The use of hormonal agents in the treatment of acne

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Abstract

Hormones and androgens play an important role in the pathogenesis of acne. Multiple hormonal modulators are now available for the treatment of acne. The efficacies and side effects of currently available hormonal agents are reviewed here including the use of oral contraceptives, spironolactone, flutamide, cyproterone acetate, finasteride, and cortexolone 17α-propionate. Hormonal therapies are an efficacious treatment option for acne among females. With the growing need to reduce antibiotic exposures, hormonal therapies should be more widely studied and incorporated into acne treatment strategies.

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Acne vulgaris is one of the most common chronic inflammatory skin diseases. On a global scale, it is the 8th most common disease with a prevalence of 9.4% that includes both adult and pediatric populations of diverse ethnic backgrounds.[1] While acne is frequently associated with the adolescent population, it is increasingly emerging as a chronic disease beginning as early as ages 7-9 years and persisting into adulthood past 50 years of age.

Acne vulgaris develops around the pilosebaceous unit and manifests as open and closed comedones, as well as inflammatory papules, pustules, and nodules. Acne pathogenesis involves abnormal keratinization that causes impaction and distension of the lower portion of the infundibulum, forming the comedo.[2-4] Other factors include a complex interplay among sebum production, with changes in lipid composition, hypersensitivity to androgen stimulation, *Propionibacterium acnes* (*P acnes*) colonization, and local inflammatory cytokines mediated by the innate immune system.[5,6]

Androgen stimulation is one of the major etiologic factors contributing to acne as prepubertal castration was shown to prevent the development of acne.[7] While androgens are primarily produced by the gonads and adrenal glands, they are also produced locally at the level of the sebaceous glands. Adrenal and gonadal androgens are converted to testosterone and dihydrotestosterone (DHT) by type 1 5α-reductase, which is located within the follicular infundibulum.[8,9] At the level of the sebaceous glands, androgens promote keratinocyte and sebaceous gland proliferation.[10,11] It has been shown that sebaceous glands are also androgen target tissues. When androgens act on the androgen receptors (AR) in the epithelial cells of the sebaceous glands, sebum production is increased and this likely contributes to sebum hypersecretion; additionally, stimulation of AR can promote the inflammatory response mediated by macrophages and neutrophils.[12,13]

The exact mechanisms by which androgens and AR regulate sebocyte activity and sebum production in acne is not completely understood; however there are 3 primary hypotheses. First, AR may enhance the activities of fibroblast growth factor receptor 2 (FGFR2), which was shown to be imperative in sebaceous gland development and homeostasis.[14,15] Second, AR may enhance lipogenesis in sebocytes by increasing the expression of sterol-regulatory element-binding proteins (SREBPs).[16] Third, androgens may communicate with the insulin-like growth factor-1 (IGF-1) pathway in regulating acne development.[16,17]

Androgens and their receptors are the main players in the hormonal pathogenesis of acne, and thus are the major target of systemic hormonal therapies. These therapies will be the focus of this review.

Therapies

Acne therapies rely on both topical and systemic formulations of a handful of medications from several different pharmacological classes. Topical therapies are indicated for mild-to-moderate acne and as adjunctive treatment for severe and nodular-cystic acne. Topical therapies include benzoyl peroxide, retinoids, antibiotics, and azaleic acid. Systemic therapies are indicated for moderate-to-severe and nodular-cystic acne, and include oral antibiotics, hormonal modulators, and isotretinoin. Currently, hormonal therapies are directed toward females who are the focus of this review (Figure).

