Off-Label Drug Uses

Flutamide: Hirsutism in Women

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This *Hospital Pharmacy* feature is extracted from *Off-Label Drug Facts*, a publication available from Wolters Kluwer Health. *Off-Label Drug Facts* is a practitioner-oriented resource for information about specific drug uses that are unapproved by the US Food and Drug Administration. This new guide to the literature enables the health care professional or clinician to quickly identify published studies on off-label uses and determine if a specific use is rational in a patient care scenario. References direct the reader to the full literature for more comprehensive information before patient care decisions are made. Direct questions or comments regarding *Off-Label Drug Uses* to jgeneral@ku.edu.

BACKGROUND

In women, hirsutism presents as excessive terminal hair growth in locations where hair is normally minimal or absent. Hirsutism can be caused by non-androgenic factors or androgenic excess, or it can be of idiopathic etiology.¹ Androgenic causes, including polycystic ovary syndrome (PCOS), contribute to the majority of hirsutism cases in women. To properly treat this condition, a detailed examination is necessary. In cases in which androgen excess is suspected, therapy that reduces androgen circulation, either directly or indirectly, is suggested (eg, oral contraceptives, finasteride, flutamide, spironolactone).²⁻⁴

PATIENT POPULATION

Adult women with hirsutism.

DOSAGE AND DURATION

The recommended dosage is 62.5 to 500 mg daily in combination with oral contraceptives.²⁻⁴ Because of the potential for dose-related hepatotoxicity, the lowest effective dose should be used with close monitoring. The Androgen Excess and Polycystic Ovary Syndrome Society recommends daily doses of less than 250 mg.²

Because of the potential for teratogenicity, flutamide should be administered in combination with appropriate contraception in premenopausal women.

RESULTS

Guidelines and a position statement support the use of antiandrogens for the treatment of hirsutism based on expert consensus/opinion and several small controlled trials of low-quality methodology.²⁻⁴ Although flutamide has demonstrated benefit in the management of hirsutism, particularly when used in combination with oral contraceptives, its use is limited by the risk for significant hepatotoxicity and teratogenicity.⁵⁻¹⁵

Guidelines

Endocrine Society

Endocrine Society evidence-based clinical practice guidelines³ for the treatment of hirsutism in premenopausal women recommend pharmacological therapy or direct hair removal for women who do not respond to cosmetic measures. If pharmacological therapy is appropriate, oral contraceptive monotherapy is suggested for the majority of women. Agents not recommended as monotherapy include flutamide, topical antiandrogens, insulin-lowering drugs, and gonadotropin-releasing hormone (GnRH) agonists. If refractory to at least 6 months of contraceptive monotherapy, an antiandrogen (spironolactone, finasteride, flutamide) may be added. Antiandrogen therapy is not recommended unless adequate contraception is used. A systematic review of 5 pla-

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cebo-controlled trials suggests that antiandrogens are superior to placebo, with no differences among the antiandrogen agents. In randomized controlled trials, flutamide demonstrated efficacy at doses ranging from 250 to 750 mg daily, with 500 mg daily being the most frequently used dose. Some experts suggest that 250 mg daily is as effective as 500 mg daily. There is no evidence from controlled trials that doses less than 250 mg are effective for hirsutism. Because of the significant risk for hepatotoxicity, flutamide is not considered first-line therapy; if used, the lowest effective dose is recommended along with close monitoring.

American College of Obstetricians and Gynecologists

American College of Obstetricians and Gynecologists (ACOG) clinical guidelines⁴ for the management of PCOS state that there is no clear primary treatment for PCOS-related hirsutism based on expert consensus/opinion and due to limited controlled data. Although antiandrogens (eg, spironolactone, flutamide, finasteride) are listed as potential therapeutic options that may offer some benefit, their use is limited by the risk for teratogenicity and, in the case of flutamide, the risk for hepatotoxicity.⁴

Androgen Excess and Polycystic Ovary Syndrome Society

According to an Androgen Excess and Polycystic Ovary Syndrome Society position statement² regarding androgen excess and PCOS-related hirsutism, lifestyle changes and cosmetic measures are recommended as first-line therapy in mild or localized cases. If pharmacological intervention is appropriate, topical elornithine as monotherapy or in combination with other measures is recommended in cases of facial involvement. A low-dose neutral or antiandrogenic oral contraceptive is recommended as first-line therapy (as monotherapy in mild cases, or as adjuvant therapy to antiandrogens in moderate to severe cases in order to provide adequate contraception or guarantee regular menstrual activity). Insulin sensitizers, including metformin, are not recommended for hirsutism due to a lack of efficacy compared with placebo.

Antiandrogens in combination with oral contraceptives are recommended for moderate to severe cases or in milder refractory cases. Antiandrogen monotherapy is recommended when oral contraceptives are contraindicated; however, another reliable contraceptive method must be used. Although antiandrogens are considered the agents most likely to

be effective in the treatment of hirsutism, evidence supporting their use is limited to several randomized controlled trials of variable methodology. Due to flutamide's similar efficacy to other antiandrogens and the increased risk of severe hepatotoxicity associated with its use, the position statement recommends finasteride, cyproterone acetate, or spironolactone over flutamide when an antiandrogen is needed. When flutamide is used, dosages of less than 250 mg daily are recommended.²

Meta-analysis

A meta-analysis reviewed 12 randomized controlled trials of low-quality methodology (poor blinding mechanisms) that evaluated antiandrogen therapy (duration of at least 6 months) in women with hirsutism.⁵ In the 5 studies comparing antiandrogens with placebo, patients receiving antiandrogen therapy had significantly lower hirsutism scores than the placebo group, with no difference among the agents (spironolactone, finasteride, flutamide). In 3 trials comparing antiandrogens (1 with spironolactone and 2 with flutamide) with metformin, patients receiving antiandrogen therapy had significantly lower hirsutism scores than the metformin alone group, but the results were limited by large inconsistencies across studies. In 2 trials in which flutamide was added to metformin therapy, the combination was significantly more effective than metformin alone. The authors concluded there is weak evidence suggesting antiandrogens are mildly effective for the treatment of hirsutism.

