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Marked Suppression of Dihydrotestosterone in Men with Benign Prostatic Hyperplasia by Dutasteride, a Dual 5α-Reductase Inhibitor

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Dihydrotestosterone (DHT) is the primary metabolite of testosterone in the prostate and skin. Testosterone is converted to DHT by 5α-reductase, which exists in two isoenzyme forms (types 1 and 2). DHT is associated with development of benign prostatic hyperplasia (BPH), and reduction in its level with 5α-reductase inhibitors improves the symptoms associated with BPH and reduces the risk of acute urinary retention and prostate surgery. A selective inhibitor of the type 2 isoenzyme (finasteride) has been shown to decrease serum DHT by about 70%. We hypothesized that inhibition of both isoenzymes with the dual inhibitor dutasteride would more effectively suppress serum DHT levels than selective inhibition of only the type 2 isoenzyme.

A total of 399 patients with BPH were randomized to receive once-daily dosing for 24 wk of dutasteride (0.01, 0.05, 0.5, 2.5, or 5.0 mg), 5 mg finasteride, or placebo. The mean percent decrease in DHT was 98.4 ± 1.2% with 5.0 mg dutasteride and 94.7 ± 3.3% with 0.5 mg dutasteride, significantly lower ($P < 0.001$) and with less variability than the 70.8 ± 18.3% suppression observed with 5 mg finasteride. Mean testosterone levels increased but remained in the normal range for all treatment groups. Dutasteride appeared to be well tolerated with an adverse event profile similar to placebo. (*J Clin Endocrinol Metab* 89: 2179–2184, 2004)

DIHYDROTESTOSTERONE (DHT), A STEROID hormone produced from testosterone by the enzyme 5α-reductase is the primary active metabolite of testosterone (1). In male fetal development and puberty, it is essential for normal masculinization of the external genitalia and normal development of the prostate gland. In later life, DHT is associated with the development of benign prostatic hyperplasia (BPH) and androgenetic alopecia.

The enzyme 5α-reductase is present throughout the body in two forms, type 1 and type 2 (2). Type 1 has been reported to be located predominantly in the skin, both in hair follicles and sebaceous glands, as well as in the liver, prostate, and kidney (3–5). Type 2 is found in the male genitalia and the prostate (6–8); recent research has also identified type 1 mRNA and enzyme activity in the prostate (9–11).

The role of DHT in male fetal development was recognized when a deficiency of the type 2 5α-reductase isoenzyme was described in association with a clinical syndrome characterized by male pseudohermaphroditism (12, 13). These individuals are born with impaired masculinization of the external genitalia and a rudimentary prostate. In later life, they do not develop BPH or prostate cancer (14, 15). This lack of development of BPH led to the development of an inhibitor of 5α-reductase to treat this common condition (16). The first available 5α-reductase inhibitor (finasteride) is selective for the type 2 isoenzyme (17). Its clinical utility in reducing enlarged prostates, relieving symptoms associated with BPH, and reducing the risk of associated complications has been documented in several clinical trials (18, 19). More recently, 5α-reductase inhibition has been proven effective in treating androgenetic alopecia (20). Finasteride suppresses serum DHT by about 70% (21).

Dutasteride is a 6-azasteroid, which inhibits both type 1 and type 2 5α-reductase isoenzymes. The IC_{50} for type 1 5α-reductase is 0.7 and 81.0 nM for dutasteride and finasteride, respectively, and for type 2 5α-reductase, 0.05 and 0.16 nM, respectively (22). Based on animal studies and preliminary studies in man, it was hypothesized that a dual inhibitor of 5α-reductase would suppress DHT levels more effectively than a selective type 2 inhibitor. This phase II dose-response study was undertaken to test this hypothesis.

