Gao and Mahto. J Dermatol Res Ther 2016, 2:023
Volume 2 | Issue 2
ISSN: 2469-5750
DOI: 10.23937/2469-5750/1510023

Journal of
Dermatology Research and Therapy

Review Article: Open Access

Anti-Androgen Therapy in Female Adult Acne

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Keywords

Acne, Androgens, Spironolactone, Cyproterone

Introduction

Acne vulgaris is a multifactorial disease of the pilosebaceous unit as a result of androgen-induced increased sebum production, altered keratinisation, inflammation, and hair follicle bacterial colonisation by *Propionibacterium acnes* (*P. acnes*) [1]. The clinical features of acne include seborrhea, comedones, and papules and pustules. Nodules and cysts are seen in severe nodulocystic acne and scarring can follow. Acne can occur alone or with signs of hyperandrogenism such as hirsutism, alopecia and menstrual irregularity.

Acne vulgaris is a common reason why adult women present to dermatologists and can be a clinical challenge to treat. Although acne is most commonly associated with adolescence [2], it often persists into adulthood [3]. Perkins et al studies prevalence of acne in 2895 women and found more than a quarter had acne and although acne peaked in teens it continues to be prevalent through the fifth decade [4]. Adult acne relating to circulating androgens is often referred to as late-onset or post-adolescent acne [5]. Acne can cause significant psychological distress, which has been shown to improve with effective treatment [6].

Anti-androgen therapy is indicated for moderate to severe papulopustular/nodular acne in female patients resistant to first line therapy or where hyperandrogenism is identified [7]. Although standard acne therapies can be successfully used to treat acne in adult female patients, anti-androgen treatment is an effective therapeutic option that may provide an opportunity to better target acne in this population, even when other systemic therapies have been unsuccessful. This review discusses non-contraceptive hormonal therapy including cyproterone acetate, spironolactone and flutamide. Contraceptives with androgenic activities and topical treatments are beyond the scope of this review.

Pathogenesis

Androgens play an important role in the pathophysiology and treatment of acne [8,9]. Other important factors are inflammatory mediators released into the skin, alteration of the keratinisation process leading to comedones, and follicular colonisation by *P acnes* [1]. There is no acne without sebum, which serves as a nutrient source for *P acnes*, and androgens are the major sebo tropic hormones [1].

Androgens in women are derived from three sources: the ovaries, adrenal glands, and peripheral conversion. Prior to puberty, the adrenal glands produce increasing amounts of dehydroepiandrosterone sulphate (DHEAS), which is metabolized into active androgens in the skin [4]. Androgens drive enlargement of the sebaceous gland and increase sebum production. Increased or altered sebum production under androgen control is a vital step in the formation of acne in all populations [10]. Increased sensitivity of the pilosebaceous unit to androgens has also been suggested as one cause of acne [11]. In skin, androgen receptors are located in sebaceous glands and in the outer root sheath of the hair follicle. Sebocytes and keratinocytes of the pilosebaceous follicle infundibulum in patients with acne have androgen receptors that are both more numerous and more sensitive than those in normal subjects.

Clinical observations reinforce the role of androgens in acne. Conditions of hyperandrogenism, such as polycystic ovary syndrome (PCOS), are associated with acne, which is highly responsive to anti-androgens [12]. Furthermore, rising levels of dehydroepiandrosterone sulfate (DHEA-S) are associated with the onset of acne in pre-menarchal girls, and higher levels in pre-menarche may predict the development of more clinically severe acne in puberty [13]. Elevated DHEA-S also correlates with clinical acne in a subset of patients with PCOS [14]. Fluctuations in androgens during the menstrual cycle may account for cyclical flares, including the commonly reported premenstrual flares of acne.

Differential Diagnosis of Acne in Women

A thorough medical history and physical examination is necessary for assessment of female adults presenting with acne. The common differential diagnosis of adult female acne includes: rosacea, seborrheic dermatitis, and hyperandrogenism (including PCOS).