Controlled Trial

In a double-blind, placebo-controlled, parallel trial,⁸ 131 premenopausal women with moderate to severe hirsutism were randomized to receive a triphasic oral contraceptive (containing 30 mcg, 40 mcg, and 30 mcg of ethinyl estradiol and 50 mcg, 75 mcg, and 125 mcg of levonorgestrel) in combination with flutamide 125, 250, or 375 mg or placebo. A modified Ferriman-Gallwey hair growth score was obtained at baseline and at 3, 6, and 12 months. A total of 119 women were included in the intent-to-treat analysis. All flutamide groups experienced a progressive decrease in score over the 12-month trial, whereas the placebo group showed a significant decrease at 6 months, with no further advantage at 12 months. Changes in Ferriman-Gallwey scores from baseline to 12 months were as follows: 52.7% for flutamide 125 mg, 49.1% for flutamide 250 mg, 48.4% for flutamide 375 mg, and 28.8% for placebo.

Noncontrolled Trial

A retrospective observational study⁶ of 414 premenopausal women (mean age, 24 years) evaluated the efficacy of flutamide alone or in combination with oral contraceptives for 3 to 8 years. The majority of hirsutism cases were related to PCOS (67.4%) or were of idiopathic origin (17.2%). For the first 3 years, patients received yearly reducing flutamide doses of 250 mg, 125 mg, and 62.5 mg daily. Mean basal hirsutism scores decreased from 17.5 to 10.5, 7.9, 6.1, 5.6, and 5.5 after 0.5, 1, 1.5, 2, and 3 years of treatment, respectively ($P < .001$). Mean percentage improvement for the same period was 40%, 55%, 65%, 70%, and 70%, respectively. Mean hirsutism scores typically normalized after at least 1 year of treatment, with maximum results observed after 2 years of therapy. Mean basal hirsutism scores were 17.8 and 16.9 in PCOS and non-PCOS patients, respectively; at 3 years, scores significantly decreased to 5.6 in PCOS patients and to 5.3 in non-PCOS patients ($P < .001$). More than 95% of the patients were satisfied with outcomes after 3 years of treatment. During the first 3 years of the study, approximately 20% of patients withdrew from treatment (11.1%, 2.9%, and 5.8% in the first, second, and third year, respectively); a total of 332 women completed at least 3 years of therapy. Six percent of withdrawals were related to significant transaminase increases (more than 50% above upper limits of normal), with 5.6% occurring in the 250 mg dose group and 0.5% in the 125 mg dose group. No significant changes in transaminases occurred in the 62.5 mg dose group.

SAFETY

This is a limited safety profile. Refer to package labeling for complete prescribing information (eg, Warnings/Precautions, Adverse Reactions, Drug Interactions).

The risk of teratogenicity is a known complication with the use of antiandrogens, including flutamide; therefore, contraception should be used concomitantly in premenopausal women.

In a placebo-controlled trial in which varying doses of flutamide were administered in combination with an oral contraceptive, the incidence of adverse events was similar between the flutamide 125 mg dose and placebo (12.5%). Incidences were slightly but not significantly increased with higher doses of flutamide (17.3% with the 250 mg dose; 21.2% with the 375 mg dose).⁸ In a small prospective observa-

tional study, 83 women with androgenic-related hirsutism received flutamide (250 mg) either alone or in combination with oral contraceptives. Approximately 41% experienced at least 1 adverse effect during the study period (84 months); the most frequently affected systems included the gastrointestinal (62.88%), metabolic (13.4%), nervous (11.34%), and dermatologic (10.3%) systems. Approximately 60% of patients withdrew during the study for reasons possibly or probably related to the study drug. Two patients, 1 in each group, experienced significantly increased transaminase levels, but no change was observed in mean levels for either group.¹²

Hepatotoxicity, a potentially serious adverse effect of flutamide therapy, may be dose related, but it has also been reported with lower daily doses (250 mg daily or less).¹²⁻¹⁵ In a multiyear, retrospective study, 6% (25 of 332) of premenopausal women with hirsutism receiving flutamide alone or in combination with oral contraceptives withdrew due to significant increases in transaminase levels, which occurred more commonly with 250 mg and 125 mg doses (5.6% and 0.5%, respectively) than with the 62.5 mg dose (0%).⁶ In contrast, hepatotoxicity (defined as transaminase levels of 45 U/L or greater) did not occur in a long-term (1 year) study in which 214 women (mean age, 20.9 years) with hirsutism received flutamide (125 mg or 250 mg daily) alone or in combination with an oral contraceptive.¹⁵

THERAPY CONSIDERATIONS

Guidelines and a position statement support the use of antiandrogens for the treatment of hirsutism, based on expert consensus/opinion and several small controlled trials of low-quality methodology. Although flutamide has demonstrated benefit in the management of hirsutism, particularly when used in combination with oral contraceptives, its use is limited by the risk for significant hepatotoxicity and teratogenicity.

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