Subjects and Methods

Study design

The study (ARIA2001) was a double-blind, placebo-controlled, parallel group evaluation of five dosing regimens of dutasteride and finasteride. Patients received 24 wk of once-daily treatment with placebo, dutasteride (0.01, 0.05, 0.5, 2.5, or 5.0 mg) or 5.0 mg finasteride (recommended daily dose for BPH), followed by a 16-wk postdosing assessment period. Study end points were: serum DHT, testosterone, and LH levels; dutasteride pharmacokinetics; and safety and tolerability based on standard laboratory studies and adverse event reporting. Patients were assessed at 4-wk intervals during the active- and posttreatment periods. DHT and testosterone were measured in all patients at baseline and after 24 wk of treatment. In addition, a subset of 12 patients per treatment arm had DHT and testosterone assessments at wk 4, 8, 12, 16, and 20 of treatment and wk 4, 8, 12, and 16 post treatment. An additional subset of 20 patients in the placebo, 0.5-mg dutasteride, and finasteride

Abbreviations: BPH, Benign prostatic hyperplasia; DHT, dihydrotestosterone.

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groups had serum LH measured at baseline and wk 24. Investigators were instructed to collect all blood samples in the morning.

Study population

A total of 399 male patients were enrolled at 33 medical centers in the United States and Canada. All centers had approval for this study from their institutional review board or equivalent, and all patients signed informed consents before beginning the study. Patients were 50 yr of age and older with a prior diagnosis of BPH according to medical history and physical examination and a baseline prostate volume of 30 cc and greater.

Statistics

Statistical analyses and summaries were performed with SAS software (version 6, SAS Institute, Cary, NC) for demographics, pharmacodynamic, and safety data. These analyses were performed using two-sided tests of significance with comparisons between placebo and each of the six active treatment groups and between finasteride and the five dutasteride treatment groups. The reported P values for analyses correspond to these pairwise comparisons. Dose response and pharmacokinetic analyses were performed using WinNonlin Pro, version 1.5 (Pharsight Corporation, Mountain View, CA) and SAS software, version 6, to generate a sigmoid Emax model. The primary analysis of DHT focused on percent change from baseline. Treatment groups were compared in terms of percent change from baseline by logarithmically transformed data using a general linear model:

$$\text{Log(postbaseline DHT/baseline DHT)} = \text{treatment} + \log(\text{baseline DHT})$$

Pairwise comparisons of treatment groups were performed by Student's t test from the general linear model. Testosterone levels were analyzed similarly. Analysis of LH focused on change from baseline with a general linear model:

$$\text{Change from baseline LH} = \text{treatment} + \text{baseline LH}.$$

Estimates were based on the adjusted (least squares) means from the general linear model. The proportion of patients reporting adverse events was compared using Fisher's exact test. $P < 0.05$ was considered statistically significant.

Hormonal and dutasteride assays

Serum DHT levels were measured by a validated gas chromatography/mass spectrometry assay after derivatization (PPD-Pharmaco, Richmond, VA). Intra- and interassay coefficients of variation were 11.6 and 19.2%, respectively. The detection limit of the assay was between 1 and 10 pg/ml, depending on the particular assay run. Calibration curves resulted in correlation coefficients of $r \geq 0.99$ over the standard concentration range of 10–1000 pg/ml.

Serum concentrations of testosterone were measured by a central laboratory using a validated, solid-phase RIA method (Diagnostic Products Corp., Los Angeles, CA). Intra- and interassay coefficients of variation were 9.8 and 10.5%, respectively. The detection limit of the assay was 8.0 ng/dl. LH was measured by a central laboratory using a validated immunochemiluminometric assay (Endocrine Sciences, Calabasas Hills, CA). The intra- and interassay coefficients of variation were 4.7 and 10.7%, respectively. The detection limit of the assay was 0.1 mIU/ml.

