A comparative study of a gonadotropin-releasing hormone agonist and finasteride on idiopathic hirsutism

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Summary

Objective: To compare the efficacy of finasteride and GnRH agonist in the treatment of idiopathic hirsutism.

Methods: Sixty women with hirsutism were randomly assigned to receive either 5 mg of finasteride or long-acting GnRH agonist (depot leuprolide 3.75 mg) intramuscularly monthly for six months.

Main outcome measures: Hirsutism scores were measured according to the Ferriman-Gallway scoring system, and side-effects were monitored for six months of treatment. Blood samples were taken at each visit for assessment of endocrine (FSH, LH, estradiol, progesterone, total and free testosterone, androstenedione, DHEAS-S, 17-OH-P, SHBG), biochemical, and hematologic parameters.

Results: All of the patients treated with finasteride or GnRH agonist showed neither menstrual abnormalities nor side-effects. The mean percent change (±SD) in hirsutism scores in the GnRH and finasteride groups was 36%±14% and 14%±11% at six months, respectively. Serum total testosterone, free testosterone, androstenedion and DHEA-S showed a meaningful decrease in patients treated with GnRH agonist. On the other hand, only serum total testosterone and free testosterone levels decreased with finasteride treatment (p<0.05 and p<0.0001, respectively).

Key words: GnRH agonist; Leuprolide acetate; Estrogen replacement; Finasteride; Idiopathic hirsutism; Androgens.

Introduction

Hirsutism is a common and significant problem in young women. The causes are polycystic ovarian disease (PCOD), Cushing’s syndrome, congenital adrenal hyperplasia (CAH), androgen secreting ovarian or adrenal tumors, and drug induced and idiopathic hirsutism. The most common forms are idiopathic and PCOD [1]. Idiopathic hirsutism is usually defined as an increased rate of hair growth in the androgen-sensitive areas of women with regular ovulatory menstrual cycles and serum androgen (testosterone and dehydroepiandrosterone sulfate) levels in the normal range [2]. In the treatment of idiopathic hirsutism, efficiency of drugs such as oral contraceptives and dexamethasone is poor [3]. Current anti-androgen drugs, spironolactone, cyproterone acetate, and flutamide act by androgen receptor blockades at target organ sites. However, none of these drugs are sufficiently effective or without side-effects. GnRH agonists such as leuprolide acetate are known to produce a state of complete, yet reversible, suppression of pituitary gonadotropin secretion. Leuprolide acetate has been shown to be effective in suppressing ovarian androgen levels in several studies [4]. Finasteride, a member of a new class of drugs called azasteroids, inhibits 5α-reductase activity and blocks the conversion of testosterone into dihydrotestosterone (DHT) in peripheral tissues [5]. Some authors have reported that, finasteride was also well-tolerated and effective in the treatment of idiopathic hirsutism [6]. Moghetti et al. [7] showed that finasteride is as efficient as flutamide and spironolactone. To date, no study has compared the effects of long-acting GnRH agonist (depot leuprolide) and 5α-reductase inhibitor (finasteride).

The purpose of the present study was to determine whether the long-acting leuprolide acetate (LA) in combination with an ERT regimen and finasteride is effective in the treatment of idiopathic hirsutism and to compare these two agents on the basis of endocrinological and clinical parameters.

Materials and Methods

Subjects

Sixty women with idiopathic hirsutism, ranging in age from 18-30 years (22±4), were accepted in the study. Patients were informed of the fact that finasteride had never been previously used in the treatment of hirsutism and of its potential benefits and risks, with a particular caution to avoid pregnancies because of possible male fetus feminization. Patients were treated with long-acting GnRH agonist, depot leuprolide acetate, and to avoid problems associated with estrogen deficiency, estrogen-progestin add-back therapy was initiated. All patients were fully informed of the potential risk of pregnancy, thus barrier or intrauterine contraception was suggested for sexually active women. Written consent was obtained from all subjects. The study was approved by the local Ethics Committee.

The subjects in the study were selected randomly from hirsute patients consecutively referred to Gynecology and Endocrinology departments, according to the following criteria: 1) Hirsutism, defined as a modified Ferriman Gallway (FG) score over 12, 2) Normal serum androgens, such as total and free testosterone, androstenedion and DHEA-S, 3) No clinical or biochemical evidence of polycystic ovary syndrome, 4)
Normal serum 17-OH progesterone levels. Patients with signs of adrenal or ovarian neoplasm, hyperprolactinemia, Cushing’s syndrome, congenital adrenal hyperplasia, polycystic ovary syndrome, or drug-induced hyperandrogenism were excluded. All patients had regular ovulatory menstrual cycles.

Patients had never previously received oral contraceptives or antiandrogen treatment. Patients had no any other disease or medication.

Protocol

All patients admitted to the study were divided into two groups: Group 1 consisted of 30 patients who were given long acting depot GnRH agonist (Leuprolide acetate) * at a dose of 3.75 mg intramuscularly monthly for six months. Two weeks after leuprolide acetate (LA), estrogen replacement, 0.625 mg conjugated equine estrogen and 5 mg medroxyprogesterone acetate ** was started. Group 2 also consisted of 30 patients who were given finasteride 5 mg *** orally, once daily for six months. Patients were evaluated at baseline, and after three and six months of treatment.

