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Androgens, Androgen Receptors, and the Skin

EDITORIAL

ORIGINAL ARTICLE

Game Changer in Acne Treatment

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Of the four primary pathogenic factors that drive acne vulgaris—androgen excess, increased sebum production, faulty keratinization, and overgrowth of C. acnes—androgen excess has been the most elusive therapeutic target. Oral contraceptive pills (OCPs) have direct effect on circulating hormones, but their potential use is limited to a subset of women. As such, a sizable portion of the population affected by acne vulgaris cannot even consider treatment with OCPs. While these systemic agents are generally associated with a low risk profile and have a history of safe and effective use, they are not entirely risk-free. Indirect androgen modulation through the use of spironolactone has become increasingly popular. Again, while generally safe and effective, this systemic treatment is not without risks and contraindications and it is also limited to a subset of female patients.

As noted, acne is a multifactorial process. However, it is essentially an inflammatory disease. Each of the four above-named disease drivers contributes to the underlying inflammation that is a hallmark of acne vulgaris. Therapy targeting excess androgens is thought to reduce inflammation in two key ways. Androgens have been shown to promote sebum production, thus supporting the overgrowth of C. acnes and its inflammatory by-products. Additionally, androgens are shown to directly promote inflammatory responses within follicles.[1]

Enter clascoterone, a first-in-class topical androgen receptor agonist now under review by the U.S. Food and Drug Administration (FDA) in a novel 1% cream formulation. Clascoterone is a new chemical entity that has been studied in the treatment of moderate to severe acne in individuals as young as age 9. Importantly, it is appropriate for use by a vast majority of male and female patients, with no significant systemic effects observed in users to date.

Clascoterone shares a 4-ring backbone identical to dihydrotestosterone (DHT) and spironolactone. It targets androgen receptors in the skin to block the effects of circulating endogenous androgens and competes with DHT for binding to the androgen receptor to limit or block transcription of androgen responsive genes. Additionally, it has downstream impact on sebum production and inflammation.[2]

Data for topical clascoterone, described in the pages ahead, are very promising. Preliminary analysis of data from two phase 3 trials suggest that topical clascoterone is an effective treatment for acne vulgaris, particularly with regards to reduction of inflammatory lesions. In fact, the treatment met its primary endpoints, achieving statistically significantly greater rates of IGA Treatment Success (≥2-point reduction in Investigator Global Assessment (IGA) and score Clear (0) or Almost Clear (1)) at week 12. The study population included both males and non-pregnant females with both inflammatory and non-inflammatory lesions and baseline IGA score of 3 (moderate) or 4 (severe). There were no adverse events that suggested systemic anti-androgen exposure with topical treatment. And the rates of Treatment-Emergent Adverse Events (TEAE) were similarly low in the active and placebo groups in both studies.

Clearly, the notion of hormonal modulation to manage acne is not new. However, options have been limited to women and have not been considered first-line interventions for the disease.[1] Clascoterone may change all that. It appears to have no effects beyond the site of application; as a topical androgen inhibitor with seemingly no systemic effects, clascoterone may become a treatment option for a majority of acne patients, inhibiting the cycle of physiologic events and associated inflammation that leads to acne lesion formation. Clinical experience will determine an ideal role for the drug, whether as a stand-alone treatment or in combination with other treatments shown to target the complex pathogenesis of inflammatory acne vulgaris.

DISCLOSURE

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REFERENCES

1. Park JH, Bienenfeld A, Orlow SJ, Nagler AR. The Use of Hormonal Antiandrogen Therapy in Female Patients with Acne: A 10-Year Retrospective Study. *Am J Clin Dermatol.* 2018 Jun;19(3):449-455.
2. Data on file, Cassiopea.

 ORIGINAL ARTICLE Journal of Drugs in Dermatology

Androgens, Androgen Receptors, and the Skin: From the Laboratory to the Clinic With Emphasis on Clinical and Therapeutic Implications

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ABSTRACT

The effects of androgens on human skin include growth and differentiation of sebaceous glands, terminal hair growth, epidermal barrier function, wound healing, and modification of the cutaneous microbiome. Androgens exert their activities via ligand formation with intracytoplasmic androgen receptors which can then translocate to the nucleus and interact with genetic androgen response elements to influence signaling cascades. Differences in tissue distribution and activities of enzymes that modify androgen synthesis and catabolism, variations related to gender and ethnicity/race, and genetic polymorphisms that affect androgen receptor functionality directly impact androgen physiology and the pathophysiology associated with a variety of disease states. This manuscript reviews the fundamentals of androgen physiology, androgen synthesis and catabolism in local skin tissue, androgen receptor activity, as well as the impact of genetic polymorphisms and gender. Emphasis is placed on the roles of androgenic activity in sebaceous gland development, sebum production, and the pathophysiology of acne vulgaris.