Serum concentrations of dutasteride were measured by a validated liquid chromatography/atmospheric pressure chemical ionization/mass spectrometry detection assay after protein precipitation (Biomet Division, Glaxo Wellcome R&D, Research Triangle Park, NC) (23). Intraassay precision was ≤6.4%, and interassay accuracy expressed as percent nominal concentration was within 95.9–101.1%. Calibration curves resulted in correlation coefficients of $r \geq 0.994$ over the standard concentration range of 0.5–500 ng/ml.

Results

Study group

A total of 323 patients (81%) completed the 24-wk treatment phase and 305 patients (76%) completed both the treatment and follow-up phases. Across treatment groups, mean age was 62.6–65.5 yr and mean prostate volume was 41.9–47.3 cc (as measured by transrectal ultrasound). The proportion of subjects that discontinued during the treatment phase ranged from 11 to 25% across the treatment groups, and discontinuation in the active treatment groups was not higher than placebo. Of the 76 subjects (19%) who withdrew from the treatment phase, 25 withdrew due to adverse events (nine considered drug related), 10 failed to return to clinic for follow-up visits, five withdrew for lack of improvement in BPH symptoms, and 36 withdrew for other reasons.

DHT serum concentrations

After 24 wk of treatment, suppression of DHT was observed with a clear dose-response curve for percent change from baseline for the dutasteride treatment groups (Fig. 1). Adjusted mean ± SD decreases in DHT from baseline for the dutasteride treatment groups were as follows: 98.4 ± 1.2% (5.0 mg); 97.7 ± 2.0% (2.5 mg); 94.7 ± 3.3% (0.5 mg); 52.9 ± 22.1% (0.05 mg); and 7.5 ± 26.6% (0.01 mg). Of note is the reduction in variability (SD bars) with increase in dutasteride dose. In comparison, the adjusted mean decrease in DHT with finasteride was 70.8 ± 18.3%. The percent changes in DHT from baseline for dutasteride doses of 0.5, 2.5, and 5.0 mg were significantly greater than placebo ($P < 0.001$) and finasteride ($P < 0.001$). These results are summarized in Table 1.

The percentage of patients with DHT levels less than 10 pg/ml at the end of the 24-wk drug exposure was 10% in the 0.5-mg dutasteride group, 64% in the 2.5-mg dutasteride group, and 75% in the 5.0-mg dutasteride group. In the finasteride group, no subject had a DHT level less than 10 pg/ml, and only 9% had a DHT level less than 50 pg/ml. As the dutasteride dose increased, the variability of the response decreased from a SD of 22.1% with dutasteride at 0.05 mg to a SD of 1.2% with dutasteride at 5.0 mg.

The time courses of the changes in mean percent DHT levels for the different treatment groups during the study are shown in Fig. 2. Mean percent DHT levels returned to within 20% of baseline with dutasteride at 0.05 mg and finasteride at wk 4 post treatment and for dutasteride at 0.5 mg at wk 16 post treatment. With the highest doses of dutasteride, 2.5 and 5.0 mg, the mean percent DHT levels remained suppressed by 85% or more from baseline at 16 wk post treatment.

Testosterone serum concentrations

Testosterone levels increased in conjunction with DHT suppression for all dutasteride groups and the finasteride group. Serum testosterone concentrations did not exceed the upper limits of the normal range except in one individual in each of the placebo, 5-mg dutasteride, and finasteride groups. The increases in adjusted mean serum testosterone ranged between 4 and 21%, with statistically significant dif-

