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CLINICAL STUDY

Comparison of high-dose finasteride (5 mg/day) versus low-dose finasteride (2.5 mg/day) in the treatment of hirsutism

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Abstract

Objective: To compare the clinical efficacy and safety of high-dose (5 mg/day) and low-dose (2.5 mg/day) finasteride in the treatment of hirsutism in women.
Design: A prospective, randomized and controlled clinical trial.
Methods: Fifty-six hirsute women with moderate to severe hirsutism were prospectively evaluated to see the effects of low-dose (2.5 mg/day) and high-dose (5 mg/day) finasteride. Patients were randomly divided into two treatment groups. Group I ($n = 29$) received 2.5 mg finasteride/day and group II ($n = 27$) received 5 mg finasteride/day orally for 1 year. Hirsutism score, body mass index and hormonal parameters (FSH, LH, estradiol, androstenedione, testosterone, free testosterone, 17α-hydroxyprogesterone, dehydroepiandrosterone sulfate and sex hormone-binding globulin) were measured in all the patients before treatment and repeated at six-monthly intervals.
Results: The hirsutism scores decreased significantly at months 6 and 12 from a mean±S.D. of 18.4±4.6 to 13.3±5.2 ($P < 0.001$) and 18.4±4.6 to 8.6±4.2 ($P < 0.001$) in group I and from 18.7±5.2 to 13.9±5.3 ($P < 0.001$) and 18.7±5.2 to 10.3±5.0 ($P < 0.001$) in group II respectively. No significant changes in the blood chemistry and hormonal parameters except estradiol levels were observed. No serious side-effects were seen in the two groups. In group II, estradiol levels increased significantly at 6 and 12 months.
Conclusions: In this study, hirsutism scores decreased significantly at 6 and 12 months in both groups I and II. Low-dose (2.5 mg/day) finasteride is safe and cost effective in the treatment of hirsutism and may be used instead of high-dose finasteride (5 mg/day) therapy.

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Introduction

Hirsutism results from excess stimulation or increased sensitivity of hair follicles to circulating androgens (1). Hirsutism affects 5–8% of the whole female population of fertile age (2). Seventy to eighty percent of hirsute women have hyperandrogenism, while 6–17% have normal androgen levels and regular ovulatory menstrual cycles (3). Idiopathic hirsutism or polycystic ovary syndrome (PCOS) are the most common causes of hirsutism. Idiopathic hirsutism is caused by increased sensitivity of the pilosebaceous unit to normal circulating androgen levels, presumably caused by increased peripheral 5α-reductase enzyme activity (4). PCOS is a clinical condition characterized by altered gonadotropin secretion, chronic anovulation, hyperandrogenism and a variety of metabolic effects such as obesity and insulin resistance. Hirsutism is present in 60–83% of women with PCOS (5).

The medical treatment of hirsutism involves either suppressing ovarian or adrenal androgen production or blocking the action of androgens on the hair follicle with androgen receptor blockers (antiandrogens) or 5α-reductase inhibitors (6, 7). Finasteride specifically inhibits the type-II 5α-reductase enzyme which converts testosterone to dihydrotestosterone (DHT). The fall in serum DHT is accompanied by a reduction in the metabolites of DHT and by a rise in plasma testosterone concentration (8). It has recently been shown that finasteride improves the hirsutism score significantly (9–11).

Clinical and economic considerations are important in the treatment of hirsutism and a lower efficacious dosage would reduce costs. To our knowledge, no dose-range study using finasteride has been performed in a population of hirsute patients. In our previous study (10), we showed a significant decrease in hirsutism score in 35 women after 12 months of treatment with a standard dose of finasteride (5 mg/day). In the

present study, we compared the long-term clinical and hormonal effects of a standard dose (5 mg/day) of finasteride with a lower dose (2.5 mg/day) of finasteride in hirsute patients.

