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RESEARCH ARTICLE

Androgens and acne: perspectives on clascoterone, the first topical androgen receptor antagonist

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ABSTRACT

Introduction: Increased circulating androgens are key to the multifactorial pathogenesis of acne. Clascoterone is the first topical androgen antagonist developed to treat acne in both male and female patients and the first such agent to receive U.S. Food and Drug Administration (FDA) approval for treatment of acne. Androgens directly stimulate sebaceous gland growth and increased sebum production, creating a nourishing medium in which anaerobic *Cutibacterium acnes* (*C. acnes)* bacteria flourish. Androgens may directly contribute to inflammation in the sebaceous gland.

Areas covered: In this review, the author assesses clascoterone's potential role in the management of acne. With a 4-ring backbone identical to dihydrotestosterone (DHT) and spironolactone, topically applied clascoterone binds androgen receptors (ARs) in the sebaceous glands and hair follicles, interfering with the pathogenesis of acne and reducing acne lesions with no reported systemic effects.

Expert opinion: Phase III study results confirmed the safety and efficacy of topical clascoterone for acne, with considerable reductions in absolute non-inflammatory and inflammatory lesion counts at week 12. The approval of a first-in-class topical androgen antagonist is indeed a 'game-changer' for acne management. This topical agent is expected to be quickly adopted in clinical practice, likely within combination regiments, yet to be formally evaluated.

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Acne vulgaris; androgen receptors; clascoterone; hormones/hormonal modulation; topical therapy; inflammatory lesions; C. acnes

1. Introduction

Only relatively recently has the dermatology community come to recognize acne as primarily an inflammatory disease[1]. Evidence shows that inflammation is at the heart of the disease, with inflammatory mediators evident in the precursor lesion of acne – the microcomedo, in the papules, pustules, and open and closed comedones of active acne, and even in resolving skin lesions and scars[2]. *Cutibacterium acnes* (*C. acnes*, formerly *P. acnes*) is shown to activate innate immunity via the expression of protease activated receptors (PARs), tumor necrosis factor (TNF) α and toll-like receptors (TLRs), and the production of interferon (INF) γ, interleukins (IL-8, IL12, IL-1), TNF, and matrix metalloproteinases (MMPs)[2].

This emergent recognition of the inflammatory nature of acne has fundamentally changed the way that we conceptualize the disease, but it does not replace the previously understood, multifactorial framework that has for decades underpinned our concept of the pathogenesis of acne. Rather, inflammation elegantly provides a key for understanding the interplay between androgens, hyperproliferation of keratinocytes, excess sebum production, and colonization by *C. acnes*. Acne treatment guidelines emphasize the inflammatory nature of the disease, recommending multimodal approaches to treatment to address the multifactorial pathogenesis of the disease and its inflammatory drivers[3].

In fact, topical therapies historically have been employed that address hyperkeratinization and/or provide antibacterial effects. These have proven effective for the management of acne for many patients. We have come to recognize that these therapies also often confer some degree of anti-inflammatory benefit.

However, topical approaches aimed at the androgenetic component of acne have not been successfully developed until now. Clascoterone or cortexolone 17α-propionate is a new chemical entity with direct anti-androgen effects. Clascoterone cream 1% (Winlevi, Cassiopea Pharmaceuticals) has recently been approved by the U. S. Food and Drug Administration (FDA) for the treatment of acne in patients 12 years of age and older. Although the precise mechanism of action of topical clascoterone has not been fully elucidated, the agent is shown to compete with androgens, specifically dihydrotestosterone (DHT), for binding to the androgen receptors within the sebaceous gland and hair follicles[4] (Figures 1). In two identical Phase III randomized trials, clascoterone cream, 1% was associated with greater treatment success compared to vehicle and with considerable reductions in absolute non-inflammatory and inflammatory lesion counts at week 12[5].

2. Assessing the role of androgens in acne

Nearly 30 years ago, acne expert and therapeutic pioneer, Dr. James Leyden co-wrote a paper that elegantly summarized the pathogenesis of acne, stating that it, 'involves abnormal follicular hyperkeratosis and obstruction of the follicle,

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Article highlights

- Increased levels of circulating androgens contribute to acne pathogenesis through the lifecycle of affected individuals.
- Treatment strategies aimed at androgen modulation, such as oral contraceptive pills and spironolactone, have been tried. However, these treatments have only been available to women.
- Clascoterone is the first topical androgen antagonist developed to treat acne in both men and women and is the first such agent to receive FDA approval for treatment of acne.
- In Phase III clinical trials, at week 12 clascoterone met all three co-primary efficacy end points: proportion of patients achieving treatment success, absolute change from baseline in non-inflammatory lesion count (NILC), and absolute change from baseline in inflammatory lesion count (ILC).
- Only 13 treatment emergent adverse events (TEAE) were identified for clascoterone cream, 1%, in both studies. All TEAEs were mild in severity.