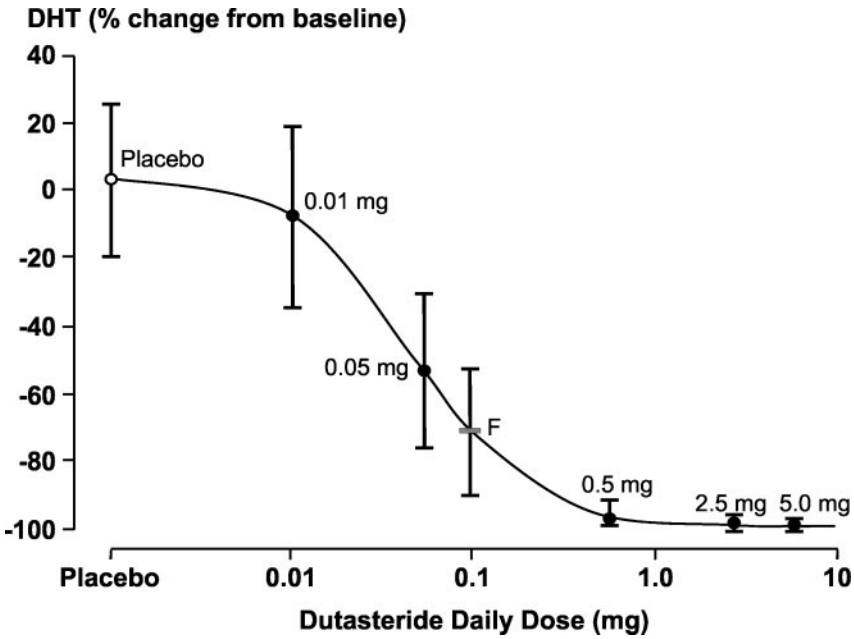

FIG. 1. The dose-response relationship of suppression of DHT serum levels from baseline after 24 wk of treatment with a range of dutasteride doses and 5 mg finasteride (F). The relationship is based on a sigmoid Emax model. Each point denotes adjusted mean percent change (±SD) for each treatment group.

TABLE 1. Changes in DHT, testosterone, and dutasteride (Dut) levels from baseline to end of active treatment (24 wk)

Treatment	DHT			Testosterone			Dutasteride
	Baseline	24 wk	% Change	Baseline	24 wk	% Change	24 wk
Placebo	385.7 ± 221.4	399.2 ± 236.5	1.6 ± 22.8	407.6 ± 168.1	429.8 ± 185.4	4.2 ± 26.1	NA
Dut (0.01 mg)	417.7 ± 205.1	366.7 ± 137.5	−7.5 ± 26.6	444.8 ± 144.5	476.0 ± 140.0	10.1 ± 31.2	Undetectable
Dut (0.05 mg)	392.6 ± 184.4	185.9 ± 92.9	−52.9 ± 22.1[a]	427.4 ± 150.3	451.5 ± 165.5	5.6 ± 31.1	1.1 ± 0.6
Dut (0.5 mg)	380.0 ± 154.8	23.8 ± 13.1	−94.7 ± 3.3[b]	422.6 ± 145.3	506.0 ± 125.2	21.2 ± 37.8[c]	38 ± 13
Dut (2.5 mg)	387.5 ± 152.7	10.2 ± 7.4	−97.7 ± 2.0[b]	418.7 ± 169.2	482.9 ± 163.2	19.0 ± 50.3[c]	272 ± 94
Dut (5.0 mg)	390.2 ± 185.5	7.3 ± 5.1	−98.4 ± 1.2[b]	402.5 ± 157.7	485.7 ± 189.0	13.7 ± 38.3	535 ± 183
Finasteride	375.4 ± 193.0	117.6 ± 88.9	−70.8 ± 18.3[a]	413.5 ± 134.3	474.7 ± 178.5	13.6 ± 34.7	NA

Hormonal values are absolute means ± SD. DHT, picograms per milliliter; testosterone, nanograms per deciliter; dutasteride, nanograms per milliliter. Percent change values are adjusted means ± SD (not calculable from absolute values).

[a] $P < 0.001$ compared to placebo; [b] $P < 0.001$ compared to placebo and finasteride; [c] $P < 0.05$ compared to placebo.

ferences from placebo seen with 0.5 mg dutasteride (21.2 ± 37.8%) and 2.5 mg dutasteride (19.0 ± 50.3%) (Table 1).