Oral contraceptives

Combined oral contraceptives (COCs) are an increasingly common option for acne treatment. The three US Food and Drug Administration (FDA) approved COCs for acne treatment are: norgestimate-ethinyl estradiol (Ortho Tri-cyclen®, Ortho-McNeil-Janssen Pharmaceuticals, Inc, Raritan, New Jersey), ethinyl estradiol with norethindrone (Estrostep®, Warner-Chilcott, Rockaway, New Jersey), and ethinyl estradiol with drospirenone (Yaz®, Bayer Healthcare Pharmaceuticals Inc, Whippany, New Jersey; Table 1). These 3 formulations are all approved for the treatment of moderate acne in menstruating females at least 14 or 15 years old.[18] Although there are only three FDA-approved COCs for the treatment of acne, a Cochrane review demonstrated that 6 different COCs (levonorgestrel, norethindrone acetate, norgestimate, dro-

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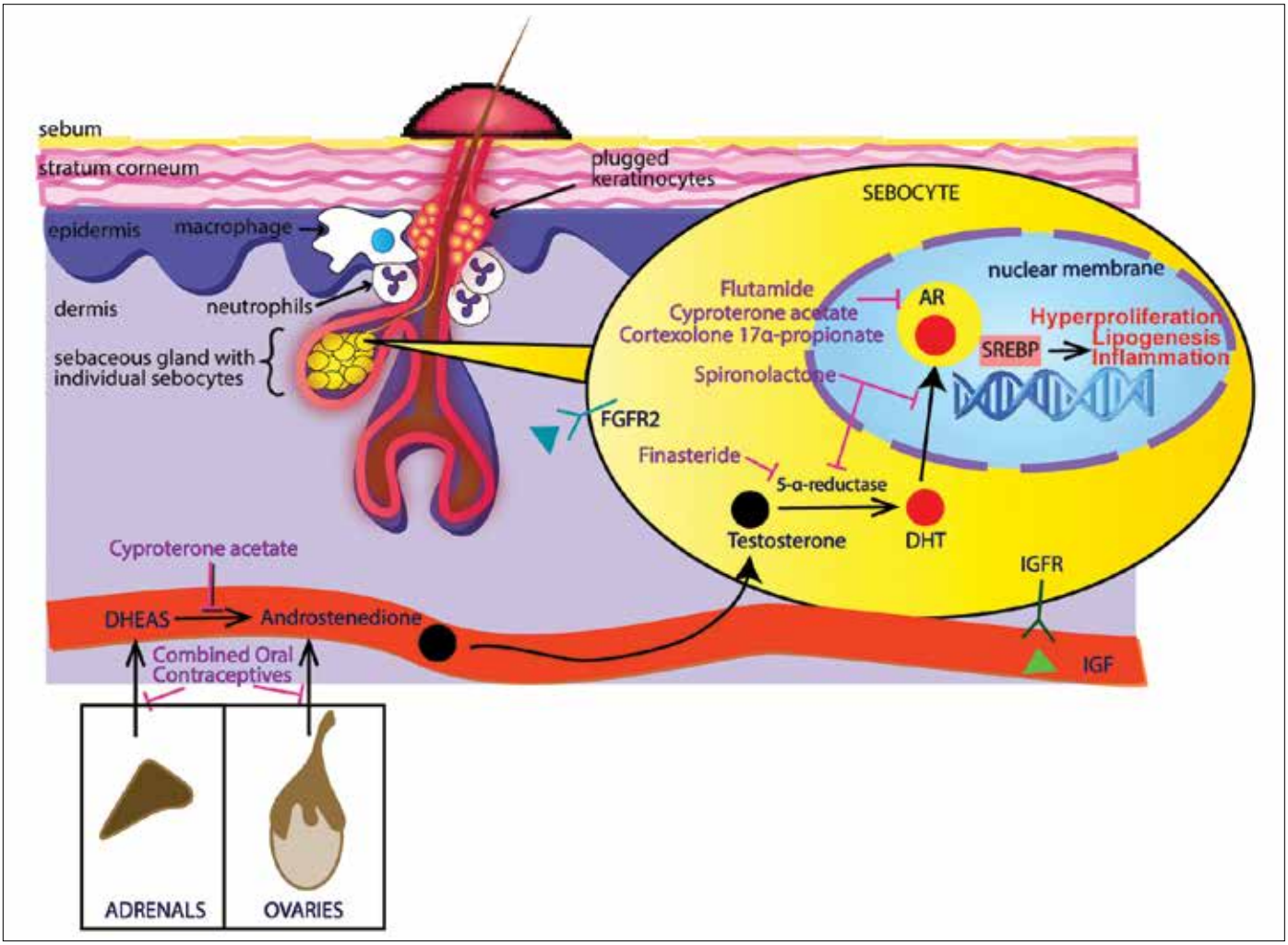