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INTRODUCTION

The major steroid sex hormones, androgens and estrogens, play vital roles in maintaining gender characteristics, normal activities of reproductive organs, and other physiologic functions in different organ systems, including skin. Both androgens and estrogens are primarily synthesized in the adrenal glands, ovaries, and testis, and induce their effects via specific intracellular receptor interactions.[1] Physiological activities of androgens on human skin include growth and differentiation of sebaceous glands, terminal hair growth, epidermal barrier function, wound healing, and modification of the cutaneous microbiome secondary to presence of sebum.[1-4] Interestingly, many skin cells independently exhibit complete enzymatic capability to synthesize androgens de novo from endogenous cholesterol or via conversion of circulating adrenal precursors. Specifically, sebocytes and dermal papilla cells can convert adrenal precursor compounds such as dehydroepiandrosterone sulfate [DHEA-S] and androstenedione into more potent androgens (ie, testosterone [T], dihydrotestosterone [DHT]) via skin-specific isoforms of 5α-reductase enzymes.[1,2] Importantly, DHT exhibits the greatest androgenic potency with higher androgen receptor (AR) affinity compared to other androgens and is purely androgenic as it cannot be metabolically aromatized to estrogen.[1] In males, DHT is mainly derived from T, while in females, the main precursor of T is androstenedione.[3] Homeostatic control of androgen concentrations is via specific enzymes involved in either the synthesis or catabolism of androgens.[1]

The correlation between sexual maturation and gender with development of androgenetic alopecia (AGA) was recognized by Aristotle as far back as the 4th century BC.[2] In the field of dermatology, the role of androgens is widely recognized in association with disorders such as acne vulgaris (AV), AGA, and hirsutism.[1-5] Over time, additional research information has become available on androgen tissue metabolism, the roles and locations of specific enzymes involved in androgen physiology, specific tissue activities of androgen hormones, androgen receptor physiology and function, the influences of genetic variability (ie polymorphism) and other factors such as ethnicity and age, impact of anatomic location, and the role of androgens in cutaneous pathophysiology associated with different skin disorders.[1-7] Despite extensive research completed over several decades related to androgens and the skin, there is much more to be learned through additional studies about the molecular activities of androgens, their participation in specific skin diseases, androgen receptors, and therapeutic interventions based on identified tissue targets.[1-7]

This manuscript serves to review the diverse roles of androgens in skin, regulation of sebocyte activity by androgen receptors in health and disease, fluctuation in androgen receptors during puberty in both genders, differences in androgen receptors based on genetic and ethnic variables, and factors influencing clinical presentations of androgen-sensitive skin disorders, with emphasis on AV. Therapeutic agents that target androgen activities and hormonal aspects of skin diseases are also summarized, including discussion of sebaceous glands, sebocytes, and sebum. An important disclaimer is that information on androgen physiology and pathophysiology, including androgen receptor functionality, local tissue variability, gender differences, impact of genetic polymorphisms, ethnic/race-related variables, enzyme function and tissue distribution, and androgen-related disease pathophysiology are "moving targets". As a result, the information presented here is based on our best interpretation of available data at this time. It is important that the reader maintain an open mind as new research information is sure to develop and can alter our understanding of specific aspects of this subject.