LH serum concentrations

Baseline LH levels were variable: 6.3 ± 3.5 mIU/ml in the placebo group, 4.5 ± 1.9 mIU/ml in the finasteride group, and 6.9 ± 3.8 mIU/ml in the 0.5-mg dutasteride group. The placebo group showed an adjusted mean decrease from baseline of 0.9 ± 1.4 mIU/ml. Observed were small increases of 0.3 ± 2.7 mIU/ml for dutasteride at 0.5 mg and 0.2 ± 1.4 mIU/ml for finasteride, which were not significantly different from placebo.

Dutasteride serum concentrations

Dutasteride was eliminated in a nonlinear fashion, with a clearance rate of 0.83–1.54 liters/h and a large volume of distribution of 300–500 liters. Mean dutasteride serum concentrations after 24 wk of dosing are presented in Table 1. As dose increased, time to reach steady state increased from 4 to 8 wk in the dutasteride 0.05-mg group to more than 24 wk in the dutasteride 2.5- and 5.0-mg groups. In the 0.5-mg dutasteride group, the majority of patients reached steady state at 24 wk with a serum concentration of 38 ± 13 ng/ml. After discontinuing treatment with dutasteride, the time to reach undetectable dutasteride serum levels in the dutasteride groups receiving 0.01 and 0.05 mg was less than 4 wk, and this increased to more than 16 wk for the dutasteride 2.5- and 5.0-mg groups. After discontinuing 0.5 mg dutasteride, 75% of patients had undetectable levels of dutasteride (quantifiable limit of 0.5 ng/ml) at 16 wk post treatment.

Adverse events

Dutasteride was well tolerated and generally had an adverse event profile similar to placebo. Figure 3 displays the percent of patients in each treatment group that reported any adverse event, had an adverse event considered by the investigator to be drug related, had a serious adverse event, or withdrew from the study due to an adverse event. In these categories, no significant differences from placebo were observed for any of the treatment groups, except for an increased reporting of serious adverse events with 0.01 mg dutasteride ($P = 0.032$). None of the serious adverse events were considered by the investigators to be drug related.

The most common adverse events (occurring in 10% or more of patients in at least one treatment group) were: ear, nose, and throat infections; malaise and fatigue; headaches;