FIGURE. Acne hormonal therapies and their targets. Androgens are thought to influence acne pathogenesis by: **1)** promoting keratinocyte/sebocyte proliferation via FGFR2; **2)** increasing lipogenesis in sebocytes by increasing expression of SREBP; **3)** communicating with the IGF-1 pathway; and **4)** promoting the inflammatory response mediated by macrophages and neutrophils. Treatments targeting these androgen pathways are shown. Abbreviations: AR, androgen receptor; DHT = dihydrotestosterone; FGFR2, fibroblast growth factor receptor 2; IGF, insulin-like growth factor; SREBP, sterol-regulatory element binding protein.

spirenone, dienogest, and chlormadinone acetate) were effective in reducing both inflammatory and noninflammatory facial acne lesions compared to placebo, with few important and consistent differences.[19]

In regards to their mechanism of action, COCs inhibit ovarian and adrenal production of androgens; and most formulations include both progestin and estrogen in order to avoid unopposed estrogen exposure, a significant risk factor for endometrial carcinoma.[20] At the same time, while progestin-only oral contraceptive pills are prescribed for contraceptive purposes, only COCs should be prescribed for acne because synthetic progestins have androgenic activity which is modulated by the addition of estrogen.[21]

In addition to the benefit of contraception in women who do not desire pregnancy, the overall effect of COCs is anti-androgenic.[21,22] These hormones inhibit the production of the gonadotropins, luteinizing hormone (LH) and follicle-stimulating hormone (FSH), and the outcome is inhibition of ovulation and LH-induced ovarian androgen production. Ethinyl estradiol increases hepatic synthesis of the sex hormone binding globulin (SHBG), which binds free testosterone in circulation, making it unavailable to bind to the AR or be converted to its more potent form, DHT.[23] In addition, some progestin agents inhibit the enzyme 5α-reductase, thereby reducing the conversion of testosterone to DHT.[24] The net effect of COCs is reduced androgens in the systemic circulation and less androgen-AR binding of the sebaceous glands. This leads to less sebum production and release, an anticipated clinical improvement in acne severity. The therapeutic effects of COCs typically take 3 months for onset. During this 3-month time period, it is important to consider combination therapy (with other topical or oral agents) to maximize a beneficial response.[18]

When patients initiate COCs, they may experience some mild adverse side effects, especially with inconsistent use including irregular vaginal bleeding and diminished acne improvement. Even in those patients that ascribe to regular COC use, it is normal for them to experience some amount of spotting within the first 3 months of initiating treatment;[25] as well as headache, nausea, mood

TABLE 1. Combination oral contraceptive pills FDA-approved to treat moderate acne vulgaris

Trade name	Estrogen	Progestin
Ortho Tri-cyclen®	Ethinyl estradiol 35 µg	Norgestimate 180 mg, 215 mg, 250 mg
Estrostep®	Ethinyl estradiol 20 µg, 30 µg, 35 µg	Norethinodrone acetate 1 mg
Yaz®	Ethinyl estradiol 20 µg	Drospirenone 3 mg

changes, breast tenderness;[26,27] and a modest amount of weight gain likely due to water retention.[28,29] The majority of these potential side effects, with the exception of spotting, may be limited by reducing the dose of ethinyl estradiol.