Androgen Receptors and Skin

Androgens elicit their physiologic activity through androgen receptors (AR), which are located primarily in epidermal and follicular keratinocytes of the hair follicle outer root sheath, dermal papilla cells, the basal layer of the sebaceous gland, and dermal fibroblasts.[2,3,5]

The AR is a soluble molecule compartmentalized in cytoplasm and complexed with specific heat shock proteins (HSPs).[1] When an androgen (ie, DHT, T) ligands with the AR, dissociation of the AR from the HSP complex occurs leading to transport of the AR-ligand to the nucleus. Within the nucleus, the AR can then interact with specific response elements located in the promoter regions of androgen-regulated genes resulting in elicitation of signaling cascades that produce clinical effects.[1,2] The direct relationship between androgen stimulation, sebaceous gland proliferation and activity, and sebum production suggests that the AR is an important therapeutic target for AV treatment, as well as other androgen-related cutaneous disease states.[1,2,4,8]

Cutaneous Metabolism of Androgens

It would simplify our understanding of this subject if the relationship between androgens and their physiologic and/or pathologic effects via ARs related only to the concentration of circulating androgens. However, this is not the only factor. In fact, androgen physiology is a complicated subject that is at present only partially understood. Serum levels of T do not necessarily correlate uniformly with sebaceous gland activity and despite markedly higher levels of serum T in males versus females, sebum secretion rates are only slightly higher in males overall, with marked overlap noted between genders.[5,9] The majority of females with AV exhibit serum androgen levels that trend higher than in females without AV, but are still within normal levels.[5,10] It has also been shown that preadolescent girls exhibiting early onset of AV exhibit higher circulating levels of DHEA-S, but not free and total T levels or serum concentrations of several other sex steroid hormones (ie, estrogen, progesterone), as compared to those without AV; this supports the importance of interindividual variability and differences in activity among various androgens.[11] The influence of local tissue synthesis of major androgens at different anatomic sites, affected also by genetic and age-related factors, appears to play an important role.[1,2,5,7,9] Therefore, the local synthesis and enzymatic degradation of androgens within skin warrants attention as correlations with pathophysiology or therapeutic approaches are likely to be relevant.

Multiple enzymes appear to be operative in the metabolism of androgens within skin, with the three major enzymes within sebaceous glands reported to be 3β-hydroxysteroid dehydrogenase type 1 (3β-HSD), 17β-hydroxysteroid dehydrogenase type 2 (17β-HSD) and 5α-reductase (type 1).[2,5,9] The relative presence and/or activity of these enzymes and their isoforms can vary in anatomic distribution and clinical significance. For example, 17β-HSD, located within the pilosebaceous unit and epidermal keratinocytes exists in multiple isoforms, with some increasing the reductive formation of active androgens (types 1, 3, 5), whereas other isoforms of 17β-HSD (types 2, 4) inactivate potent androgens via oxidation.[2] Interestingly, the face has been shown to exhibit greater 17β-HSD reductive isoform activity within sebaceous glands than in non-acne prone skin sites which supports greater local androgen production on facial skin.[2] Human sebaceous glands exhibit the cellular capability to transcribe genes required to incite both the reductive and oxidative isoforms of 17β-HSD which allows for the onset or offset of androgen production locally; variations in 17β-HSD isoform activity also exists within outer root sheath of hair follicles.[2] The multiplicity of enzyme isoforms and their functions demonstrates that skin tissues are dynamic, and have the localized potential to either increase androgen activity or protect against excessive androgenic effects.

Table 1 summarizes the enzymes involved in androgen metabolism within skin. It is important to recognize that the activity of these enzymes is not fixed in relative magnitude or within anatomic sites among different individuals which explains the heterogenous presentations of androgen activities within "normal" populations and between various disease states.

Androgens, Sebaceous Glands, and Androgen Receptor Functionality

The androgens DHT and T are the predominant agents that stimulate sebaceous gland development, sebocyte proliferation, and sebum production via AR interactions, with

TABLE 1.

Major Enzymes Involved in Stimulation of Androgen Activity or Decativation of Androgens Within Skin	
Enzyme	**Activity**
Steroid Sulfatase	• Initial step with conversion of DHEA-S to DHEA
3β-Hydroxysteroid Dehydrogenase	• Conversion of DHEA to androstenedione • Type 1 isoform expressed in human skin in sebaceous gland; activity also detected in human terminal hair dermal papillae
17β-Hydroxysteroid Dehydrogenase	• Conversion of androstenedione to T • Mainly in pilosebaceous unit and epidermal keratinocytes • Multiple isoforms exist that may vary in relative anatomic distribution and in ability to increase androgens (reduction) or decrease androgens (oxidation)
5α-Reductase	• Conversion of T to DHT • Type 1 isoform dominant in skin with predominant expression in sebaceous glands
3α-Hydroxysteroid Dehydrogenase	• Catabolizes androgens to metabolites that do not ligand with AR • Exists in three isoforms
Aromatase	• Conversion of T and androstenedione to estrogens in certain cell types