This box summarizes key points contained in the article.

stimulation of sebaceous gland secretion by androgens, and proliferation of Propionibacterium acnes, which promotes inflammation.'[6] While this statement reflects long-established belief that is still held today, our understanding of the inflammatory skin disease has become exponentially more sophisticated. It is established that increased circulating androgens directly stimulate the sebaceous glands to increase sebum production, creating a nourishing medium in which anaerobic *C. acnes* bacteria can flourish. The temporal onset of acne during adolescence is directly correlated to this increase in circulating androgens in peripubescent and pubescent males and females. Androgens, especially DHT, which exhibits potent androgenic activity, are shown to induce both sebaceous gland growth and increased sebum production[7].

Microcomedones, the earliest lesions of acne, begin to appear at adrenarche (typically occurs at about 8 years of age), as adrenal androgens begin to stimulate follicular hyperkeratosis and sebaceous hyperplasia in pilosebaceous units on the face. Within about two years, androgens of gonadal origin are produced. Combined with increased colonization with *C. acnes*, the result is the formation of comedones[8]. Importantly, *C. acnes* and its proinflammatory metabolic by-products are shown to elicit both immune and inflammatory responses within the sebaceous gland[9].

Increased levels of circulating androgens contribute to acne pathogenesis through the lifecycle of affected individuals. One study identified clinical hyperandrogenism in 71.67% of individuals in one cohort of 120 adult female patients with acne [10]. Of note, the majority of women with clinical hyperandrogenism (HA) may not have biochemical hyperandrogenism. Only 18.33% of women in the cohort had biochemical hyperandrogenism. Analysis of acne characteristics in this group showed that late onset acne was more common in adult acne patients (56.6%); persistent acne in women was associated with younger age, a past history of adolescent acne, truncal distribution of acne, polycystic ovary syndrome (PCOS), irregular menses, and hirsutism.

Evidence now suggests that, beyond stimulating sebum production and thus supporting subsequent *C. acnes* colonization, androgens may directly contribute to inflammation in the sebaceous gland. Sebocytes express functional androgen receptors (ARs), and androgens may stimulate lipogenic differentiation by these cells; this can lead to increases in both sebum production and in pro-inflammatory cytokine production by sebocytes[11].

A recent review article provides a comprehensive overview of the functions of androgens and ARs in the skin and their roles in the pathogenesis of certain skin diseases, especially acne[12]. The author directs readers to this article for greater insight. For the sake of the current discourse, it should be noted that the AR, a soluble molecule compartmentalized in cytoplasm and complexed with specific heat shock proteins (HSPs), is able to bind with free DHT or testosterone. With this binding, the AR disassociates from the HSP complex and the AR-ligand transports to the nucleus. Within the nucleus, the AR can then elicit signaling cascades, including immune and inflammatory processes, that produce clinical effects[12].

Early evidence suggests that the effects of androgens may even be pertinent to the yet unsettled question of dietary-mediated inflammatory influence on acne. Although it has been shown that diet may influence synthesis of proinflammatory sebaceous lipids that may induce inflammation in the skin, research also has identified cell signaling pathways that may involve an interplay of androgens, insulin, insulin-like growth factor (IGF1), and high glycemic index diet in acne[13].

3. Historical strategies targeting androgens in acne

Given that the role of androgens in acne has been well known – if not fully understood – for some time, treatment strategies aimed at androgen modulation have been tried.

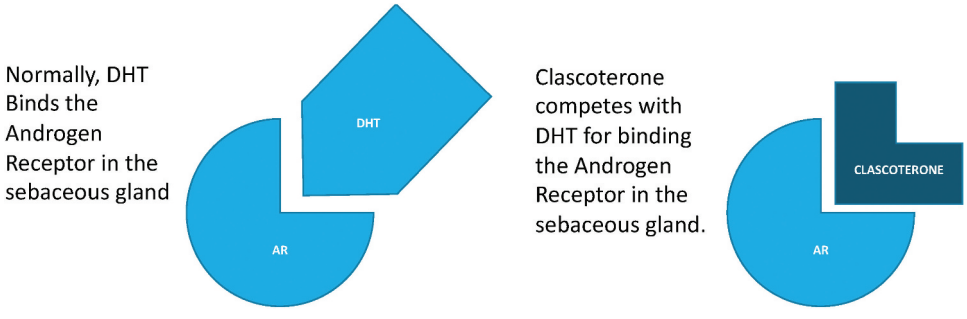

Figure 1. Proposed activity of clascoterone.