Clinical evaluation

All patients were requested not to do cosmetic measures such as depilation. The degree of hirsutism was evaluated by a modified Ferriman-Gallway scoring, based on nine body regions [1]. All evaluations for hirsutism were carried out by the same physician. After baseline evaluations, subsequent evaluations were performed at the third and sixth months of treatments. Each woman was studied in the early follicular phase of her menstrual cycle (within 3–6 days after the onset of menstrual bleeding). All blood samples were collected between 08:00 and 09:00 after an overnight fasting period.

Biochemical safety analysis was performed at baseline, the third and sixth months.

Assays

Total testosterone, androstenedione, dehydroepiandrosterone sulfate (DHEA-S) and free testosterone and 17-hydroxyprogesterone were measured by RIA, with kits from DSL (Diagnostic System Laboratories, Webster Texas USA). Gonadotropins, estradiol and progesterone were measured by RIA with a kit from DSL (Diagnostic System Laboratories, Webster Texas USA). Sex hormone binding globulin (SHBG) was measured by Immunolab-2000 with a chemiluminescence method.

All serum samples from each patient were studied in the same assay.

Statistical analysis

Results were analyzed by Student’s t test for unpaired data and one-way analyses of variance (ANOVA). All tests of significance were two tailed, and p<0.05 was considered to indicate significance. Data are shown as the mean ± SD.

Results

Tolerability and safety

All of the patients treated with finasteride or GnRH agonist showed neither menstrual abnormalities nor side-effects. Serum lipid profile did not show any significant change. All other metabolic parameters, including liver and kidney function tests, remained within normal range.

Evaluation of hirsutism

After treatment with depot GnRH-a and E2-progestin add-back therapy, there was a meaningful reduction of hirsutism in patients after six cycles of depot GnRH, whereas the FG score did not show the same degree of improvement in patients treated with finasteride. The mean Ferriman-Gallway score and the changes with the treatment are shown as Table 1.

When comparing both groups using the unpaired t-test, the difference is meaningful. In Group 1, the FG score decreased in six months 36%±14%. On the other hand the FG score decreased only 14%±11% in Group 2. Treatment with GnRH analogue was more efficient than the finasteride treatment (p<0.0001) in idiopathic hirsutism (Table 1).

Hormonal evaluation

All the hormonal levels (mean standard), baseline and by treatment with GnRH agonist and finasteride are shown in Table 2. In Group 1, both FSH and LH decreased with the long acting depot GnRH agonist treatment (p<0.0001). On the contrary, neither FSH nor LH showed any change during the treatment with finasteride in Group 2. Serum estradiol level also decreased in Group 1, whereas it did not change significantly in Group 2. Serum total testosterone, free testosterone, androstenediol and DHEA-S showed a meaningful decrease in patients treated with the GnRH agonist. On the other hand, only serum total testosterone and free testosterone levels decreased with the finasteride treatment in Group 2 (p<0.05 and p<0.0001, respectively). All other hormones of the patients in both groups did not show any modifications.

Table 1. — Ferriman-Gallway scores of the patients and the changes related to treatment.

<table>
<thead>
<tr>
<th></th>
<th>Basal</th>
<th>3* month</th>
<th>6* month</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1 (GnRH-a)</td>
<td>19±3.5</td>
<td>16.4±2.6</td>
<td>12±2.9</td>
</tr>
<tr>
<td>Group 2 (Finasteride)</td>
<td>17.7±1.8</td>
<td>15±2.2</td>
<td>14±1.9</td>
</tr>
</tbody>
</table>

*p<0.0001; **p<0.01.

Table 2. — Hormonal parameters with GnRH analog and finasteride treatment.

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Group 1 (GnRH a)</th>
<th>Group 2 (Finasteride)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3* month</td>
<td>6* month</td>
<td>3* month</td>
</tr>
<tr>
<td>FSH</td>
<td>6.7±3.1</td>
<td>3.9±3.2</td>
<td>1.3±0.9**</td>
</tr>
<tr>
<td>LH</td>
<td>9.5±6.5</td>
<td>4.5±4.8</td>
<td>1.7±1.5***</td>
</tr>
<tr>
<td>T17O</td>
<td>85.7±37.5</td>
<td>59.8±32</td>
<td>58.7±26.2**</td>
</tr>
<tr>
<td>T-E2</td>
<td>0.8±0.3</td>
<td>0.7±0.3</td>
<td>0.5±0.1**</td>
</tr>
<tr>
<td>Free T</td>
<td>2.2±0.9</td>
<td>1.8±1</td>
<td>1.5±0.8**</td>
</tr>
<tr>
<td>Androstenediol</td>
<td>2.2±2.2</td>
<td>1.2±0.8</td>
<td>1.3±0.8**</td>
</tr>
<tr>
<td>DHEA-S</td>
<td>237±114</td>
<td>29.2±115</td>
<td>178±82**</td>
</tr>
<tr>
<td>17 OH Pro.</td>
<td>1.5±0.9</td>
<td>1.1±0.7</td>
<td>0.9±0.6</td>
</tr>
<tr>
<td>SHBG</td>
<td>1.8±0.7</td>
<td>2.9±0.8**</td>
<td>3.1±0.6**</td>
</tr>
</tbody>
</table>

*p<0.0001; **p<0.002; ***p<0.05.
Discussion

The purpose of this study was to determine the effects of leuprolide acetate (in combination with estrogen and progestin), a long acting GnRH analog, and finasteride, a 5α-reductase inhibitor, on idiopathic hirsutism. In addition to the tolerability and efficacy of finasteride on hirsutism and serum sex hormones were studied. The dose of estrogen was chosen to achieve levels of serum E2 similar to those found in untreated young hyperandrogenic women.