Key: DHEA-S, dehydroepiandrosterone sulfate; DHEA, dehydroepiandrosterone; T, testosterone; DHT, dihydrotestosterone; AR, androgen receptor.
References: 1,2,5,8

DHT exhibiting a 5-10-fold greater affinity for the AR.[1-3,5,8] Other hormone receptors present in sebaceous glands, such as corticotropin-releasing hormone (CRH) receptors, melanocyte stimulating hormone (MSH) receptors 1 and 5, and some neuropeptides from closely associated neurons (ie, substance P), may also selectively contribute to modulation of sebocyte differentiation, lipid synthesis, and inflammatory cytokine production.[3] Although the AR appears to be the most important therapeutic target for skin diseases such as AV and AGA, some of these other receptors may also serve as potential targets for drug development, especially AV.

Sebaceous gland development increases along with the natural progression of androgen production and stimulation at adrenarche/puberty.[1-5] Other than ectopic sebaceous glands at specific anatomic sites (ie, oral mucosa, eyelids, genitalia), sebaceous glands connect via their duct to the infundibulum of the pilosebaceous unit. Sebocytes that comprise the gland, after a differentiation lifespan of two to three weeks, fully disintegrate and excrete their lipid contents (sebum) into the duct (holocrine secretion).[3,5] The density of sebaceous glands varies in different anatomic locations, and is highest on the scalp, face, and upper chest and back.[1-3,8] The function of sebaceous glands is not limited to sebum production. These glands also play important roles in innate immunity, androgen metabolism, cytokine production, and antimicrobial peptide activity.[3,12] The effects of androgens and sebum in AV pathophysiology are addressed later in this manuscript.

ARs are intracellular protein transcription factors with three functional domains: the ligand-binding domain, the DNA-binding domain, and the transactivation domain.[1,6] Importantly, the AR genetic profile is not fixed in its structure or type of androgenic activity. Rather, the AR genetic structure exhibits marked polymorphism primarily in the length of trinucleotide CAG (cytosine-adenine-guanine) repeats that encode a polyglutamine stretch in the transactivation domain.[6] The basal and ligand-induced AR transactivational activity correlates inversely with the length of the AR CAG repeat.[6,7,13,14] From a clinical perspective, this indicates that the magnitude and type of androgenic effect that an AR modulates is dependent on its structure (CAG repeat length). Coactivator proteins that may vary within different tissues can modulate the impact induced by the CAG repeat length on androgenic activity.[6] Studies evaluating the normal ranges of CAG chain repeat lengths have started to define differences among ethnic populations that may define relative androgenicity and also associations with various disease states.[1,2,4,6,7,13,14]

Sebaceous Glands, Sebum, and Acne Vulgaris

Sebaceous glands are present at birth with an initial high level of sebum production that declines rapidly within months until the onset of adrenarche and emergence of pubery.[3,8] Androgen stimulation of sebaceous glands begins in the neonatal period with luteinizing hormone (LH) stimulating testicular production of T in boys over six to twelve months, and by the adrenal "fetal zone", which produces DHEA-S/DHEA with involution by age one year.[8] Androgen levels are then very low and sebaceous glands remain quiescent until adrenarche (around 7-8 years of age) at which time adrenal glands start to produce DHEA-S.[3,8] Sebaceous gland growth and increased sebum production are primarily induced by androgens, especially DHT which exhibits potent androgenic activity.[3] Single androgen compounds appear to be unable to modulate sebocyte differentiation and lipogenesis, requiring participation by peroxisome proliferator-activated receptors (PPAR).[5,12,15] Specific PPARs have been identified in basal sebocytes and in differentiated sebocytes.[5]

TABLE 2.