While COCs offer the dual advantage of acne improvement and contraception, not all women are good candidates for this therapeutic option. Overwhelmingly, the use of COCs is limited in certain demographics of women due to increased risk of thrombotic, ischemic, or hemorrhagic events.[30-33] Women who are pregnant, nursing women less than 6 weeks postpartum, and women aged 35 years or older who smoke more than 15 cigarettes per day are advised against the use of COCs.[34] Women of any age who experience migraine headaches with neurological symptoms and women aged 35 years and older with migraines of any type are also advised not to take COCs.[34] Additionally, current breast cancer, hypertension, and heart disease are all contraindications for COC use.[35] COCs are contraindicated in patients with a history of or current deep venous thrombosis and/or pulmonary embolism, major surgery with extensive immobilization, heart disease, or stroke.[32,33,35,36] Finally, patients with liver disease such as active viral hepatitis, cirrhosis, or benign or malignant liver tumors are ineligible for COC use as well.[34]

The potential risk of prolonged COC use and breast cancer has been well studied and documented.[37,38] The 2 studies were mixed in the role of duration of COCs and breast cancer. One meta-analysis estimated that women with 4 years of COC use between the ages of 20 and 34 had a 50% increase (relative risk of 1.50) and those with 8 years of COC use had a 73% risk increase (relative risk of 1.73) of developing invasive breast cancer in the future ($P < .001$). On the other hand, another meta-analysis found no time-dependent relationship with the duration of COC use.[38] This study found that breast cancer risk significantly decreased in a time-dependent fashion with regards to the time since last contraception use. In addition to breast cancer, HPV-positive women with COC have an elevated risk for the development of cervical cancer.[38,39]

In conclusion, while COCs have some associated risks and are not indicated for certain populations of women including those with multiple cardiovascular risk factors, they are an effective, safe, and well-tolerated option for female patients with acne.

Spironolactone

Spironolactone, a relatively weak antihypertensive, is not FDA approved for acne therapy (Table 2), and therefore, it is utilized off-label in the treatment of acne in females. Although it is not often considered a primary option, it is becoming an increasingly common agent especially in the subgroup of post-teenage patients with hormonal pattern acne that clinically manifests as primarily inflammatory papules located mostly in the lower half of the face and the anterior-lateral neck region.[40]

Oral spironolactone was first synthesized as an aldosterone antagonist in 1957; and prior to its use in acne therapy, was initially used as a potassium-sparing diuretic in the treatment of hypertension and congestive heart failure. Its effect on blood pressure is minimal, reportedly averaging 5 mmhg and 2.6 mmhg decreases in the systolic and diastolic pressures, respectively.[41] Relevant to its application in dermatology, spironolactone exhibits a dual effect as an androgen-receptor blocking agent as well as an inhibitor

TABLE 2. Hormonal therapies prescribed off-label to treat acne

Name (brand name)	Dosing in acne	FDA-approved indication(s)
Spirinolactone (Aldactone®)*	50-250 mg once daily	• Essential hypertension • Edema associated with excessive aldosterone secretion or with congestive HF • Primary hyperaldosteronism • Hypokalemia • Cirrhosis accompanied by edema or ascites • Nephrotic syndrome • Severe HF (NYHA class III-IV)
Flutamide**	62.5 mg, 125 mg, and 250 mg daily	Prostate cancer
Cyproterone Acetate**	• 2 mg once daily (in combination with 35- 50 µg ethinyl estradiol) • 50-100 mg daily when used alone	• NOT approved in United States • Prostate cancer, advanced

Abbreviations: HF, heart failure; NYHA, New York Heart Association Functional Classification.
*Aldactone®, Pfizer Pharmaceuticals, New York, NY.
**Not FDA approved for use in women.

of 5α-reductase, the enzyme responsible for converting testosterone to the more potent DHT. The net effect of spironolactone is a reduction in sebum production and ultimately an improvement in acne severity.[42,43] Improvement is reported within 4 to 6 weeks; however, 3 months is the typical response time.[44]

