count is shown in Fig 5.

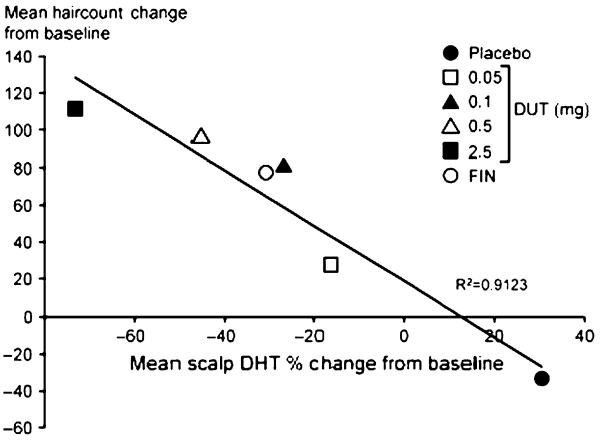

Fig 5. Relationship between 24-week mean percentage change from baseline in scalp dihydrotestosterone (*DHT*) and mean change in hair count for placebo, dutasteride (*DUT*) (0.05-2.5 mg), and finasteride (*FIN*).

Safety and tolerability

There were no significant differences in total adverse events, serious adverse events, or withdrawals due to adverse events among any of the treatment groups, including placebo. In total, 11 subjects withdrew because of adverse events: 3 were in the placebo group (irritable bowel syndrome and impotency), 7 in the dutasteride 0.1 mg group (decreased libido, malaise and fatigue, mood disorders, skin disorders, injuries caused by trauma, and gastrointestinal- and neurology-related complaints) and 1 in the dutasteride 0.5 mg group (gastrointestinal discomfort and pain). Some subjects had more than one adverse event.

As questions have previously arisen concerning a possible impact of 5α-reductase inhibitors on sexual function, these adverse events were examined in greater detail and are summarized in Table V. Decreased libido was noted in 2 subjects in the placebo group, 2 subjects in each of the 0.05-mg and 0.1-mg dutasteride groups, 1 subject in the 0.5-mg dutasteride group, 9 subjects in the 2.5 mg dutasteride group, and 3 subjects in the finasteride group. Of the 9 subjects with decreased libido in the 2.5-mg dutasteride group, 4 resolved while receiving therapy; 1 resolved within 3 weeks and another within 8 weeks of stopping drug therapy; in 1 subject, decreased libido continued after therapy had been stopped and was presumed by the subject to be unrelated to the trial or drug therapy; 2 subjects switched to finasteride at the end of the active phase and were lost to follow-up (dutasteride was not commercially available at the time the study ended). None of these 9 subjects discontinued study therapy because of this side effect. There was no increase among the active treatment groups in the reported incidence of impotence, with 3 subjects in the placebo group, 2 subjects in the 0.05-mg dutasteride group, and one subject in the finasteride group reporting such difficulty. These sexual adverse events were characterized as either mild or moderate in severity and only one subject's withdrawal was thought to be as a result of this adverse event (ie, decreased libido—in the 0.1-mg dutasteride group; Table V). The only subject to develop gynecomastia was in the placebo group.

DISCUSSION

Dutasteride, the first dual 5α-reductase inhibitor, is currently approved for treatment of symptomatic BPH. It is about 3 times as potent as finasteride at inhibiting type 2 5α-reductase and more than 100 times as potent at inhibiting type 1 5α-reductase.[14] Whereas 5-mg finasteride decreases serum DHT by about 70%,[19] dutasteride can decrease serum DHT by more than 90%.[20]

In this phase II, dose-ranging study, 2.5-mg dutasteride was superior to 5-mg finasteride in improving scalp hair growth in men between ages 21 and 45 years with MPHL as judged by target area hair counts, expert panel assessment, and investigator assessment at 12 and 24 weeks. From the investigator assessment of hair growth, a significant effect was evident at 12 weeks with 2.5-mg dutasteride but not until 24 weeks with finasteride. The subjects' assessment was less sensitive to changes in hair growth: this may have been at least partially due to the fact that this assessment used only a 3-point scale, compared with the 7-point scale used for the expert panel and investigator assessments. The effect of 24-week treatment with 5-mg finasteride in this study was similar to that previously reported by Kaufman et al for 52-week treatment with 1-mg finasteride[5] and 5-mg finasteride.[21] Kaufman et al[21] showed that for 1-year treatment with 5-mg finasteride, the mean change from baseline hair count in a 1 inch diameter target area was 95 compared with 75.6 in the same-sized target area in this study, and the change in serum DHT was −69.2% compared with −73%

Table V. Proportion of subjects experiencing the most frequent sexual AEs* following randomization, proportion of sexual AEs resolving (and those resolved during therapy), and proportion of sexual AEs leading to withdrawal from the study