Observations Related to Androgen Physiology in Acne Vulgaris Including Gender-Associated Characteristics
Acne-affected skin produces higher levels of T and DHT than in healthy individuals
Conversion of T to DHT is 30-fold higher in AV-affected skin compared to normal skin
Androgen stimulation of sebocyte proliferation is greatest in facial skin
Serum levels of DHEA-S at onset of AV in preadolescent girls are an accurate predictor of the potential for greater AV severity in the future
DHT has been shown to increase sebum production and pro-inflammatory cytokine production by sebocytes
Increased reduction activity of 17β-HSD is indicative of increased local T synthesis in sebaceous glands from AV-affected skin as compared to normal skin
17β-HSD isoforms that convert androstenedione to T are preferentially expressed on facial sebaceous glands
Sebum production increases at puberty and is greater overall in males compared to females
Increased DHT and 3-α-androstanediol glucuronide plasma levels are often found in females with AV whereas DHEA-S, T, and androstenedione are within normal limits

Key: T, testosterone; DHT, dihydrotestosterone; AV, acne vulgaris; DHEA-S, dehydroepiandrosterone sulfate; 17β-HSD, 17β-hydroxysteroid dehydrogenase.
References: 1,3,8

The development of AV correlates directly with the emergence of puberty which is associated with increased androgen levels and production of sebum.[1-4,8] Sebum, an admixture of triglycerides, diglycerides, wax esters, squalene, cholesterol, and sterol esters, is produced by sebocytes, with some contribution by lipases produced by commensal bacteria (*Cutibacterium acnes* [formerly *Propionibacterium acnes*]) within the follicular canal, which hydrolyze triglycerides to free fatty acids (FFA).[3,5] Sebum production varies among individuals and races, and from the end of puberty remains relatively constant through mid-adulthood, followed by a decline in both genders later in life.[3] In addition, androgen (ie, DHT) stimulation also appears to contribute to lipogenic differentiation by functional AR-expressive sebocytes and can increase both sebum production and pro-inflammatory cytokine production by sebocytes.[1,16] It is also recognized that sebaceous glands and sebum play a role in innate immunity and antimicrobial defense.[3,5,8] Sebaceous glands/sebocytes express certain pattern recognition receptors (ie, Toll-like receptors) involved in cutaneous innate immune defense.[5] Several antimicrobial peptides (ie, cathelicidins, defensins, psoriasin) are expressed within sebaceous glands, and FFAs in sebum are active against gram-positive bacteria via upregulation of β-defensin-2 expression.[5,17,18]

Although increased androgens and sebum contribute to AV development, presence of sebum alone is not sufficient to induce AV.[3] Overall, AV is associated with larger sebaceous glands and higher sebum production.[3] Sebum in individuals with AV is similar overall in composition to sebum from non-acne affected skin, but with higher levels of squalene monosaturated FAs and less linoleic acid.[8] A major role of sebum in AV pathophysiology is to provide a follicular microenvironment and nutrient source for *C acnes* proliferation within the pilosebaceous unit which stimulates innate immune response and pro-inflammatory cytokine production by sebocytes, keratinocytes, and perifollicular monocytes.[1,8] *C acnes* lipases also convert sebum triglycerides and diglycerides into FFAs which may promote follicular keratinization and stimulate chemotaxis.[3,8] Inhibition of androgen stimulation that augments sebaceous gland proliferation and sebum production can produce downstream therapeutic benefit by reducing the microenvironment conducive to *C acnes*-related activity in AV.

Androgen Physiology, Androgen Receptors, and Cutaneous Diseases Including Impact of Gender and Ethnicity/Race

The close interplay that circulating androgens, local tissue androgen production/ degradation, and AR functionality have with sebaceous gland activity and sebum production can play a major role in AV pathophysiology, especially when genetic polymorphisms and AR dysfunctions occur. In fact, aberrations in sex hormone physiology, AR genetic polymorphisms, and/or enzymatic abnormalities have been shown to be associated with a variety of systemic diseases (ie obesity, diabetes, prostate cancer, male infertility) and cutaneous diseases (ie AV, AGA, hirsutism, hidradenitis suppurativa).[1,2,13,14,19] With regard to cutaneous disease states, AV is the focus of discussion in this manuscript, however, the roles of androgens and AR functionality in other cutaneous diseases have been reviewed elsewhere.[1,2,13]

Several observations have been associated with androgen-related physiology including gender-related characteristics. Table 2 depicts important observations related to androgen activity and also gender-related factors.

Ethnic/racial variations in physiologic responses, enzyme function, chemical/drug metabolism, and disease propensities are well recognized. These differences appear to occur due to genetic polymorphisms, tissue receptor functionality and distribution, tissue enzyme activity and distribution, circulating hormone levels, and environmental/exogenous factors.[19]

Within the normal range of AR CAG repeat chain lengths, ethnic differences have been observed in healthy men. The

mean number of AR CAG repeat chain lengths is reported to be shortest for men of African descent (≤18--20), followed by Caucasian men (21--22), and with the longest AR CAG repeat chain lengths noted in East Asian men (22-23).[6] As noted above, shorter AR CAG repeat chain lengths correlate directly with increased AR transcriptional activity in both normal skin and in association with disease states.[6,7,13,14] Table 3 reviews important observations related to genetic and ethnic variations in androgen receptors and androgen physiology.