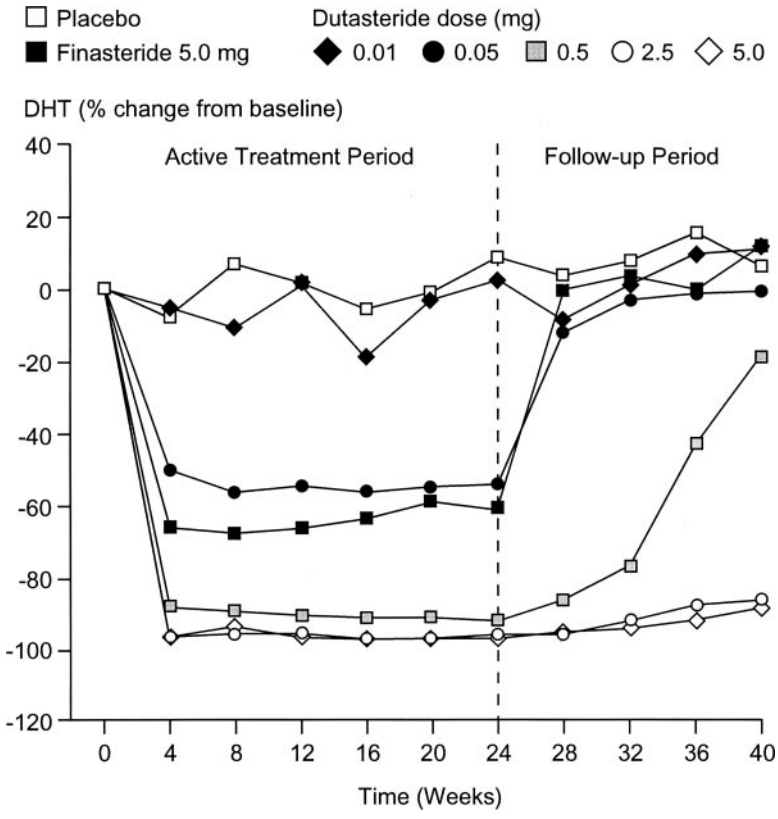

FIG. 2. The time course of percent change from baseline in DHT during active treatment with varying doses of dutasteride (wk 4–24) and after cessation of treatment (wk 28–40). Percent changes displayed are arithmetic means.

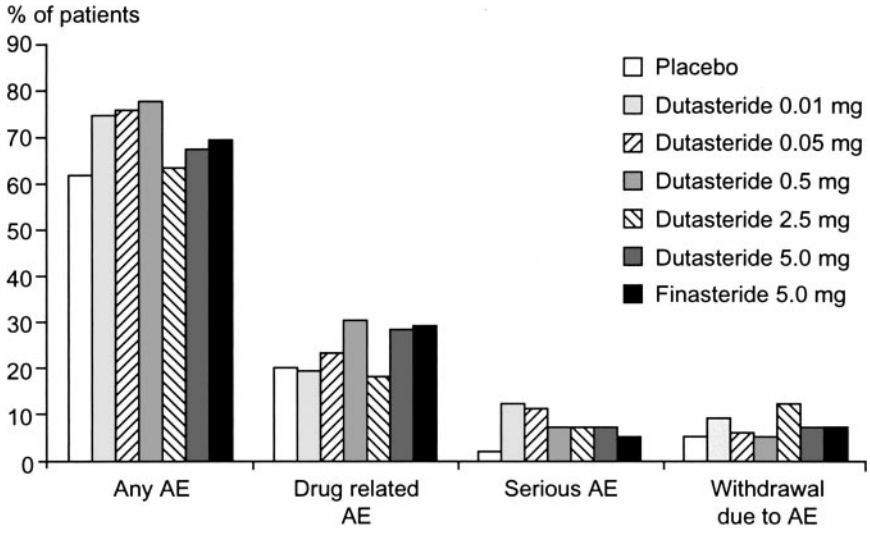

FIG. 3. Adverse event (AE) profile according to treatment group.

altered libido; musculoskeletal pain; erectile dysfunction; and dizziness (Table 2). There were no significant differences in the reporting of the most common adverse events between the active treatment groups and the placebo group apart from the increased reporting of altered libido in the highest-dose dutasteride group (5 mg) and the finasteride group, which both had similar reporting rates.

Laboratory tests, including hematology, blood chemistry, liver functions, renal functions, and lipid profiles, showed normal variation over time among individuals for the duration of the study; no trends were observed. The proportion of patients with any laboratory abnormality was comparable across all treatment groups. Only one subject had a laboratory value outside the normal range that was regarded as an adverse event (decreased white blood cell count in the 0.01-mg dutasteride group). No significant changes were noted in blood pressure, pulse, electrocardiogram, or cardiac rhythm for any treatment group.

Discussion

The results of this study support the hypothesis that suppression of both 5α-reductase isoenzymes with dutasteride can result in greater and more consistent suppression of

TABLE 2. Summary of most common[a] (≥10%) adverse events (intent-to-treat population in protocol ARIA2001)