Materials and methods

Fifty-six hirsute women with moderate to severe hirsutism (hirsutism score >12) ranging in age from 18 to 41 years were included in the study. The study was approved by the Ethical Committee of Erciyes University Medical School and written informed consent was obtained from all women. Patients with signs of an adrenal and ovarian neoplasm, Cushing's syndrome, congenital adrenal hyperplasia, prolactinoma, a history of drug-induced hyperandrogenism or thyroid disorder were excluded. Of the 56 patients, 35 (62.5%) had PCOS and 21 (37.5%) had idiopathic hirsutism. The women had not used any hormonal medication known to influence hair growth or hormone levels for 6 months before entering the study. The diagnosis of PCOS was made by the presence of polycystic ovaries on pelvic or vaginal ultrasound examination combined with three or more of the following criteria: oligo/amenorrhea, hirsutism, hyperandrogenemia and ratio of luteinizing hormone (LH) to follicle-stimulating hormone (FSH) >2 (5, 12, 13). Oligomenorrhea was present in 27 (77.1%) patients with PCOS, while secondary amenorrhea was present in 8 (22.9%) patients with PCOS.

Patients were advised to avoid pregnancy during treatment because of possible feminization of a male fetus. Sexually active women were advised to use barrier methods of contraception and estrogens were not administered during the study. A serum human chorionic gonadotropin test was negative before starting the protocol.

Patients were consecutively divided into two groups at random. Group I ($n = 29$) received 2.5 mg finasteride/day (Proscar; Merck-Sharp-Dohme Ltd, Hertfordshire, UK) and group II ($n = 27$) received 5 mg finasteride/day. Both treatments were administered for 12 months. We did not allow the patients the use of electrolysis during the study period.

Hirsutism score was graded according to a modified Ferriman–Gallwey scoring system (13). Hirsutism was graded in all cases by the some observer (I I M). The treating physician (F B) and the observer were different. The mean±S.D. age (23.6±5.7 versus 22.8±5.5 years) and the mean±S.D. body mass index (BMI) (24.8±4.7 versus 24.4±4.4 kg/m^2) were similar between group I and group II respectively. All patients were warned about the possible side-effects of medication. No significant variations were seen in BMI during finasteride therapy.

During therapy, all hirsute women had an interview every 6 months in order to establish the course of the menstrual cycles, side-effects and hirsutism scores. Before therapy, multiscreen blood chemistry, complete blood cell count and hormonal analyses (FSH, LH, sex hormone-binding globulin (SHBG), 17α-hydroxyprogesterone (17-OHP), estradiol (E_2), androstenedione, total testosterone, free testosterone and dehydroepiandrosterone sulfate (DHEAS)) were performed. These parameters and hirsutism scores were repeated at 6 and 12 months of the therapy. Hormonal assays were assessed in the early follicular phase (days 2–9) of spontaneous menstrual cycles and amenorrhea or in the case of oligomenorrhea when the serum progesterone level was <2.5 ng/ml (8.0 nmol/l). After centrifugation, sera were stored at $-20\,^{\circ}C$ until assayed.

Serum total testosterone, free testosterone, androstenedione, DHEAS, FSH, LH, E_2 and 17-OHP were measured by radioimmunoassay using commercial kits (DPC, Los Angeles CA, USA). SHBG was measured by immunoradiometric assay (Orion Diagnostica, Espo, Finland). The intra- and inter-assay precision coefficients of variation were 3.2% and 4.4% for FSH, 6.8% and 7.9% for LH, 5.2% and 5.5% for E_2, 10% and 10.4% for testosterone, 4.3% and 5.5% for free testosterone, 8.3% and 9.2% for androstenedione, 39% and 7.0% for DHEAS, 5.6% and 4.5% for 17-OHP, and 4.0% and 5.5% for SHBG respectively.

All results are given as means±S.D. For statistical analysis, Student's paired and unpaired *t*-tests were used for comparisons within the same group and between the groups respectively.

Results

Table 1 shows the hormone levels and hirsutism scores during therapy in groups I and II. The modified Ferriman–Gallwey scores for hirsutism before treatment and at 6 and 12 months of treatment were similar between the groups. The scores decreased significantly at 6 and 12 months from a mean±S.D. of 18.4±4.6 to 13.3±5.2 ($P < 0.001$) and 18.4±4.6 to 8.6±4.2 ($P < 0.001$) in group I and from 18.7±5.2 to 13.9±5.3 ($P < 0.001$) and 18.7±5.2 to 10.3±5.0 ($P < 0.001$) in group II respectively.

An improvement in the hirsutism score was observed in all patients treated with 2.5 mg finasteride/day and 5 mg finasteride/day for 12 months. The percent reduction in hirsutism scores was similar in group I at 6 months (29.2±14.5%) and at 12 months (55.7±14.9%) and in group II at 6 months (27.1±10.9%) and at 12 months (46.1±11.2%) (Fig. 1). The percent reduction in hirsutism scores at 6 months was not different between group I and group II ($P > 0.05$), but the percent reduction in hirsutism scores at 12 months was different within both groups ($P < 0.01$).