Signs and symptoms of hyperandrogenism include hirsutism, alopecia, amenorrhea or oligomenorrhea, and virilization, as evidenced by deepening of the voice, clitoromegaly and increased muscle mass. Hirsutism is the most common manifestation (70-80%) and is highly associated with elevated levels of free testosterone [15].

The most common cause of hyperandrogenism is PCOS. The Rotterdam consensus criteria define diagnosis of PCOS as two of the following three criteria: amenorrhea or oligomenorrhea, biochemical or clinical hyperandrogenism, and ultrasonographic documentation of increased follicle count (> 12) or follicular volume (> 10 cm^3) per ovary. Dermatologists should be familiar with the diagnostic work-up of PCOS, which consists of assessment of endocrine (total and

Citation: Gao J, Mahto A (2016) Anti-Androgen Therapy in Female Adult Acne. J Dermatol Res Ther 2:023

Received: March 05, 2016: **Accepted:** April 18, 2016: **Published:** April 20, 2016

free testosterone, FSH, LH, prolactin, 17-hydroxyprogesterone and DHEA) and metabolic parameters (fasting insulin and lipids).

An important differential to be aware of is androgen-secreting tumours which can occur in all ages and present with rapid onset acne. High levels of testosterone (> 150-200 ngdL-1) associated with normal levels of DHEA are suggestive for ovarian tumour. High levels of DHEA (> 8000 ng mL-1) are suggestive for adrenal tumours. Mildly elevated levels of DHEA (4000-8000 ng mL-1) are found in CAH, PCOS and Cushing disease. High levels of 17-OHP and a positive adrenocorticotropic hormone (ACTH) stimulation test are essential to make the diagnosis of CAH [16].

Anti-Androgen Therapy

Anti-androgens are agents that inhibit directly the binding of dihydrotestosterone (DHT) to its receptor in a competitive way. They include cyproterone acetate (CPA), spironolactone, and flutamide. All antiandrogens are contraindicated in men because they result in feminization, and also in women during pregnancy [17].

Cyproterone acetate

Cyproterone acetate is a progestational anti-androgen synthetic steroidal agent. It blocks the androgen receptor, in particular those sensitive to DHT [18]. CPA is the only anti-androgen that also has anti-gonadotropin action and inhibits ovulation [19]. It is used with an oestrogen in the treatment of majority of acne cases such as in combined oral contraceptives (COC) but it can be used alone. CPA inhibits the conversion of DHEA to androstenedione by 3-beta hydroxysteroid dehydrogenase, decreasing adrenal androgen production. CPA also inhibits the production of follicle-stimulating hormone and luteinizing hormone, which blocks ovarian function and reduces serum androgen levels. Treatment with anti-androgen also reduce comedones indirectly by an increase of sebaceous linoleate concentration [18].

Treatment with CPA should begin on the first or fifth day of the menstrual cycle and should be stopped on the 14th day just before ovulation [19]. When used alone, the recommended dose is 50 to 100 mg daily. Studies have shown that an overall improvement of acne in 75-90% of cases can be seen [20,21].

Side effects of CPA include menstrual irregularities, breast tenderness, fluid retention, headache and nausea [22]. The most concerning side effect reported is liver toxicity, which is dose dependent [23]. The rate of menstrual irregularities is significantly reduced when CPA is combined with an oestrogen [19].

During the first 10-15 days of the menstrual cycle, CPA at a dosage of 12.5-50 mg daily can be added to COC already containing CPA. This avoids menstrual irregularities caused during treatment with CPA alone [22]. A recent review of the benefits and risks of co-cyprindiol following concerns in France about the risk of venous thromboembolism concluded that the 'balance of benefits and risks remains positive' for treatment of skin conditions related to androgen sensitivity such as severe acne with or without seborrhea [24].

CPA is contraindicated in those with liver disease, malignancy (other than prostate cancer), history of meningioma, severe diabetes, haematological disorders, and chronic severe depression. Patients on CPA should have liver function monitoring.