Event	Placebo (n = 59)		Dutasteride (0.01 mg) (n = 58)		Dutasteride (0.05 mg) (n = 53)		Dutasteride (0.5 mg) (n = 57)		Dutasteride (2.5 mg) (n = 57)		Dutasteride (5.0 mg) (n = 60)		Finasteride (5.0 mg) (n = 55)	
	No.[b]	%	No.[b]	%	No.[b]	%	No.[b]	%	No.[b]	%	No.[b]	%	No.[b]	%
Any adverse event	36	61	43	74	40	75	44	77	36	63	40	67	38	69
Any drug-related adverse event	12	20	11	19	12	23	17	30	10	18	17	28	16	29
Most common adverse event														
Ear, nose, and throat infections	6	10	2	3	7	13	7	12	4	7	6	10	8	15
Altered libido	1	2	4	7	2	4	6	11	4	7	8[c]	13	7[c]	13
Malaise and fatigue	6	10	3	5	5	9	3	5	2	4	6	10	3	5
Musculoskeletal pain	6	10	1	2	3	6	4	7	3	5	4	7	6	11
Headaches	2	3	4	7	5	9	2	4	2	4	4	7	6	11
Impotence	2	3	1	2	6	11	3	5	2	4	5	8	6	11
Dizziness	5	8	6	10	0	0	4	7	0	0	3	5	2	4

[a] Events occurring in at least 10% of subjects in at least one treatment group.
[b] Represents the number of subjects reporting one or more adverse events.
[c] $P < 0.05$ *vs.* placebo based on a Fisher's exact test in terms of the percentage of subjects experiencing the most common adverse events.

serum DHT than that observed with the selective inhibitor of type 2 5α-reductase, finasteride. The higher doses of dutasteride (2.5 and 5.0 mg) induced almost complete suppression of DHT at 98.4%, compared with 70.8% with finasteride, consistent with other studies reported in the literature for finasteride (21, 24, 25). The lowest maximally effective dose of dutasteride (0.5 mg) resulted in DHT suppression of 94.7%.

The relative importance of type 1 and type 2 5α-reductase in promoting prostate growth has yet to be fully defined. Although both mRNA and enzyme activity consistent with type 1 5α-reductase have been found in the prostate, the type 2 isoenzyme predominates in this organ (26). Selective inhibition of type 2 5α-reductase by finasteride reduces DHT levels in prostate tissue homogenates by 80% (26). However, the effect of type 1 5α-reductase inhibition has not been determined, and local effects on specific cell types and disruption of paracrine signals may be significant.

Studies with 5α-reductase have highlighted differences between the two major androgens: testosterone and DHT. Whereas testosterone is largely responsible for muscle development, libido, and potency, DHT is essential for prostate growth and its effects on hair follicles can lead to androgenetic alopecia (27). Whereas DHT can act as a potent androgen, DHT does not appear to be essential in the adult male. Skeletal muscle has little 5α-reductase activity, so testosterone is thought to be the major androgen in this tissue, although circulating DHT may contribute a minor effect in normal men. Treatment with finasteride for 4 yr has not shown an adverse effect on bone mineral density associated with decreased DHT levels (28). The short-term safety data in the present study appear to support the tolerability of reduced DHT levels because no unexpected adverse events were reported in conjunction with the almost complete suppression of DHT. Although mean serum testosterone levels rose in association with DHT suppression, testosterone concentrations did not exceed the normal range. This safety profile is further supported by phase III studies with dutasteride (29).

Testosterone, DHT, estradiol, and progesterone all feedback at the hypothalamus and pituitary level to control gonadotropin secretion. Selective inhibition of type 2 5α-reductase in man has little effect on serum gonadotropin levels or the LH response to GnRH (30). Although DHT levels in this study were markedly suppressed, and testosterone levels increased within the normal range, LH levels showed little change. These results support the hypothesis that there is minimal change in overall androgenic activity with dual inhibition of type 1 and type 2 5α-reductase by dutasteride. The fall in DHT and the rise in testosterone seem to balance with no change in gonadotropin levels, and by inference, no evidence of a change in hypothalamic perception of androgenic feedback, suggesting possible androgen deficiency.

In conclusion, this phase II study has demonstrated that dual inhibition of 5α-reductase can result in almost complete suppression of serum DHT levels. Potentially beneficial implications of such marked suppression of DHT are under investigation for overall prostatic health.

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