No significant alterations in blood chemistry including cholesterol, triglyceride, liver functions, renal functions and complete blood count were observed during

Table 1 Hormonal parameters, hirsutism scores and BMI before and after finasteride therapy in both groups. Values are means±S.D.

	Basal		6 months		12 months	
Hormone	2.5 mg/day	5 mg/day	2.5 mg/day	5 mg/day	2.5 mg/day	5 mg/day
FSH (mIU/ml)	6.0±2.3	5.8±2.6	6.5±2.7	6.3±2.5	6.1±2.5	6.4±1.8
LH (mIU/ml)	7.5±5.9	7.9±4.2	6.6±4.8	7.2±3.6	6.6±4.3	7.3±3.5
E_2 (pg/ml)	56.9±35.5	61.8±35.5	57.5±29.9	82.8±39.6[a]	56.4±26.7	94.0±37.5[b]
Testosterone (ng/dl)	92.8±42.1	86.5±49.0	97.0±55.3	92.8±57.7	93.5±50.0	89.4±49.0
Free testosterone (pg/ml)	3.0±1.3	3.4±1.8	2.9±1.5	3.2±1.5	3.0±1.5	3.2±0.8
Androstenedione (ng/ml)	3.4±1.7	3.3±1.4	3.1±1.6	3.2±1.8	3.5±1.6	2.9±1.1
SHBG (nmol/l)	49.1±20.8	43.4±18.2	51.7±31.9	57.4±12.4	50.4±30.9	47.2±15.6
17-OHP (ng/ml)	1.1±0.6	1.1±0.5	0.81±0.43	1.1±0.5	0.78±0.37	1.0±0.6
DHEAS (mg/dl)	271.5±152.2	285.2±149.2	270.0±121.7	300.4±137.0	300.4±149.2	271.4±121.7
Hirsutism score	18.4±4.6	18.7±5.2	13.3±5.2	13.9±5.3	8.6±4.2[c]	10.3±5.0[c]
BMI (kg/m^2)	24.8±4.7	24.4±4.4			23.9±5.4	21.3±4.1

[a]$P < 0.02$, [b]$P < 0.001$ and [c]$P < 0.001$; comparison between 6- and 12-month values.

the therapy. Finasteride treatment did not change the menstrual cycles in women with PCOS. Moderate side-effects due to 2.5 mg finasteride/day were dry skin in one patient, reduction in libido in one, headache in two and gastrointestinal disorders in one patient. Side-effects due to 5 mg finasteride/day were dry skin in three patients, reduction in libido in four, headache in one and gastrointestinal disorders in four.

There were no significant differences in FSH, LH, testosterone, free testosterone, androstenedione, SHBG, 17-OHP and DHEAS levels and BMI during therapy in both groups. On the contrary, the treatment with 5 mg finasteride/day (group II) increased E_2 from 61.8±35.5 to 82.8±39.6 ($P < 0.02$) and 61.8±35.5 to 94.0±37.5 ($P < 0.0001$) at 6 and 12 months respectively.

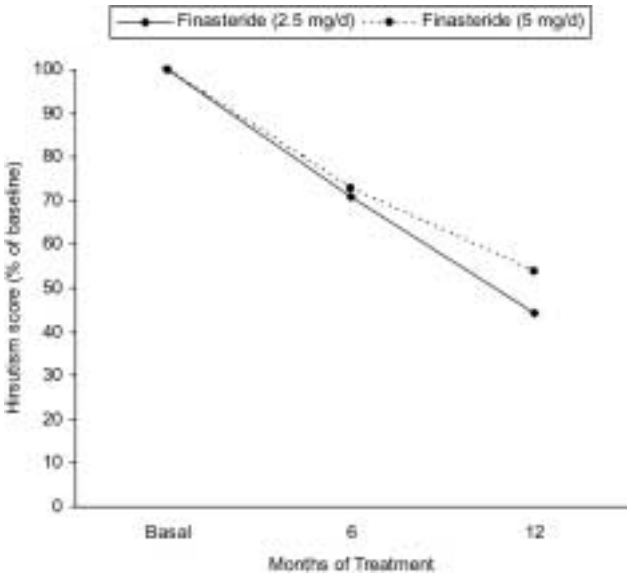

Figure 1 Changes in the hirsutism score during 12 months of therapy with 2.5 mg finasteride/day and 5 mg finasteride/day. The values of the hirsutism scores are expressed as a percentage of baseline mean hirsutism scores.

