Usefulness of a 12-month treatment with finasteride in idiophatic and polycystic ovary syndrome-associated hirsutism

A. Petrone, *M.D.*; **R. M. Civitillo,** *M.D.*; **L. Galante,** *M.D.*; **F. Giannotti,** *M.D.*; **V. D'Antò,** *M.D.*; **G. Rippa**[1], *M.D.*; **A. Tolino,** *M.D., Ph.D.*

Departments of Obstetrics and Gynecology-Gynecopathology, School of Medicine "Federico II", University Naples (Italy)
[1]Clinique "Nostra Signora di Lourdes" Massa di Somma (Naples)

Summary

Objective: Hirsutism is considered as a skin disease due to increased 5α-reductase activity in the pilosebaceous unit and finasteride is a drug that inhibits this enzymatic activity. This study showed the effectiveness of a chronic treatment with a selective 5α–reductase inhibitor, finasteride, in idiopathic and PCOS-associated hirsutism.

Methods: Finasteride was administered orally at a daily dose of 5 mg for a period of 12 months to 20 women with IH and 20 women with PCOS.

Main outcome measures: Each group was submitted to clinical (with Ferriman-Gallwey method) and serum hormonal (FSH, LH, 17β-estradiol, total and free T, Δ4-androstenedione, DHEAS, dihydrotestosterone, 3α-androstanediol glucuronide) studies at baseline and after 3, 6 and 12 months of treatment.

Results: After 3 months of finasteride treatment, a significant decrease in the average hirsutism scores was recorded both in IH ($p<0.0001$) and PCOS patients ($p<0.0001$). A progressive significant decrease of hirsutism score was observed in IH patients after 6 and 12 months ($p<0.002$) and in PCOS patients after 6 but not 12 months. In fact, the maximal therapeutic effect on the hirsutism was obtained after 12 months in the IH and 6 months in PCOS group.

Key words: Finasteride; Idiopathic hirsutism; Polycystic ovary syndrome; 5α-reductase activity; Dihydrotestosterone, 3α-androstenediol glucuronide; Pilosebaceous unit.

Introduction

Hirsutism is a woman's clinical disease characterized by enhanced hair growth with a male pattern. This condition can be considered a symptom resulting from increased androgen production by the ovaries or by the adrenal glands.

Nevertheless, idiopathic hirsutism (IH), may be defined as hirsutism in women with normal androgen levels, normal ovulatory cycles and without any other evident endocrine disorders [1, 2]. According to the world literature, the etiology of IH has been ascribed to the increased 5α-reductase activity (5α-RA) in the skin (especially in the pilosebaceous unit), with enhanced conversion of testosterone (T) into diydrotestosterone (DHT) [3, 5]. Also In the polycystic ovary syndrome (PCOS) this etiopathogenetic hypothesis for hirsutism has been suggested [6, 7]. No ideal therapy exists for hirsutism [8, 9] and several pharmacological approaches have been evaluated so far, such as: oral contraceptive agents alone or in combination with spironolactone [10, 11], glucocorticoids [12], cyproterone acetate [13], cimetidine [14], flutamide [15-17]. However, at present, none of the above-mentioned pharmacological approaches causes relevant clinical improvement and is lacking any adverse reactions; therefore, cosmetic measures are often necessary. Finasteride, a member of a new class of drugs called azasteroids used in prostatic disease [18], inhibits 5α-RA and blocks the conversion of T into DHT in peripheral tissues [19-22]. Previously, a short treatment with finasteride alone [23-25] or in combination with spironolactone [26] was reported to improve clinical hyrsutism in a few hirsute women. Moreover, controversial results have been reported on the effect of finasteride treatment on gonadotropin secretion [27]. The aim of this study was to evaluate the long-term effectiveness and tolerability of finasteride in the treatment of hirsutism, in a series of women with IH and PCOS.