However, these treatments have only been available to women. The general success of these treatments over many years supports the fundamental role of androgens in acne pathogenesis.

Oral contraceptive pills have been used for the treatment of acne for several decades. Three contraceptive pills are FDA approved for use in acne treatment, while several others are used off-label. Combined oral contraceptive medications are thought to primarily exert anti-androgen effects through the action of estrogen, which may both bind androgens and inhibit conversion of testosterone to DHT. An analysis of 36 studies determined that all COCs exhibit some degree of efficacy in the reduction of acne lesion counts[14].

Use of COCs is associated with a relative increase in certain cardiovascular risk factors, including deep vein thrombosis but seem to be associated with a reduced risk for certain gynecological cancers[15]. In the above-reference analysis, in patients with acne who were treated with COC medications, the most commonly reported treatment-related adverse events were well known and expected for low-dose combined oral contraceptive medications. They included headache, menstrual cycle irregularities, and emotional lability. Severe adverse events related to COC use were rare: two cases of clinical depression and one case of ovarian cyst formation were reported[14].

Oral spironolactone is an orally administered androgen receptor antagonist that has been used off-label for the treatment of acne in women with success. There is remarkably little data from large controlled trials of the agent for acne treatment. However, case series have demonstrated notable improvement with minimal risk for side effects[16].

Findings from a retrospective case series assessing 395 patients (median age, 32 years) receiving spironolactone (median dose of 100 mg daily), show that 66.1% of patients had a complete response and 85.1% had either a complete response or a partial response greater than 50%[17].

Clascosterone is thought to block local production of DHT that contributes to acne[18], and it is thus approved for use in male as well as female patients. As such, it should not be generally considered an alternative to systemic treatment options for women with clearly identifiable clinical and/or biochemical hyperandrogenenism.

4. Clascoterone: a novel approach

Clascoterone is the first topical androgen antagonist developed to treat acne in both male and female patients and is the first such agent to receive FDA approval for treatment of acne. Clascoterone's chemical structure shares a 4-ring backbone identical to DHT and spironolactone.

Importantly, topically applied clascoterone has been shown to exert androgen binding effects in the androgen receptors only at the site of application in the skin with no systemic anti-androgen effect. When topically applied clascoterone binds ARs in the sebaceous glands and hair follicles, DHT binding is inhibited[4]. In Phase I/II studies, topical clascoterone demonstrated a safety profile similar to vehicle [19,20].

Phase III study results confirmed the safety and efficacy observations from the earlier phase trials. The identical Phase III studies recruited male and nonpregnant female patients age 9 years or older with moderate to severe facial acne vulgaris (grade 3 or 4 on the Investigator's Global Assessment [IGA] scale)[5]. Across both studies, a total of 722 patients were randomized to treatment with clascoterone cream, 1% and 718 participants were randomized to treatment with vehicle cream.

The three co-primary efficacy end points were proportion of patients achieving treatment success at week 12, absolute change from baseline in non-inflammatory lesion count (NILC), and absolute change from baseline in inflammatory lesion count (ILC) at week 12. Treatment success was defined as at least a 2-point reduction in IGA score from baseline and a score of clear (0) or almost clear (1). Secondary efficacy end points for both studies included percentage change from baseline in TLC at week 12, and absolute change from baseline in TLC at week 12.

Both trials met the primary efficacy end points. Considerably more patients receiving clascoterone cream, 1% achieved treatment success: 18.4% (95% CI, 1.4–3.8; $P < .001$) and 20.3% (95% CI, 2.2–6.3; $P < .001$) vs 9.0% and 6.5% with vehicle, respectively. There was also substantially greater absolute change from baseline in NILC and ILC at week 12 with use of clascoterone cream, 1%, compared to vehicle (Figures 2 and