Modulation of Androgen Physiology and Therapeutic Interventions in Acne Vulgaris

Despite the central importance of androgens and sebaceous gland activity in the pathophysiology of AV, the availability of therapeutic agents that modulate androgen physiology and AR activity has been relatively limited.[4,8,20,21] In the United States (US), the two major approaches have been systemic (oral) therapy with spironolactone (not Food and Drug Administration [FDA]-approved for AV), combination oral contraceptives

TABLE 3.

Observations Related to Genetic and Ethnic Variations in Androgen Receptors and Androgen Physiology
Levels of DHT reported to be lower in Asian men compared to white men and black men
Differences between T production in Asian men and white men when Asian men studied in country of origin but not when both groups studied within the US
After correction for comorbid factors and BMI in men (N>500), black males had significantly higher DHT levels and DHT to T conversion ratios than white men and Hispanic men, but no differences in serum T, DHEA-S, and SHBG levels
After correction for comorbid factors, age and BMI in men (N=1413), serum T levels were similar in non-Hispanic white men (n=674), non-Hispanic black men (n=363) and Mexican-Asian men (n=376) with levels higher in the latter group after adjustment for percent body fat; SHBG levels were similar among all groups after adjustment for percent body fat
Longer AR CAG repeat chain lengths correlate with lower AR transcriptional activity in both normal skin and in disease states
Low fat diet shown to decrease serum and urinary androgens, T production rates and serum estradiol levels in healthy men
Polymorphisms of 5α-reductase and aromatase exist but are poorly studied
Coactivators and corepressors of steroid hormone receptors vary in different tissues and require additional research

Key: DHT, dihydrotestosterone; BMI, body mass index; AR, androgen receptor; CAG, cytosine-adenine-guanine; T, testosterone; DHEA-S, dehydroepiandrosterone sulfate; SHBG, sex hormone binding globulin.
References: 6,7,13,14,19

TABLE 4.

Therapeutic Approaches Currently Available or in Development in The United States for Acne Vulgaris that Exhibit Anti-Androgenic Properties	
Agent	**Pharmacologic/Therapeutic Activity**
Oral Agent	
Combination Oral Contraceptives	• Contain ethinyl estradiol and a progestin • Type of progestin affects interactions with AR and other hormone receptors and the relative magnitude of androgenic or anti-androgenic effects • Block ovarian androgen production through suppression of gonadotropins (FSH, LH) • Ethinyl estradiol increases SHBG which decreases free T levels, reduced T binding to AR, and lower conversion of T to DHT • Demonstrated equivalent efficacy in AV lesion reduction to oral antibiotics after 6 months duration of therapy
Spironolactone	• Supported by widespread anecdotal use and available literature for treatment of AV, hirsutism, and AGA • Inhibition of sebaceous gland activity with 30%-75% dose-dependent reduction in sebum excretion • Reduce 5α-reductase activity with increased T clearance via augmented liver hydroxylase activity • Decreased circulating free testosterone via increase in SHBG
Flutamide	• Non-steroidal androgen receptor blocker (approved for therapy of prostate cancer) that may effectively treat AV, AGA, and hirsutism • Active metabolite (2-hydroxyflutamide) a potent competitive inhibitor of DHT binding to AR • Usage limited by hepatic and hematological adverse effects and absolute need to avoid during pregnancy (male fetus pseudo-hermaphroditism)
Topcal Agents	
Clascoterone	• NDA submitted to FDA for approval • Also referred to as cortexolone 17β propionate • Efficacy and safety evaluated in pivotal trials • AR inhibition with suppression of AR-mediated transcription • Reduced lipid and inflammatory cytokine synthesis by sebocytes

Key: AR, androgen receptor; FSH, follicle-stimulating hormone; LH, luteinizing hormone; SHBG, sex hormone binding globulin; T, testosterone; DHT, dihydrotestosterone; AV, acne vulgaris; AGA, androgenetic alopecia; NDA, new drug application.
References: 4,8,20-30