Patients and Methods

Patients: Forty hirsute women aged 18-41 years (28±1.7 yrs; mean±SEM) volunteered for the study after their written consent had been obtained. Final diagnosis was IH in 20 patients and PCOS in the other 20. The patients were fully informed on the potential risk of pregnancy and were advised to use non-hormonal forms of contraception. The study was approved by the local Ethical Committee. Patients with IH had regular menses, normal body weight, normal serum LH, FSH and androgen levels and no abnormality of adrenal and ovarian hormone levels. Patients with PCOS had a history of menstrual irregularities (oligomenorrhea), chronic anovulation, enlargement of ovaries on pelvic examination, obesity and elevated serum androgen levels with clinical symptoms of hyperandrogenism. Serum LH and FSH ratio was >2. Pretreatment average hirsutism score, measured according to the Ferriman-Gallwey methods (FG), was 22.6±0.8 in the IH group and 21.3±0.9 in the PCOS group (*Table 1*). Patients were free of drugs for at least one month before entering the study and during finasteride treatment.

Study protocol: Finasteride (Proscar, Merck, Sharp, and Dohme, Rahway, NJ) was administered to all patients at a daily

Revised manuscript accepted for publication July 8, 1999

Table 1. — *Clinical evaluation with Ferriman-Gallwey method (FG) of hirsutism before and during treatment with finasteride.*

FG score	baseline	3 months	6 months	12 months
Patients with IH	22.6±0.8	14.7±1.0[a]	7.9±0.7[a, b]	4.8±0.6[a, b, c]
Patients with PCOS	21.3±0.9	13.9±0.9[a]	7.2±0.7[a, b]	6.2±0.5[a, b]

Values are the mean±SEM. [a]p<0.0001 vs baseline; [b]p<0.0001 vs 3 months; [c]p<0.002 vs 6 months.

dose of 5 mg for 12 months. Clinical and hormonal evaluations were performed before and after 3, 6, 12 months of treatment.

Clinical evaluation: In all patients the hirsutism score was evaluated in agreement with the method of FG and rated on a scale from 0 to 4 over nine body regions: hirsutism scores ranged from 15 to 28 [28]. Pretreatment scores were determined twice within a 3-month interval. All data were collected by one examiner and subsequent evaluations were performed by the same physicians after 3, 6 and 12 months of treatment. Furthermore, self-evaluations of clinical outcome during finasteride treatment were recorded by all patients and were classified as follows: poor, medium, good and very good.

Biochemical test and assays: All the patients underwent a complete hormonal assessment before and after 3, 6 and 12 months of the finasteride treatment. During the early follicular phase of the spontaneous or induced menstrual cycle, all the hormonal evaluations were carried out in the morning after an overnight fast and at least 2 hrs of bedrest. Serum total T (TT) and free T (FT), DHT, Δ4-androstenedione (Δ4-A), dehydroepiandrosterone sulfate (DHEA-S), FSH, LH, 17β-estradiol (E_2) and 3α-androstenediol glucuronide (3α-diolG) levels were measured by specific RIAs using commercial kits (Radim Pomezia Italy and Diagnostic Systems Laboratories, Webster, Texas) [29-32]. The main biochemistry parameters of kidney and liver function were analyzed before and during the study period.

Statistical analysis: The results were analyzed using the analysis of variance followed by the Student-Newman-Keuls' test. Clinical and hormonal data were expressed as the mean ± SEM.

Results

Effect on clinical picture and hormonal values

Patients with idiopathic hirsutism: After 3 months of inasteride treatment the FG scores significantly decreased from 22.6±0.8 to 14.7±1.0 (p<0.001) and were further reduced after 6 (7.9±0.7; p<0.05) and 12 months (4.8±0.6; p<0.05, *Table 1*). Clinical improvement of the hirsutism was recorded by almost all patients during the treatment. Patients' ratings of their own clinical outcome at the end of the study were as follows: poor in 1, medium in 4, good in 10 and very good in 5 patients. According to the diagnosis of IH, serum androgen levels (TT, FT, Δ4-A, DHEA-S) were in the normal range before the treatment. Serum levels of DHT and 3α-diolG were high before the treatment and were reduced after 3 (p<0.05), 6 (p<0.05) and 12 months (p<0.05) of finasteride treatment. Conversely, no significant change of serum FSH, LH and E_2 levels was observed during finasteride administration (*Table 2*).