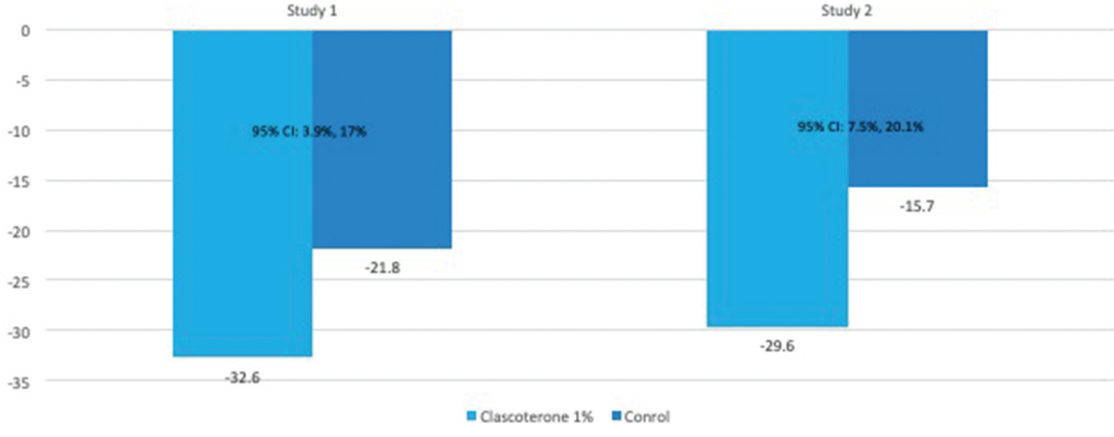

Figure 2. Mean percent reduction: non-inflammatory lesions.

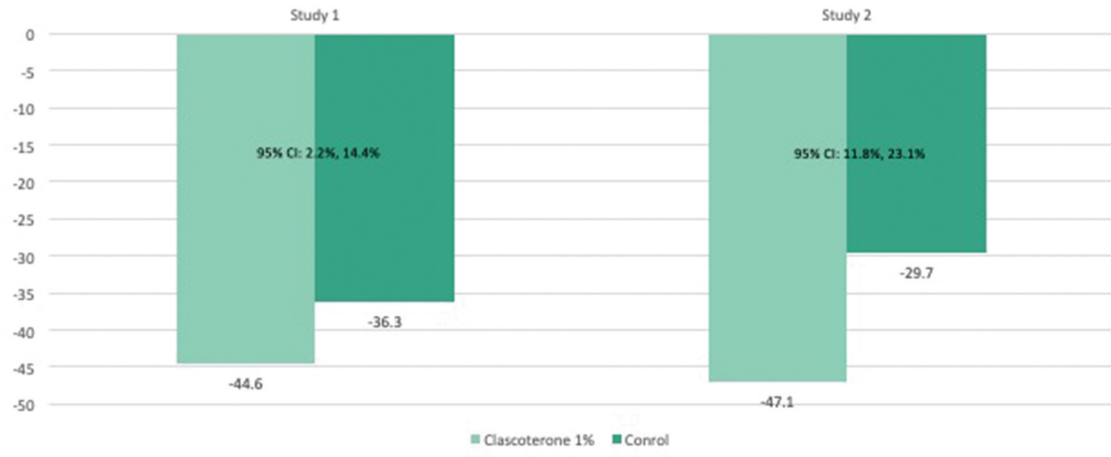

Figure 3. Mean percent reduction: inflammatory lesions.

Figures 3)[21]. The reduction in absolute noninflammatory lesions from baseline was −19.4 (95% CI −10.3 to −2.6; $P < .001$) and −19.4 (95% CI −12.3 to −4.9; $P < .001$) vs −13 and −10.8 with vehicle, respectively. Reduction in inflammatory lesions from baseline was −19.3 (95% CI −6.4 to −1.3; $P < .001$) and −20.0 (95% CI −9.8 to −5.1; $P < .001$) vs −15.5 and −12.6 with vehicle, respectively [5,21].

Only 13 treatment emergent adverse events (TEAE) were identified for clascoterone cream, 1%, in both studies. These included application site pain, oropharyngeal pain, application site dryness, application site erythema, application site hypertrichosis, acne, dermatitis contact,

hair color changes, eye irritation, peritonsillar abscess, and headache, and application site hypersensitivity. All TEAEs were mild in severity. No AEs were suggestive of systemic antiandrogen exposure. The prescribing information does, however, contain cautions regarding potential systemic effects, including hypothalamic-pituitary-adrenal (HPA) axis suppression and hyperkalemia[21].

The authors of the Phase III trial reports note that the studies are limited by the small sample sizes available for subgroup analyses, such as race and age. Furthermore, there was no analysis of the influence of concomitant acne therapies. Further studies are needed to evaluate long-term safety[5].

5. Conclusion

The dermatology community has long recognized that increased circulating androgens are one of the four key pathogenic features of acne. Androgens directly stimulate sebaceous gland growth and increased sebum production, creating a nourishing medium in which anaerobic *Cutibacterium acnes* (*C. acnes)* bacteria can flourish. However, topical therapeutic approaches aimed at modulating androgens have been elusive.