The efficacy of spironolactone has been demonstrated in several clinical trials. For instance, Krunic et al conducted a prospective study examining the efficacy of a COC (30 μg ethinyl estradiol and 3 mg drospirenone; Yasmin®, Bayer Healthcare Pharmaceuticals, Inc), and 100 mg of spironolactone taken daily in the treatment of 27 women with either severe papular or nodulocystic acne. This combination therapy was effective with 85% of subjects entirely clear of acne or with excellent improvement; also, there were no significant elevations in serum potassium nor were there any adverse events significant enough to warrant discontinuation of treatment in any of the subjects.[45] Of note, drospirenone is a more potent analog of spironolactone with similarly significant anti-androgenic and anti-mineralocorticoid activity.[45,46] A retrospective chart review of 41 women with cyclical acne conducted by Lessner et al determined that the use of spironolactone (between 50-200 mg) with topical retinoid therapy was more effective than the use of topical retinoids alone.[47] In a randomized, placebo-controlled, double-blinded trial, oral spironolactone 200 mg daily caused significant improvement in inflammatory lesions ($P < .001$) as well as subjective benefit ($P < .001$) for women with mild-to-moderate acne.[48]

Topical formulations of spironolactone have been evaluated as well. Double-blind, clinical trials have demonstrated that spironolactone 5% gel induces a therapeutic response in females with mild-to-moderate acne as evidenced by a statistically significant decrease in total lesion count ($P = .007$).[49,50] However, unlike oral spironolactone which is known to affect sebum production, studies evaluating spironolactone cream have shown that it does not significantly decrease the sebum excretion rate, suggesting that it exerts its therapeutic effect through another mechanism.[51]

The most common side effects of spironolactone include headache, diuretic effects, menstrual irregularities, and breast tenderness.[41] However, these appear to be dose-dependent, are rarely severe enough to cause discontinuation, and can be blunted with the use of appropriate concomitant oral contraceptive pill (OCP) therapy. The most serious and feared complication is hyperkalemia, which can cause fatal cardiac irregularities, paresthesias, muscle weakness, fatigue, flaccid paralysis of the extremities, bradycardia, and shock. For this reason, spironolactone use is best avoided in patients with renal insufficiency and heart failure as these conditions may predispose the patient to hyperkalemia.[52] In addition, spironolactone is contraindicated with other medications including diuretics and other potassium-sparing drugs (eg, amiloride, triamterene). Although the risk of hyperkalemia should be considered prior to initiating spironolactone therapy, previous studies have shown that routine monitoring in otherwise healthy women is not warranted [45,53].

Spironolactone should be avoided in pregnancy due to the risk of feminization of a male fetus. This recommendation is based on animal studies in which there is concern for hypospadias, feminization of a male fetus, and other possible adverse effects.[54]

The long-term safety of spironolactone is well documented. Shaw et al followed 91 women up to 8 years after discontinuing spironolactone therapy (average treatment length was 28.5 months and range was between 0.5 and 122 months) and found that there were no cases of serious illness attributable to this medication.[41]

There has long been speculation concerning the association between spironolactone and breast cancer, attributed to 2 reports from 1975.[55,56] As a result, the manufacturer issued a black-box warning on long-term spironolactone use in patients with increased risk of breast cancer either through personal or family history.[55] Despite the black-box warning, several human studies[40,57] have failed to demonstrate a link between spironolactone use and breast cancer. In addition, a study of 2.3 million Danish women showed no increased risk of breast, uterine or ovarian cancers in spironolactone users.[58]

Flutamide

Flutamide, a nonsteroidal androgen-blocking agent is less commonly prescribed for acne. It is FDA approved for prostate cancer but is used off-label for different hyperandrogenic states (acne, hirstuism, alopecia) in women.[59,60] After oral administration, flutamide is broken down into several metabolites, including 2-hydroxyflutamide, which mediates the drug's anti-androgenic activity.[61] This metabolite exerts its anti-androgenic effect peripherally where it acts as a competitive antagonist at the nuclear AR in target tissues.[61,62]

A retrospective, observational study conducted over 15 years followed 230 women with acne, 211 of which also had seborrhea. Findings indicated that flutamide (250 mg, 125 mg, and 62.5 mg/day), either alone or combined with OCP therapy, proved to be effective and even proposed flutamide as first-line therapy for these conditions.[63] Possible adverse reactions due to flutamide use include gastrointestinal distress (primarily diarrhea), hematological alterations, muscle cramps, and the most common and feared: acute hepatitis.[64]

Although in several studies flutamide has proven to be effective for dermatological conditions such as acne, seborrhea, and hirsutism, it does pose serious hepatotoxicity risks. Flutamide can induce varying degrees of liver injury, including acute liver failure (ALF) in a young population,[65] while it was associated with hepatotoxicity without ALF in an older population.