		Dutasteride (mg)				Finasteride
	Placebo	0.05	0.1	0.5	2.5	(5.0 mg)
No. of subjects in group	64	71	72	68	71	70
Decreased libido, No. (%)	2 (3)	2 (3)	2 (3)	1 (1)	9 (13)	3 (4)
Resolved on therapy	2	0	1	0	4	0
Resolved off therapy	0	1	1	1	2	3
Leading to withdrawal, No.	0	0	1	0	0	0
Ejaculation disorders, No. (%)	0 (0)	0 (0)	3 (4)	1 (1)	1 (1)	2 (3)
Resolved on therapy	—	—	1	0	0	0
Resolved off therapy	—	—	1	1	1	2
Leading to withdrawal, No.	0	0	0	0	0	0
Impotence, No. (%)	3 (5)	2 (3)	0	0	0	1 (1)
Resolved on therapy	1	1	—	—	—	0
Resolved off therapy	2	1	—	—	—	1
Leading to withdrawal, No.	2	0	0	0	0	0

AEs, Adverse events.
*AEs occurring in more than 2% of subjects in at least one treatment group.

reported herein. The mean change from baseline target area hair count in the phase III study evaluating 1-year treatment with 1-mg finasteride daily was 107 per 1-inch diameter target area.[5] The greater efficacy of 2.5-mg dutasteride shown herein supports the dual role of type 1 and type 2 5α-reductase in the pathogenesis of MPHL.

The results of this study also highlight the importance of scalp DHT in the pathogenesis of MPHL. The 2.5-mg dutasteride dose was consistently superior to 0.5-mg dutasteride in promoting scalp hair growth. The 2.5-mg dose was also better than the 0.5-mg dose at suppressing scalp DHT (79% vs 51%), whereas it was only marginally better at suppressing serum DHT (96% vs 92%). This difference in the dose-response of serum and scalp DHT to inhibition with dutasteride is likely to be due to the greater contribution of type 1 5α-reductase to scalp DHT concentrations. In comparison with dutasteride, finasteride reduced scalp DHT by only 41%, a value similar to the 34% reduction reported previously by Dallob et al.[19] In another study, by Drake et al,[22] 5-mg finasteride reduced scalp DHT by 69%. There is no obvious reason why the results of the study by Drake et al should differ from the present study or that of Dallob et al. However, in the Drake study, there was no dose-response relationship among finasteride groups, with 0.01-mg finasteride showing no suppression of scalp DHT and 0.05-, 0.2-, 1 and 5-mg finasteride all showing about the same degree of suppression. The present study included a larger number of subjects and showed a complete dose-response for DHT suppression ranging from 26% in the 0.05 mg dutasteride group to 79% in the 2.5 mg dutasteride group. In this context, 5 mg finasteride suppressed scalp DHT to a similar degree as 0.1 mg dutasteride group (41% and 32%, respectively). Many of the clinical effects (hair count changes, global panel assessment, and investigator assessment) were also similar in these two groups, supporting the similarity in scalp suppression between 5-mg finasteride and 0.1-mg dutasteride.

Both dutasteride and finasteride were well tolerated in this phase II study, and no new safety concerns have arisen in any of the phase II and phase III studies of dutasteride given at doses up to 5 mg daily (the 5-mg dose was used in a phase II study for BPH). Concerning possible sexual adverse events, there was no evidence in the present study that either dutasteride or finasteride was associated with impotence. However, 9 men in the 2.5-mg dutasteride group complained of decreased libido, compared with 1 man in the 0.5-mg dutasteride group and 3 men in the finasteride group. As with previous studies with finasteride, this adverse event was characterized as either mild or moderate in severity and often resolved with continuation of the medication. In the 4-year follow-up of the phase III trials in BPH, dutasteride (0.5 mg) was well tolerated and the incidence of the most common sexual adverse events was low and tended to decrease over time.[23]

It should be emphasized that the approved dose of dutasteride for treatment of BPH is 0.5 mg daily and that limited data are available on the safety of higher doses. Dutasteride is not approved for

treatment of MPHL, and the beneficial effects of dutasteride in MPHL must be weighed against the possible adverse effects reported during use in BPH, such as gynecomastia, reduced sperm count, and drug-drug interactions (in particular, interactions with cytochrome P-450 isozyme, CYP 3A4 inhibitors), as detailed in the US labeling for Avodart.[24]

The serum half-life of finasteride is 6 to 8 hours.[25] Dutasteride has a serum half-life of approximately 4 weeks, and this long half-life was evident in the persistent suppression of DHT with the 0.5-mg and 2.5-mg doses after dutasteride treatment was stopped. Because of this long half-life, men being treated with dutasteride should not donate blood until at least 6 months past their last dose to prevent administration to a pregnant female transfusion recipient.

In conclusion, 2.5-mg dutasteride, a dual 5α-reductase inhibitor, improved hair growth in balding men more rapidly and to a greater degree than finasteride, a selective type 2 inhibitor. Dutasteride was generally well tolerated. The results of this study demonstrate the significant additive effect of inhibiting both type 1 and type 2 5α-reductase in the treatment of MPHL.

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