(some agents FDA-approved for AV), or combination therapy using both agents.[4,8,20-27] In the US, use of oral flutamide (not FDA-approved for AV), a competitive inhibitor of AR binding by DHT, has been reported; its use has been limited primarily due to adverse effects and pregnancy-related concerns.[4,8,20] In Europe and Canada, cyproterone acetate has long been used as both an oral antiandrogen and progestin that exhibits marked efficacy for AV both as monotherapy and in combination with estrogen as an oral contraceptive, however, it is not available in the US.[4,8,20,21]

At present, topical antiandrogen therapy is not available. However, topical clascoterone (cortexolone 17α propionate), an AR inhibitor, has completed the formal drug development process and has been submitted to the FDA to be evaluated for approval for treatment of AV.[28-30] Clascoterone has been shown to bind the androgen receptor (AR) with high affinity in vitro, inhibit AR-regulated transcription, and antagonize androgen-mediated lipid and inflammatory cytokine production in human sebocytes, with a greater ability to inhibit inflammatory cytokine synthesis from sebocytes when compared to spironolactone.[28] These research findings reported with clascoterone further support the significance of direct inhibition of AR in the management of AV, with potential application for other androgen mediated skin disorders.

CONCLUDING REMARKS

Advances in understanding of androgen physiology including both central and local tissue mechanisms, enzymatic functions that modulate androgen synthesis and degradation, and AR functionality including the impact of genetic polymorphisms have furthered our understanding of androgen-related diseases states and potential therapeutic options. The above, coupled with increased understanding of receptors and pathways that modulate sebaceous gland activities has also expanded our perspectives on potential therapies for AV. Further elucidation of the functions of androgens and androgen receptors in specific skin disorders can help to shift our focus to the development of therapies that selectively target AR and other receptor pathways that can effectively modify disease and hopefully reduce the risk of adverse effects.

DISCLOSURES

Dr. Del Rosso has served as an advisory board member for Cassiopea, Inc. Dr. Kircik has served as an advisory board member and a consultant for Cassiopea, Inc. Dr. Stein Gold has served as a research investigator and advisor for Cassiopea Inc. Dr. Thiboutot has served as a research investigator and advisory board member for Cassiopea Inc.