Patients with polycystic syndrome: After 3 months of finasteride treatment, the FG score was significantly decreased from 21.3±0.9 to 13.9±0.9 (p<0.001) and further after 6 months (7.2±0.7; p<0.05). After 12 months the FG scores slightly improved compared with the 6-month results (6.2±0.5; p<0.05, *Table 1*). Patients' self-evaluations of clinical outcome at the end of the study showed the following results: poor in 3, medium in 5, good in 7 and very good in 5 patients. According the diagnosis of PCOS, high circulating androgen levels were found. After the treatment with finasteride, no significant change was observed in serum FSH, LH, E_2, TT, FT, Δ4-A, DHEA-S levels, whereas serum DHT and 3α-diolG levels were significantly lower after 3 months of treatment (p<0.05). This unchanged result persisted after 6 and 12 months of treatment with finasteride (p<0.05; *Table 2*).

Side-effects

Finasteride was wall tolerated by all patients (37 of 40). Mild and transient nausea, which spontaneously disappeared during the first days of therapy, was referred by three patients. No patient stopped finasteride administration. All biochemistry parameters, including kidney and liver function test, remained normal during the study.

Table 2. — *Serum hormone levels before and during treatment with finasteride in patients with IH and in patients with PCOS-associated hirsutism.*

	T (ng/dl)	Δ4A (ng/dl)	DHEAS (μg/dl)	DHT (nmol/L)	3α-diolG (ng/dl)	FSH (IU/L)	LH (IU/L)	E_2 (pmol/L)
Patients with IH								
baseline	45.1±2.8	115±7.8	255.5±32.7	1.72±0.1	407.2±36.1	8.4±0.8	14.2±1.2	79.4±5.9
3 months	48.7±3	117.9±7.8	228.1±30.7	0.8±0.1	127.8±17.6	8.5±0.7	13.8±1.1	79.1±5.4
6 months	48.1±2.4	116.7±7.2	227.2±27.1	0.6±0.08	83±13.4	8.6±0.7	13.9±1.2	78.1±5.1
12 months	48.6±2.3	113.9±6.5	217±26.3	0.6±0.06	63.5±10.9	8.6±0.6	13.8±1.1	78±5.9
Patients with PCOS								
baseline	65.3±3	221.7±9.1	524±29.7	1.9±0.09	524.8±40.1	6.1±0.7	13.9±1.2	84±8.1
3 months	62.5±2.6	212.2±9.1	521±27.9	0.76±0.1	188.7±22.5	6.3±0.6	13.2±1	81.9±7
6 months	62.7±2.8	202.1±7.6	523±26.1	0.6±0.08	118.1±14.7	6.4±0.6	12.8±1	83.3±7.2
12 months	62.4±2.7	195.8±6.3	524.3±27.2	0.5±0.06	111.5±13.1	6.5±0.5	12.7±0.8	82.9±7.3

Values are the Mean±SEM.

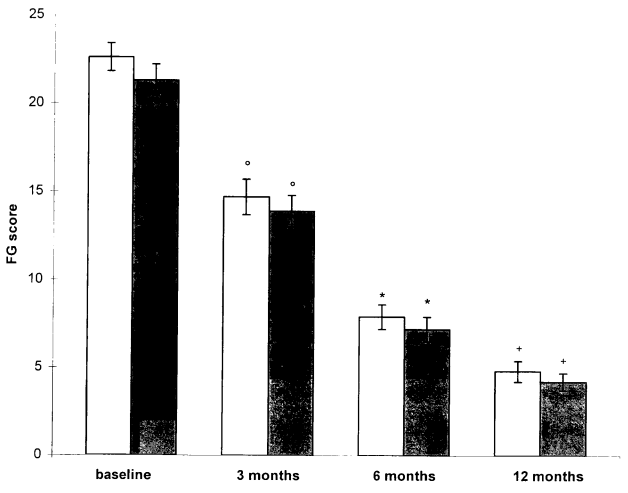

Figure 1. — Average Ferriman-Gallwey scores of hirsutism in patients with IH (open bars) and PCOS (hatched bars) treated with finasteride. Evaluations were performed before starting the treatment (0 months) and subsequently after 3, 6 and 12 months of treatment. The baseline is the mean±SM of the values at 0 months.
°p<0.0001 vs. baseline; *p<0.0001 vs. 3 months; +p<0.002 vs. 6 months.