Discussion

Several antiandrogen drugs such as spironolactone, cyproterone acetate, flutamide and finasteride have been used as a single drug or combined in the treatment of hirsutism (9, 10, 14–21). A long treatment period is always required to improve hirsutism and to prevent or to delay its relapse. Differences in clinical efficacy of antiandrogen drugs are minor and the choice of drug depends on the availability, cost and its side-effects (7). A low-dose antiandrogen may be a suitable choice in an attempt to prevent the incidence of side-effects and complications (22, 23).

Increased 5α-reductase activity has been shown on the skin of the women with idiopathic hirsutism (4). Despite normal serum androgen levels, an increased activity of type II 5α-reductase isoenzyme has been considered to be the main mechanism of hair growth in patients with hirsutism (24). The inhibition of DHT formation by 5α-reductase inhibitors may be an alternative therapy in the management of hirsutism. Previously, successful results had been obtained with finasteride in woman with hirsutism (9, 25, 26). Venturoli *et al.* (22) reported that Ferriman–Gallwey scores in 15 women with hirsutism were significantly decreased (44%) after 12 months of finasteride therapy. Falsetti *et al.* (11) observed that finasteride caused a significant reduction in the hirsutism scores in PCOS and idiopathic hirsutism at the end of 12 months. We have previously reported that finasteride is an effective drug in the treatment of patient with hirsutism (10). But, in these previous studies, finasteride was used at a high dose (5 mg/day).

At least to our knowledge, this prospective, randomized, controlled study is the first dose-range study that compares the efficacy of finasteride at 2.5 mg/day and

at 5 mg/day in the treatment of hirsutism. In this study, hirsutism scores decreased significantly at 6 and 12 months in groups I and II. Mean hirsutism scores and reductions in hirsutism scores at 6 and 12 months were similar within both groups. The percent reductions in hirsutism scores at 6 months were not different within groups I and II and at 12 months were different within both groups. This study confirms that finasteride at both 2.5 mg/day and 5 mg/day was effective in the treatment of hirsutism. The efficacy of the low-dose (2.5 mg/day) finasteride used in this study is similar to that of high-dose (5 mg/day) finasteride used previously in other studies (9, 10, 18, 25).

In this study, we observed a more marked reduction in the hirsutism score in the thigh region than in other regions in both groups. The differences observed in different regions may be due to the degree of the inhibition of 5α-reductase isoenzyme type 2 and/or to the different numbers of receptors in the area.

The administration of finasteride is associated with a decrease in DHT and DHEAS levels and an increase in total testosterone levels (9, 11, 22, 24). In our previous study (10), we have shown that serum E_2 and SHBG levels were increased and DHEAS levels were decreased significantly at 12 months. In other previous studies (9, 25, 26), it has been shown that serum E_2 levels in hirsute women during finasteride treatment were unchanged. In the present study, no significant differences in the FSH, LH, free testosterone, testosterone, androstenedione, SHBG, 17-OHP and DHEAS levels were found in either group. E_2 levels were significantly higher at the end of the 6 and 12 months of therapy when compared with baseline values ($P < 0.05$ and $P < 0.02$) only in group II (5 mg finasteride/day). Inhibition of 5α-reductase by finasteride leads to an accumulation of testosterone which is converted to E_2 by aromatase (27). It may account for higher levels of E_2 after high-dose finasteride therapy. The results of treatment with different doses of finasteride on hirsutism could be due to various factors: first, the different doses of finasteride in hirsutism may have a different degree of efficacy on the action of 5α-reductase-1 and secondly, the increase in total testosterone could have *per se* a direct effect on target tissues (especially in high-dose finasteride therapy).

Finasteride is an expensive drug. The retail cost of 5 mg (28 tablets in a box) finasteride is about $30. Because of its high cost, we have evaluated the effects of high-dose and low-dose (2.5 mg/day) finasteride in the treatment of hirsutism.

In conclusion, the high (5 mg/day) and low (2.5 mg/day) doses of finasteride are well tolerated and safe in the treatment of hirsutism. Low-dose finasteride which has a similar effect to high-dose finasteride may be used instead of high-dose finasteride (5 mg/day) because of its lower cost.

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