REFERENCES

1. Ceruti JM, Leiros GJ, Balana ME. Androgens and androgen receptor action in skin and hair follicles. *Mol Cell Endocrinol.* 2018;465:122-133.
2. Zouboulis ChC, Degitz K. Androgen action on human skin – from basic research to clinical significance. *Exp Dermatol.* 2004;13(Suppl 4);5-10.
3. Schaller M, Plewig G. Structure and function of eccrine, apocrine, and sebaceous glands. In: Bolognia JL, Schaffer JV, Cerroni L, Eds, Dermatology, 4th Edition. Elsevier, Philadelphia, PA, USA, 2018;580-587.
4. Elsaie ML. Hormonal treatment of acne vulgaris: an update. *Clin Cosmet Investig Dermatology.* 2016;9:241-248.
5. Nelson AM, Thiboutot DM. Sebum. In: Shalita AR, Del Rosso JQ, Webster GF, Eds, Acne Vulgaris. Informa Healthcare, London, United Kingdom, 2011;3-11.
6. Zitzmann M, Nieschlag E. The CAG repeat polymorphism with the androgen receptor gene and maleness. *Intl J Androl.* 2003;26(2):76-83.
7. Ackerman CM, Lowe LP, Lee H, et al. Ethnic variation in allele distribution of the androgen receptor (AR) (CAG)n repeat. *Int J Androl.* 2012;33(2):210-215.
8. Zaenglein A, Thiboutot D. Acne vulgaris. In: Bolognia JL, Schaffer JV, Cerroni L, Eds, Dermatology, 4th Edition. Elsevier, Philadelphia, PA, USA, 2018;588-603.
9. Thiboutot D, Gilliland K, Light J, Lookingbill D. Androgen metabolism in sebaceous glands from subjects with and without acne. *Arch Dermatol.* 1999;135(9):1041-1045.
10. Lookingbill DP, Horton R, Demers LM, et al. Tissue production of androgens in women with acne. *J Am Acad Dermatol.* 1985;12(3):481-487.
11. Lucky AW, Biro FM, Huster GA, et al. Acne vulgaris in premenarchal girls. An early sign of puberty associated with rising levels of dehydroepiandrosterone. *Arch Dermatol.* 1994;130(3):308-314.
12. Zouboulis CC. Acne and sebaceous gland function. *Clin Dermatol.* 2004;22(5):360-366.
13. Sawaya ME, Shalita AR. Androgen receptor polymorphisms (CAG repeat lengths) in androgenetic alopecia, hirsutism, and acne. *J Cutan Med Surg.* 1998;3(1):9-15.
14. Ferlin A, Bartoloni L, Rizzo G, et al. Androgen receptor gene CAG and GGC repeat lengths in idiopathic male infertility. *Mol Hum Reprod.* 2004;10(6):417-421.
15. Trivedi NR, Cong Z, Nelson AM, et al. Peroxisome proliferator-activated receptors increase human sebum production. *J Invest Dermatol.* 2006;126(9):2002-2009.
16. Lee WJ, Jung HD, Chi SG, et al. Effect of dihydrotestosterone on the upregulation of inflammatory cytokines in cultured sebocytes. *Arch Dermatol Res.* 2010;302(6):429-433.
17. Nakatsuji T, Kao MC, Zhang L, et al. Sebum free fatty acids enhance the innate immune defense of human sebocytes by upregulating beta-defensin-2 expression. *J Invest Dermatol.* 2010;130(4):985-994.
18. Lee DY, Yamasaki K, Rudsil J, et al. Sebocytes express functional cathelicidin antimicrobial peptides and can act to kill Propionibacterium acnes. *J Invest Dermatol.* 2008;128(7):1863-1866.
19. Wang C, Christenson P, Swerdloff R. Clinical relevance of racial and ethnic differences in sex steroids. *J Clin Endocrinol Metabolism.* 2007;92(7):2433-2435.
20. Keri J, Berson DS, Thiboutot DM. Hormonal treatment of acne in women. In: Shalita AR, Del Rosso JQ, Webster GF, Eds, Acne Vulgaris. Informa Healthcare, London, United Kingdom, 2011;146-155.
21. Barros B, Thiboutot D. Hormonal therapies for acne. *Clin Dermatol.* 2017;35(2):168-172.
22. Harper JC. Use of oral contraceptives for management of acne vulgaris: practical considerations in real world practice. *Dermatol Clin.* 2016;34(2):159-165.
23. Kim GK, Del Rosso JQ. Oral spironolactone in post-teenage female patients with acne vulgaris: practical considerations for the clinician based on current data and clinical experience. *J Clin Aesthet Dermatol.* 2012;5(3):37-50.
24. Layton AM. Top ten list of clinical pearls in the treatment of acne vulgaris. *Dermatol Clin.* 2016;34:147-157.
25. Villasenor D, Berson DS, Kroshinsky D. Treatment guidelines in adult women. In: Shalita AR, Del Rosso JQ, Webster GF, Eds, Acne Vulgaris. Informa Healthcare, London, United Kingdom, 2011;198-207.
26. Marson JW, Baldwin HE. An overview of acne therapy, part 2: hormonal therapy and isotretinoin. *Dermatol Clin.* 2019;37(2):195-203.
27. Del Rosso JQ, Harper JC, Graber EM, et al. Status report from the American Acne & Rosacea Society on medical management of acne in adult women, part 3: oral therapies. *Cutis.* 2015; 96(6):376-382.
28. Rosette C, Agan FJ, Mazzetti A, et al. Cortexolone 17α-propionate (clascoterone) is a novel androgen receptor antagonist that inhibits production of lipids and inflammatory cytokines from sebocytes in vitro. *J Drugs Dermatol.* 2019;18:412-418.
29. Mazzetti A, Moro L, Gerloni M, Cartwright M. A phase 2b, randomized, double-blind vehicle controlled, dose escalation study evaluating clascoterone 0.1%, 0.5%, and 1% topical cream in subjects with facial acne. *J Drugs Dermatol.* 2019;18(6):570.
30. Mazzetti A, Moro L, Gerloni M, Cartwright M. Pharmacokinetic profile, safety, and tolerability of clascoterone (cortexolone 17-alpha propionate, CB-03-01) topical cream, 1% in subjects with acne vulgaris: an open-label phase 2a study. *J Drugs Dermatol.* 2019;18(6):563.

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