Discussion

In recent years, pharmacotherapy of hirsutism has still been considered far from ideal. Taking into account the role of androgens in the pathogenesis of hirsutism, the medical approach is aimed at inhibiting their synthesis or secretion, the binding with sex hormone-binding globulin, their peripheral conversion and the action at the target tissues [8, 9]. On the basis of this finding, oral contraceptive agents [10, 11], GnRH agonists, glucocorticoids [12], cyproterone acetate [13], cimetidine [14], spironolactone [11] and flutamide [15, 17] have been used. However, none of the above-mentioned drugs is sufficiently effective and without side-effects in the treatment of hirsutism. In this study, we evaluated effectiveness and tolerability of finasteride [18-22], a 5α-reductase inhibitor, in the long-term treatment of hirsutism, in line with the hypothesis of an enhanced peripheral 5α-RA in the pathogenesis of this condition [3, 5]. Mauvais-Jarvis and coworkers first demonstrated that in the IH, an increase of 5a-reductase enzyme is primitively present in the skin of hirsute women with normal ovarian and adrenal androgen levels [4]. This condition DHT and its metabolite, 3α-diolG, are good serum and urinary markers for increased 5α-RA in peripheral tissues [32, 33]. Moreover, other studies have demonstrated that also in patients with PCOS there is an elevated activity of this enzyme in the skin; therefore ovarian and adrenal implications could be relevant but not the only cause for hirsutism in this condition [6, 7]. On the basis of this finding, treatment with drugs inhibiting 5α-RA appears appropriate both in IH and PCOS [23-27]. Recently, two isoenzymes of 5α-reductase have been identified in human tissues: type 1 was identified predominantly in the scalp skin and type 2 in the prostate and in genital skin. The latter has been a model for studying hirsutism and has been shown to significantly correlate with hirsutism [34-36]. In our study the administration of finasteride, a 4-azasteroid potent inhibitor of human 5α-reductase of type 2, to 40 women with IH and PCOS proved to be very effective. A rapid improvement of hirsutism in all patients has already been reported after 3 months and further at 6 months, as shown by their FG scores. Clinical results after 12 months of finasteride treatment were different in the two groups. In fact, a further improvement in respect to the 6-month results was recoreded in IH patients whereas no difference between 6- and 12-month results was found in PCOS patients. This clinical finding of long-term treatment could be explained by the different pathogenesis of hirsutism in PCOS than in IH. All different areas of the body scored with the FG method were improved by drug administration and satisfactory results were recorded by almost all patients during the self-evaluation. As a consequence of the action of finasteride, the hormonal tests in all patients showed a significant modification only in DHT and 3α-diolG, whereas in disagreement with other studies [23, 24, 26, 27], TT, FT, Δ4-A, DHEA-S, and E_2 were not found to be significantly higher than basal concentrations both in IH and the PCOS groups. Only a few patients (8/40) showed a very slight and insignificant increase (8-10%) of serum TT and/or FT levels in respect to baseline after 3-6 months of finasteride administration. In agreement with other studies no change in basal gonadotropin secretions was observed [24, 27]. No adverse effects were reported during the 12 months of treatment except for mild nausea in three patients at the beginning of therapy. The results of our study compared with other short-term studies [23, 24, 26] showed that the administration of finasteride for 12 months may significantly improve the clinical picture in women with IH and PCOS. In particular, we found the best clinical result in PCOS after 6 months whereas in IH patients the improvement was progressive until the end of 12 months. In conclusion, on the basis of our results, finasteride can be considered a promising and rational alternative in the medical management of hirsutism. In PCOS, after the achievement of the complete finasteride effect at the 6th month it could be interesting to evaluate the efficacy of the association between finasteride and other antiandrogen drugs.