While flutamide is used off label for female patients with acne, its cost and potential hepatotoxicity limit its use in clinical practice.

Cyproterone acetate

Even less commonly prescribed for acne is cyproterone acetate. Outside of the United States, physicians can prescribe cyproterone acetate, a progesterone-receptor agonist and androgen-receptor antagonist.[66,67] Its primary mechanism of action is direct AR blockade especially for those sensitive to DHT, although it also inhibits the conversion of dehydroepiandrostenedione (DHEA) to androstenedione, thereby decreasing adrenal androgen production.[9] Cyproterone acetate is often combined with estrogen, specifically as the formulation co-cyprindiol (ethinyl estradiol 35 μg + cyproterone acetate 2 mg) in the United Kingdom.[68]

While cyproterone acetate has proven to be efficacious for acne with a 75%-90% improvement in as little as 3 months; similar to flutamide, it does have potential hepatotoxicity.[66,69,70] Although this is the most concerning side effect, it is dose-dependent and more

common. Less serious side effects include menstrual irregularities, breakthrough bleeding, breast tenderness, headache, and nausea, that typically resolve with time.[71]

Finasteride

Finasteride is an oral medication that acts as an inhibitor of 5α-reductase, the enzyme responsible for reducing testosterone to its active form, DHT.[72] While finasteride exhibits selectivity for 5α-reductase type II expressed in the prostate, it has a weak effect on type I primarily expressed in the skin and scalp.[72] A retrospective study found that finasteride subjectively improves the symptoms of acne and alopecia in 75% of women with normal serum testosterone levels (9 out of 12).[73] There were no adverse events or significant side effects. Double-blind, placebo-controlled studies are lacking and needed before the role of finasteride in acne can be determined.

Cortexolone 17α-propionate

While all current commercially available hormonal therapies are indicated for women, there may be a novel medication indicated for both male and female patients on the horizon. Cortexolone 17α-propionate (CB-03-01; Cosmo S.p.A, Lainate, Italy) is a new topical steroidal anti-androgen with additional anti-inflammatory properties that easily penetrates skin and acts on local ARs without having any systemic anti-androgen effects.[74]

A pilot, randomized, double-blind, comparative trial evaluated the efficacy and tolerability of CB-03-01 1% cream in acne compared with placebo and topical tretinoin 0.05% cream.[75] This clinical trial was limited to males with mild-to-moderate acne, who applied the medication nightly for 8 weeks.[75] At the end of the study, CB-03-01 1% cream was more effective than placebo or tretinoin with regards to improving total lesion count ($P = .0017$), inflammatory lesion count ($P = .0134$), and acne severity index ($P = .0090$).[75] Further study of CB-03-01 1% cream will better delineate its role in acne therapy.

Conclusion

Overall, there are multiple hormonally based therapeutic options that are available for the treatment of acne. Spironolactone and oral contraceptive pills can be used safely with minimal side effects in most females and have shown efficacy in treating acne in multiple studies. A meta-analysis comparing the efficacy of oral contraceptives to antibiotics showed similar efficacy at 6 months after starting therapy.[76] With the growing need to reduce antibiotic use,[77] future studies should prospectively assess the comparative efficacy of hormonal therapies and antibiotics as first-line systemic therapy. Unfortunately, the currently available anti-androgens are not ideal for use in male acne sufferers. However, the AR may serve as a potential target for acne treatments in both sexes if therapeutics can be targeted specifically to sebaceous glands.

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