Original Study

Intermittent Low-Dose Finasteride Administration Is Effective for Treatment of Hirsutism in Adolescent Girls: A Pilot Study

Mario V. Tartagni MD [1], Hala Alrasheed MD [1], Gianluca R. Damiani MD [2], Monica Montagnani MD, PhD [3,*], Maria A. De Salvia PhD [3], Giovanni De Pergola MD [3], Massimo Tartagni MD [3], Giuseppe Loverro MD [3]

[1] *Faculty of Medicine, University of Kosice, Kosice, Slovakia*
[2] *Department of Obstetrics and Gynecology, Hospital of Sondrio, Sondrio, Italy*
[3] *Department of Biomedical Sciences and Human Oncology, Faculty of Medicine, University of Bari "Aldo Moro", Bari, Italy*

A B S T R A C T

Study Objective: Hirsutism has negative impact on adolescent psychosocial development for both cosmetic and endocrine reasons. This study evaluated the effectiveness of a new intermittent, low-dose finasteride regimen consisting of 2.5 mg of drug given every 3 days (1 day of treatment, 2 days of drug withdrawal) for 6 months in girls with hirsutism by polycystic ovarian syndrome (PCOS) or idiopathic hirsutism (IH).

Design and Participants: Twenty-eight girls (15-19 y old) with hirsutism were randomly assigned to 2 treatment groups and treated for 6 months. Fourteen patients (7 with IH, 7 with PCOS) received finasteride; fourteen patients (7 with IH, 7 with PCOS) received placebo. Hirsutism score (HS), clinical, and hormonal effects were compared between the 2 groups.

Results: In patients treated with finasteride, the HS value at 6 months was 52.9% lower than that observed at baseline in girls with IH, and 52.8% lower in girls with PCOS ($P < .0001$ for both). Similarly, the 3α-17 β-androstenediol glucuronide serum levels were decreased by 34.8% in patients with IH, and by 47.5% in patients with PCOS ($P < .0001$, respectively). Finasteride treatment was well tolerated and did not alter values of BMI, serum levels of sexual hormones, metabolic parameters related to liver and kidney function as well as glycemic and lipidic asset.

Conclusions: A low-dose of finasteride, given every 3 days, reduces the HS in young patients affected by PCOS or IH. Compared with conventional continuous finasteride administration, the intermittent low-dose regimen has similar efficacy with the advantage to be safer and less expensive.

Key Words: Finasteride, Hirsutism, Polycystic ovarian disease, Adolescents

Introduction

Hirsutism, defined as the presence in females of terminal hair growth in a male pattern,[1,2] is characterized by thick (usually dark) hair in areas considered as a part of the secondary masculine sexual features such as face, chest, abdomen, upper thighs, or upper arms. Hirsutism affects between 5% and 15% of women surveyed[3,4] and can be caused by either increased level of androgens[5] or increased sensitivity to androgens of pilosebaceous units.[6]

The causes of hirsutism can be various, including idiopathic hirsutism (HI), late-onset forms of congenital adrenal hyperplasia, polycystic ovarian disease (PCOS), some cases of functional hyperandrogenism, and exogenous pharmacologic sources.[7] When it coexists with normal androgen levels, hirsutism results from increased sensitivity of hair follicles to circulating androgens, due to overactivity of the skin enzyme 5α-reductase (5α-R). Three isozymes of 5α-R are known to exist,[8] and both the Type 1 5α-R isoform and the type 2 5α-R isoform have been identified.[9,10] Type 1 5α-R is widely distributed throughout the body, and is most abundant in the liver where it catabolizes steroids. Type 2 5α-R is primarily expressed in target tissues for androgens, is responsible for converting testosterone (T) into dihydrotestosterone (DHT) and differentiating external genitalia and the prostate in males, and is essential for hair growth in both sexes.[11] Of note, there is a positive and close correlation between type 2 5α-R activity and the hirsutism score in patients with idiopathic hirsutism (IH).[12]

Although physiological hyperandrogenism can be observed during puberty and at the menarche,[13] the presence of hirsutism may be extremely distressing for young patients and may have profound negative impact on their psychosocial development for at least 2 reasons: a cosmetic reason, since excessive body, and particularly facial, hair in women is considered unattractive in Western societies; and an endocrine reason, as hirsutism may be the outcome of increased ovarian or adrenal androgen production.[14]

There are little data on intervention in the adolescent population with hirsutism.[15,16] The therapeutic options of hirsutism can be divided into systemic, topical, and dermocosmetic therapies. Patients should be informed that the response to systemic agents is slow, occurring up to 3-6 months after therapy has begun. Systemic treatment of hirsutism includes drugs inhibiting ovarian or adrenal

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* *Address correspondence to:* Monica Montagnani, MD, PhD, Department of Biomedical Sciences and Human Oncology - Pharmacology Section, Medical School, University of Bari "Aldo Moro," Policlinico - P.zza G. Cesare, 11, 70124 Bari – Italy; Phone: 39 080 547 8583; fax: 39 080 547 8449

E-mail address: monica.montagnani@uniba.it (M. Montagnani).

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androgen production, and drugs that inhibit androgen activity either by blocking androgen cytochrome P450 receptors or by inhibiting 5α-R activity.[17] The observation that in all hirsute women, with or without hyperandrogenism, the 5α-R activity in the skin is steadily elevated[18] underlines the key role of 5α-R in hirsutism.