References

[1] Lobo R. A.: "Androgen excess". In: "Infertility, contraception and reproductive endocrinology" eds. D. R. Mishell, V. Davajan, R. A. Lobo, Blackwell, 3rd ed. Boston, 1991, 422.
[2] Carr B. R., Wilson J. D.: "Disorders of the ovary and female reproductive tract". In: "Harrison's principles of internal medicine" eds. E. Braunwald, K. J. Isselbacher, R. G. Petersdof, J. D. Wilson, J. B. Martin, A. S. Fauci. Mc-Graw-Hill, 11th ed. New York, 1987, 1818.
[3] Serafini P., Lobo R. A.: "Increased 5α-reductase activity in idiopathatic hirsutism". *Fertil. Steril.*, 1985, *43*, 74.
[4] Kutten F., Mowszowicz I., Schaison G., Mauvais-Jarvis P.: "Androgen production and skin metabolism in hirsutism". *J. Endocrinol.*, 1977, *75*, 83.

[5] Toscano V.: "Hirsutism: pilosebaceous unit disregulation role of peripheral and glandular factors". *J. Endocrinol. Invest.*, 1991, *14*, 153.
[6] Stewart P. M., Sackletown C. H. L., Beastall G. H., Edwards C. R. W.: "5α-reductase activity in polycystic ovary syndrome". *Lancet*, 1990, *335*, 431.
[7] Lobo R. A., Goebelsmann U., Horton R.: "Evidence for the importance of peripheral tissue events in the development of hirsutism in polycystic ovary syndrome". *J. Clin. Endocrinol. Metab.*, 1983, *57*, 393.
[8] Ehrmann D. A., Rosenfield R. L.: "Clinical review 10. An endocrinologic approach to the patient with hirsutism". *J. Clin. Endocrinol. Metab.*, 1990, *71 (1)*, 1.
[9] Jeffcoate W.: "The treatment of women with hirsutism". *Clin. Endocrinol. (Oxf.)*, 1993, *39*, 143.
[10] Hancock K. W., Levell M. J.: "The use of oestrogen/progestogen preparations in the treatment of hirsutism in the female". *J. Obstet. Gynaecol. Br. Comm.*, 1974, *81*, 804.
[11] Chapman M. G., Dowsett M., Dewhurst C. J., Jeffcoate S. L.: "Spironolactone in combination with an oral contraceptive: an alternative treatment for hirsutism". *Br. J. Obstet. Gynaecol.*, 1985, *92*, 983.
[12] Rittmaster R. S., Givner M. L.: "Effect of daily and alternate day low dose prednisone on serum cortisol and adrenal androgens in hirsute women". *J. Clin. Endocrinol. Metab.*, 1988, *67*, 400.
[13] Underhill R., Dewhurst C. J.: "Further clinical experience in the treatment of hirsutism with cyproterone acetate". *Br. J. Obstet. Gynaecol.*, 1979, *86*, 139.
[14] Vigersky R. A., Mehlman I., Glass A. R., Smith C. E.: "Treatment of hirsute women with cimetidine". *N. Engl. J. Med.*, 1980, *303*, 1042.
[15] Cusan L., Dupont A., Tremblay R., Labrie F.: "Treatment of hirsutism with the pure antiandrogen flutamide". *Rec. Res. Gynecol. Endocrinol.*, 1988, *1*, 577.
[16] Marcondes J. A. M., Minnani S. L., Luthold W. W., Wajchenberg B. L., Samojilik E., Kirschner M. A.: "Treatment of hirsutism in women with flutamide". *Fertil. Steril.*, 1992, *57*, 543.
[17] Marugo M., Bernasconi D., Meozzi M., Cuva A., Fazzuoli L.: "Efficacy of flutamide in the treatment of hirsute women". *J. Endocrinol. Invest.*, 1991, *14 (2)*, 168.
[18] Geller J.: "Effect of finasteride, a 5α-reductase inhibitor on prostate tissue androgens and prostatic-specific antigen". *J. Clin. Endocrinol. Metab.*, 1990, *71*, 1552.
[19] Stoner E.: "The clinical development of 5α-reductase inhibitor, finasteride". *J. Ster. Bioch. Mol. B.*, 1990, *37*, 375.