Our results demonstrate that 3.75 mg leuprolide acetate given as a monthly IM injection is sufficient to significantly suppress FSH, LH, E2, total testosterone, free testosterone, androstenedione and DHEA-S, whereas serum SHBG levels increased significantly. Several studies have reported the efficacy of GnRH-a therapy on hirsutism [1]. Therapy with LA + estrogen/progestin can achieve positive results in the treatment of hirsutism because it is capable of lowering the overall pituitary gonadotropins and, consequently, LH-dependent ovarian androgen production. Furthermore the estrogenic component exerts a direct effect which results in enhanced SHBG synthesis. In this study we can say that the high and constant reduction of serum LH, FSH levels induced by GnRH agonist, caused a decrease in the gonadotropin supported androgen biosynthesis in theca-interstitial cells. Ciotta et al. [8] also found similar results. Serum SHBG levels significantly increased with leuprolide acetate plus estrogen/progestin treatment. The last hormonal modification was probably linked to the oral administration of estrogen because it is likely that long-term treatment with GnRH-a does not have any effect on SHBG levels [9].

In this study, LA associated with conjugated estrogen plus progestin was efficacious in significantly reducing the hirsutism score in idiopathic hirsutism. This data is compatible with previous studies. The efficacy of GnRH analog on hirsutism has been shown previously [10]. A prospective randomized study which showed that a greater improvement in hirsutism was seen in GnRH-a treated women which appears to be more closely correlated with the degree of gonadotropin suppression [11]. Elkind-Hirsch et al. [12] showed that combination gonadotropin-releasing hormone agonist and oral contraceptive therapy are more efficient than not only oral contraceptives, but also GnRH-a alone. Therefore we can claim that depot Leuprolide acetate, a GnRH-agonist, is useful in the treatment of idiopathic hirsutism.

Finasteride, a specific inhibitor of 5α-reductase, is effective in the treatment of some conditions depending on the conversion of testosterone to DHT, such as benign prostate hyperplasia [13], and is under evaluation in prostate cancer [14]. In our patients, both total and free testosterone levels decreased with finasteride treatment. In addition, the Ferriman-Gallway score showed a significant decrease level. Hirsutism is considered to be a skin disease due to increased 5α-reductase activity in the pilosebaceous unit and finasteride is a drug that inhibits this enzyme activity. For this reason, we can say that FG scoring of the patients decreased due to reduced 5α-reductase activity. Some authors have reported that finasteride was also well-tolerated and effective in the treatment of idiopathic hirsutism [6]. Many studies have shown that finasteride is quite an efficient therapy for hirsutism. Moghetti et al. [7] showed that finasteride was as efficient as flutamide and spironolactone. On the contrary, Falsetti et al. [15] found flutamide to be more powerful than finasteride.

In this study GnRH-a treatment suppressed gonadotropin and testosterone secretion more completely than finasteride therapy. We have demonstrated that GnRH-a plus estrogen/progestin as add-back therapy was more effective in suppressing androgen levels compared with finasteride treatment. The more suppressive effect on gonadotropin and testosterone levels in patients treated with GnRH-a may be responsible for this result. We could not find any report in the literature review about a comparison of leuprolide versus finasteride on idiopathic hirsutism.

Serum SHBG levels, which were in the normal range initially, slightly and non-significantly increased during finasteride treatment. Moghetti et al. [6] showed that 5α-reductase activity is greatly inhibited in the liver (where SHBG is synthesized), by finasteride treatment. Therefore it is possible to speculate that reduction of DHT might play a role in slightly increasing SHBG levels. On the other hand, it has been claimed in some reports that androgens per se do not regulate serum SHBG levels. This result is compatible with the results of Couzinot and Winnek [16, 17].

In patients treated with finasteride and GnRH-a, serum and urinary markers of 5α-reductase activity could not be measured due to technical failure.

In this study both GnRH-a and finasteride treatment were well-tolerated and leuprolide acetate depot formulation administered IM once a month will provide obvious advantages over daily injections.

In conclusion, depot leuprolide acetate, a long-acting GnRH agonist, can successfully improve the Ferriman-Gallway score in idiopathic hirsute women. Finasteride, a 5α-reductase inhibitor, is also efficient in the treatment of idiopathic hirsutism, however leuprolide acetate is more efficient. Furthermore neither leuprolide nor finasteride causes any adverse event in women with idiopathic hirsutism.

References


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