As a result of recent FDA approval, clascoterone is the first topical androgen antagonist developed to treat acne in both men and women. Studies document efficacy, favorable safety, and good tolerability. Clinicians are interested in identifying ideal combination strategies that combine clascoterone with existing topical treatments that target other pathogenic factors in acne. Early clinical experience has been positive, and there is anticipation in the dermatology community that this new agent will become a standard option for acne management.

6. Expert opinion

Several developments have shaped the acne treatment landscape in the past few years, producing new systemic and topical treatment options for an inflammatory skin disease that affects a majority of individuals at some point in their lifetime. However, the approval of a first-in-class topical androgen antagonist is indeed a 'game-changer' for acne management.

Androgen stimulation of the sebaceous gland is shown to mediate acne in multiple ways. Androgens can directly mediate enlargement of the gland and increase sebum production; excess, lipid-rich sebum is an ideal medium for proliferation of *C. acnes*. Androgens appear to directly mediate inflammation in the sebaceous glands.

Of course, the notion of hormone modulation for management of acne is not new, and there is a lengthy history of successful direct and indirect hormonal modulation used to manage acne in women. Nonetheless, these hormonally focused therapies generally have not been considered first line interventions for acne – even in women[22]. Systemic antiandrogens and hormonal modulation are, indeed, effective for certain women with acne, however, concerns about systemic exposure limit utility in others[23]. No hormonal modulating agent has been adopted for use in men with acne, suggesting that roughly half of all patients with acne are not candidates for such therapies.

As an androgen inhibitor, clascoterone is thought to displace androgen hormones, especially DHT, from the androgen receptors located at the sebaceous gland and hair follicle, thus inhibiting the cycle of physiologic events that leads to *C. acnes* proliferation and local inflammation in the skin. Clascoterone is applied topically and acts locally on androgen receptors in

the skin, with no systemic exposure seen. Therefore, its use would be appropriate in both males and non-pregnant females. Results of one pilot study suggest that once-daily topical clascoterone was as or more effective than topical tretinoin with better tolerability[24]. Although clascoterone is approved for use in male patients, the notion of using a hormonal modulating treatment in men is something of a novel concept, and there may be hesitation to adopt it early on.

Similarly, the notion of 'hormone modulating' therapy in adolescents may not be readily understood or accepted by some patients and parents who fear potential impacts on developing youth. Topical clascoterone is not shown to induce systemic effects and is thought to act locally in the skin, suggesting that such concerns are not justified. Data from two Phase III trials confirm the safety and efficacy of topical clascoterone in patients as young as 9[5]. Of note, the product is indicated for use in those as young as age 12.

It may be noted that the efficacy of clascoterone in pivotal clinical trials compares favorably to the efficacy seen with topical retinoids, a mainstay of acne treatment. A recent systematic review finds that the Investigator Global Assessments for topical retinoids range from 24.1–28.8%. When a topical retinoid is combined with benzoyl peroxide, IGA improvement ranges from 26.1–34.9% at Week 12[25]. Studies have yet to investigate the benefit of topical retinoids and/or benzoyl peroxide used in combination with clascoterone, but it is reasonable to expect that combination therapy will yield greater improvement in acne than clascoterone alone.

Although elevated androgen levels are widely implicated in acne pathogenesis, there is evidence to suggest that significant androgen excess is not present in a certain percentage of patients with acne[26]. Additionally, acne severity has not been shown to correlate directly with acne severity[27].

With recent FDA approval, clascoterone is poised to become an essential component of the topical treatment regimen for many acne patients. The proposed tube size should last about 30–45 days with BID treatment (1 gram per treatment) of the face, supporting patient convenience and adherence. As with any first-in-class drug, patient education on the action and safety of the treatment may be especially important during early adoption.

Clascoterone has not been studied in combination with other commonly used topical treatments for acne and is approved only as monotherapy. However, there is no reason to believe that the agent cannot be safely used by patient who are also using established therapies like topical antibacterials and/or retinoids. Specific regimens for sequential application of topical treatments are sure to emerge.

Of interest, topical clascoterone is currently under investigation for the treatment of androgenetic alopecia (AGA) in men.

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Declaration of interest

LH Kircik has served as a consultant and as an advisory board member for Cassiopea. He is also the Medical Director of DermResearch, PLLC, Physicians Skin Care, PLLC and Skin Sciences PLLC. He has no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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•• **This article is important because it summarizes the pivotal Phase III data.**

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