[20] Gormley G. J., Stoner E., Rittmaster R. S., Gregg H., Thompson D. L., Lasseter K. J. *et al.*: "Effects of finasteride (MK-906), a 5α-reductase inhibitor, on circulating androgens in male volunteers". *J. Clin. Endocrinol. Metab.*, 1990, *70*, 1136.
[21] Dallob A. L., Sadick N. S., Unger W., Lipert S., Geissler L. A., Gregoire S. L. *et al.*: "The effect of finasteride, a 5α-reductase inhibitor, on scalp skin testosterone and dighydrotestosterone concentrations in patients with male pattern baldness". *J. Clin. Endocrinol. Metab.*, 1994, *79*, 703.
[22] Rittmaster R. S.: "Finasteride". *N. Engl. J. Med.*, 1994, *330*, 120.
[23] Moghetti P., Castello R., Magnani C. M., Tosi F., Negri C., Armanini D. *et al.*: "Clinical and hormonal effects of the 5α-reductase inhibitor finasteride in idiopathic hirsutism". *J. Clin. Endocrinol. Metab.*, 1994, *79*, 1115.
[24] Ciotta L., Cianci A., Calogero A. E., Palumbo M. A., Marletta E., Sciuto A., Palumbo G.: "Clinical and endocrine effects of finasteride, a 5α-reductase inhibitor, in women with idiopathic hirsutism". *Fertil. Steril.*, 1995, *64 (2)*, 299.
[25] Tolino A., Petrone A., Sarnacchiaro F., Cirillo D., Ronsini S., Lombardi G., Nappi C.: "Finasteride in the treatment of hirsutism: new therapeutic perspectives". *Fertil. Steril.*, 1996, *66 (1)*, 61.
[26] Lane Wong I., Morris R. S., Chang L., Spahn M., Stanzyk F. Z., Lobo R. A.: "A prospective randomized trial comparing finasteride to spironolactone in the treatment of hirsute women". *J. Clin. Endocrinol. Metab.*, 1995, *80*, 223.
[27] Fruzzetti F., De Lorenzo D., Parrini D., Ricci C.: "Effects of finasteride, a 5α-reductase inhibitor, on circulating androgens and gonadotropin secretion in hirsute women". *J. Clin. Endocrinol. Metab.*, 1994, *79*, 831.
[28] Ferriman D., Gallwey J. D.: "Clinical assessment of body hair growth in women". *J. Clin. Endocrinol. Metab.*, 1961, *21*, 1440.
[29] Horton R., Endres D., Galmarini M.: "Ideal conditions for hydrolysis of androstenediol 3α, 17β-diol glucuronide in plasma". *J. Clin. Endocrinol. Metab.*, 1984, *59*, 1027.
[30] Ito T., Horton R.: "The source of plasma DHT in man". *J. Clin. Invest.*, 1971, *50*, 1621.
[31] Barberia J., Pages L., Horton R.: "Measurement of androstanediol in plasma in a radioimmunoassay using celite column chromatography". *Fertil. Steril.*, 1976, *27*, 1101.
[32] Pauson R. J., Serafini P. C., Catalino J. A., Lobo R. A.: "Measurements of 3α, 17β-androstanediol glucuronide in serum and urine and the correlation with skin 5α-reductase activity". *Fertil. Steril.*, 1986, *46*, 222.
[33] Kirschner M. A., Samojlik E., Szmal E.: "Clinical usefulness of plasma androstanediol glucuronide measurements in women with idiopathic hirsutism". *J. Clin. Endocrinol. Metab.*, 1987, *65*, 597.
[34] Thigpen A. E., Silver R. I., Guileyardo J. M., Casey M. L., McConnell J. D., Russell D. W.: "Tissue distribution and ontogeny of steroid 5α-reductase isoenzyme expression". *J. Clin. Invest.*, 1993, *92*, 903.
[35] Jenkins E. P., Andersson S., Imperato-McGinley J., Wilson J. D., Russell D. W.: "Genetic and pharmachological evidence for more than one human steroid 5α-reductase". *J. Clin. Invest.*, 1992, *89*, 293.
[36] Serafini P. C., Ablan F., Lobo R. A.: "5α-reductase activity in genital screen of hirsute women". *J. Clin. Endocrinol. Metab.*, 1985, *60*, 349.

Address reprint requests to:
ALFREDO PETRONE, M.D.
I. Traversa Via Pietravalle, 4
80131 Napoli (Italy)