Finasteride (17-β-N-ter-butylcarbamoyl-4-aza-5-α-androstan-1-en-3-one), a synthetic 4-azasteroid, is an antiandrogen drug that competitively inhibits 5α-R type 2.[19] By selectively inhibiting 5α-R type 2,[20,21] finasteride lowers levels of 5α-DHT, a hormone at least 100-fold more potent than T. Importantly, finasteride does not display androgenic, antiandrogenic, or steroid hormone-related properties and has no affinity for androgen receptors.[22] In a previous study[23] comparing the clinical efficacy and safety of high-dose (5 mg/day) and low-dose (2.5 mg/day) finasteride in the treatment of hirsutism, a significant decrease in hirsutism score was observed in patients receiving either standard or low dose-finasteride for 12 months, with no serious side effects or changes in the menstrual cycle reported in both groups. At dosages ranging from 2.5 to 5 mg/day,[24,25] continuous finasteride administration has been shown to be effective in decreasing hirsutism symptoms in women with PCOS or IH.[23,26–28] Although the treatment was well tolerated by all patients, and no withdrawal was necessary, finasteride may induce side effects such as reduced libido, depression, headaches, and gastrointestinal disorders.[24,26] Considering that causes of hirsutism can be rarely permanently removed, and that treatment withdrawn results in recurrence of symptoms within a few months, long-term administration of finasteride is usually required. Therefore, to reduce the incidence of side effects and also limit costs of treatment, finasteride should be used at the lowest effective dosage. This study is aimed at evaluating the effectiveness of a new intermittent, low-dose finasteride regimen consisting of 2.5 mg of drug given every 3 days (1 day of treatment, followed by 2 days of drug withdrawal) for 6 months in adolescent girls with hirsutism by PCOS or IH. For this purpose, clinical and hormonal effects in patients undergoing this regimen were compared with those obtained in patients under continuous administrations of placebo.

Materials and Methods

Twenty-eight girls diagnosed with hirsutism ranging in age from 15 to 19 years were consecutively recruited between January 2010 and November 2012. All patients enrolled were at least 3 years beyond menarche, had normal glucose tolerance according to the American Diabetes Association recommendation[29] and normal markers of thyroid, liver, and kidney function. None of them had been taking oral contraceptives or other long-term drugs in the last 6 months before the start of the study. None of the subjects enrolled was observing a specific diet.

Pregnancy risk was an important exclusion criterion taken into account at study start in the finasteride group. Other exclusion criteria were: evidence of anemia, bleeding disorders, glucose intolerance, diabetes, late-onset adrenal hyperplasia, abnormal electrolytes, abnormal screening of liver, thyroid, or kidney function.

All patients were informed about potential risk of treatment on a male fetus and received advice for nonhormonal forms of contraception. Written consent was obtained from participants older than 18 years. Parents' written consent was obtained for patients younger than 18 years. All procedures were in accordance with the Helsinki Declaration on Human Experimentation and approved by the local Ethic Committee.

Hirsutism was evaluated by a modified form of Ferriman-Gallwey scoring system.[1] In brief, the degree of hirsutism was rated on a scale from 0 to 4 over 11 body regions. The hirsutism score was obtained by totaling the score for each body region. In each patient, the test was performed at baseline and after 3 and 6 months of treatment. The score evaluation was performed by a single physician who was unaware of the treatment assigned. The patients' subjective opinion of the clinical outcome of therapy (excellent, good, fair, or poor) was also obtained at the end of the treatment period.

Of the 28 participants, 14 patients (age 15-18 y) were affected by IH and had regular menstrual cycles, normal body weight, normal androgen serum levels, and a serum luteinizing hormone (LH) to follicle-stimulating hormone (FSH) < 2. None of them showed any ovarian or adrenal abnormality on ultrasonographic examination.

The other 14 patients (age 15-19 y) were diagnosed with POS according to consensus criteria.[30] They had menstrual irregularities (oligoamenorrhea), chronic anovulation, serum LH to FSH ≥ 2, hyperandrogenemia, and micropolycystic ovarian appearance on ultrasonographic examination.

Clinical and biochemical evaluations were performed at baseline, and at 3 and 6 months of treatment. Body mass index (BMI, in kg/m^2), menstrual cycle characteristics, and HS levels were evaluated. At each clinical follow-up visit, side effects of the treatment were evaluated by means of a semi-structured talk. In addition, serum levels of transaminases (aspartate aminotransferase, AST; alanine aminotransferase, ALT), total and direct bilirubin, uric acid, creatine, triglycerides, total and high-density lipoprotein (HDL)-cholesterol, blood glucose, and estradiol (E_2) were measured by standard procedures.[25] A recombinant immunoassay was used to measure serum levels of FSH, LH, total T, DHT, dehydroepiandrosterone (DHEAS), androstenedione (A), and 3α-17 β-androstenediol glucuronide (3α Diol-G). Sex hormone binding globulin (SHBG) levels were measured by a RIA assay. For all measurements, appropriate commercial kits were used (Diagnostic System Laboratories, Webster, TX) with intra-assay and interassay coefficients of variation $< 10\%$.

Patients were randomly assigned to 2 treatment groups on the basis of a computer-generated randomization sequence. Fourteen patients (7 with IH and 7 with PCOS) were assigned to Group 1 and treated with 2.5 mg finasteride every 3 days; fourteen patients (7 with IH and 7 with PCOS) were assigned to Group 2 and received placebo. Patients were treated for 6 months.

Values are reported as means ± SD. One-way analysis of variance was used for comparison within and between treatment groups, respectively; Student's paired test was