Spironolactone

Spironolactone is an aldosterone antagonist. The mechanisms of action are as follows1. Decrease the activity of 5-alpha reductase via increased clearance of testosterone secondary to augmented liver hydroxylase activity 2. Compete with dihydrotestosterone for androgen receptors and decreasing the amount of sebum production stimulated by androgens 3. Reduce levels of free testosterone by increasing binding to sex hormone binding globulin [25].

Spironolactone is well documented to be an effective treatment for hormonally mediated acne [26-29]. It has been successfully used for female patients with acne, hirsutism and alopecia for years [30]. In doses of 50 to 100 mg once or twice daily, taken with meals, it has been shown to reduce sebum excretion rate by 30% to 50% and improve acne [17,31,32]. Clinical improvement of acne is generally seen after 3 months and effective maintenance doses range from 25 to 50 mg daily.

However, the Cochrane review in 2009 considers there to be too little evidence for use of spironolactone in acne due to limited number of trials and small sample size [33]. It should be reserved for therapy-recalcitrant cases resistant to conventional therapy, and it is useful in countries where other hormonal treatments are contraindicated or unavailable [17].

Adverse effects are dose-dependent. Low doses of 25 to 50 mg daily are generally well tolerated [17]. Common side effects include diuresis, menstrual irregularities, breast tenderness or enlargement, reduced libido and hypercalcaemia. These side effects are usually mild in severity and a reduction of the dosage is sufficient to reduce them to acceptable levels. Irregular menstrual bleeding and other side effects are improved when spironolactone is used in combination with an oestrogen [17].

Spironolactone is used as a potassium sparing diuretic and hyperkalemia is an uncommon side effect. A recent retrospective study of 974 young women found the rate of hyperkalemia in healthy young women taking spironolactone for acne is equivalent to the baseline rate of hyperkalemia in this population [34]. Routine monitoring of potassium is not recommended but potassium supplementation and angiotensin-converting enzyme inhibitors should be avoided [34].

Spironolactone should be avoided in patients at risk of breast cancer or other oestrogen dependent malignancies. The potential for it to induce oestrogen dependent malignancies remains a controversial topic [35]. Treatment with spironolactone during pregnancy is contraindicated (FDA pregnancy category C) and may lead to abnormalities of the male fetal genitalia, such as hypospadias [32].

Flutamide

Flutamide is a non-steroidal androgen antagonist used in the management of prostate hypertrophy, prostate cancer, and hirsutism. The anti-androgen activity is due to competitive inhibition of androgen receptors, especially the ones that bind DHT. Flutamide also enhances androgens breakdown to inactive metabolites. Flutamide can be effective for the treatment of acne, hirsutism and alopecia [32]. It can be used alone or in combination with metformin or COC in patients with PCOS.

Most randomized control trials on flutamide have focused on hirsutism. Only two randomized control trial identified for this review specifically studied acne [36,37]. The trials compared the efficacy of flutamide with cyproterone-estradiol combinations in treating acne. It found flutamide to be at least as effective at treating acne but called for further studies with larger sample sizes. Eight other studies were identified which found a marked improvement in acne treated with flutamide compared with baseline or placebo [38-45].

Hepatic toxicity limits the use of flutamide. There are cases of fatal hepatitis reported [17,32]. Regular liver function tests and monitoring is mandatory if used. Other major side effects are gastrointestinal disorders (diarrhea), muscle cramps and gynecomastia.

Flutamide is also contraindicated in pregnancy as it can cross the placental barrier and causes feminization of the male fetus [36].

Conclusion

Acne in female adult has significant psychosocial comorbidity and may be challenging to treat. In the latest European guidelines anti-androgens are indicated as a treatment option for severe papulopustular acne when combined with oral antibiotics or topical therapy [46]. They are a safe and effective option for adult female patients with moderate to severe acne resistant to first line treatment

or with features of hyperandrogenism. Isotretinoin remains a highly effective treatment option in this patient population but anti-androgens such as CPA and spironolactone provide an important option even when other treatments have failed. It is difficult to draw conclusions comparing the efficacy of different anti-androgens on the available date. More high quality studies into the benefits of anti-androgen therapies are needed.

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