REVIEW

Overview of the Efficacy and Safety of Topical Hormonal Therapies for the Treatment of Acne Vulgaris: A Narrative Review

by JAMES Q. DEL ROSSO, DO; HILARY BALDWIN, MD; and ALISON M. LAYTON, MBChB, FRCP

Dr. Del Rosso is with Touro University Nevada in Henderson, Nevada and JDR Dermatology Research in Las Vegas, Nevada. Dr. Baldwin is Medical Director at The Acne Treatment and Research Center in Brooklyn, New York and Clinical Associate Professor of Dermatology at Rutgers Robert Wood Johnson Medical School in New Brunswick, New Jersey. Dr. Layton is Professor of Dermatology and Clinical Lead Skin Research Centre at the University of York in York, United Kingdom.

J Clin Aesthet Dermatol. 2026;19(1):34–40.

OBJECTIVE: Although systemic hormonal therapies (spironolactone, oral contraceptives) are clinically effective for the treatment of acne vulgaris (AV) in female patients, perceived safety concerns have contributed to the growing interest in topical hormonal AV therapies. **METHODS:** We searched PubMed using the terms "topical," "antiandrogen," "hormonal," "clascoterone," "spironolactone," and "acne vulgaris." **RESULTS:** The majority of articles identified related to clascoterone and topical spironolactone. Clascoterone cream 1% was approved in 2020 by the US Food and Drug Administration (FDA) for patients with AV aged 12 years or older based on two Phase III randomized controlled trials (RCTs) in 1440 patients (722 randomized to clascoterone) and an open-label extension study; other evaluations included a Phase IIa pharmacokinetic study and a Phase IIb RCT. Six clinical studies—mostly small, randomized trials—reported 193 patients treated with topical spironolactone as 5% cream, 5% gel, 2% solution, and 1% nanogel, and 1 RCT evaluated topical flutamide gel in 27 patients. The efficacy and safety of topical spironolactone and flutamide are supported by limited data with some conflicting results; neither agent is approved by the FDA and both must be compounded extemporaneously with no supporting pharmacokinetic data. **LIMITATIONS:** Clinical studies of topical spironolactone are limited by the small number of patients and wide range of formulations evaluated. **CONCLUSION:** Available evidence supports the use of clascoterone cream 1% and suggests potential benefits and limitations of topical spironolactone in patients with AV; however, for topical spironolactone, pharmacokinetic studies and large-scale RCTs are needed to better characterize both efficacy and safety profiles. **KEYWORDS:** Acne, topical, clascoterone, spironolactone, efficacy, safety, sebum

Acne vulgaris (AV) is a chronic dermatological condition that typically presents in puberty and can persist or worsen during adulthood.[1] The pathophysiology of AV begins with an androgen-mediated increase in sebum production by the sebaceous glands.[2] The effects of androgens on the sebaceous glands are mediated via binding to androgen receptors within sebocytes, which increases the production of sebum and inflammatory cytokines.[3-5] Systemic hormonal agents (eg, spironolactone, oral contraceptives) are often used to target the hormonal component of AV pathophysiology in female patients with AV.[2]

Although AV may be associated with other clinical features of hyperandrogenism (eg, polycystic ovary syndrome),[6] most individuals with AV have normal circulating hormone levels,[6,7] suggesting that local biosynthesis of androgens within the skin likely contributes to the condition. Consequently, there has been growing interest in topical hormonal therapies that have the potential to overcome some of the adverse effects and safety concerns associated with systemic therapies, including combined oral contraceptives. Although clascoterone cream 1% is currently the only topical antiandrogen therapy approved by the US Food and Drug Administration (FDA) for the treatment of AV,[8] other topical antiandrogen formulations have also been evaluated in clinical studies, including topical spironolactone and topical flutamide.

In this article, we review the clinical landscape of topical hormonal therapies for AV and discuss potential safety and clinical considerations related to their use in clinical practice.

FUNDING: Manuscript preparation and editorial support were funded by Sun Pharma.

DISCLOSURES: Dr. Del Rosso has served as a clinical research investigator, consultant/advisor, and/or speaker for AbbVie, Aclaris, Almirall, Amgen, AnaptysBio, Apogee Therapeutics, Arcutis Biotherapeutics, Aslan, Athenex, Bausch, Beiersdorf, Biofrontera, BioPharmX, Biorasi, Blue Creek, Botanix, Brickell, Bristol Myers Squibb, Cara Therapeutics, Cassiopea, Dermata, Dermavant, Encore, EPI Health, Evommune, Ferndale, Galderma, Genentech, Incyte, Janssen, JEM Health, LEO Pharma, La Roche-Posay, Lilly, MC2, Nektar, Novan, Nutrafol, Pfizer, Ralexar, Regeneron Pharmaceuticals, Sanofi-Genzyme, Sente, Sol-Gel, Sonoma, Sun Pharma, UCB, Verrica, and Vyne. Dr. Baldwin has served as an advisor, investigator, and on speakers' bureaus for Almirall, Beiersdorf, BioPharmX, Cassiopea, Dermata, Foamix, Galderma, La Roche-Posay, Nutrafol, Ortho Dermatologics, Sol-Gel, and Sun Pharma. Dr. Layton has acted as a research investigator, consultant, advisor, and/or speaker receiving honoraria to deliver unrestricted educational events for Almirall, Alliance, Beiersdorf, Eligo, Glenmark, Galderma, Incyte, La Roche-Posay, LEO Pharma, L'Oréal, Novartis, Sanofi, and Vanoka.

CORRESPONDENCE: James Q. Del Rosso, DO; Email: jqdelrosso@yahoo.com

WHAT ROLE DO ANDROGENS PLAY IN THE PATHOPHYSIOLOGY OF ACNE?

Acne most often begins at the onset of adrenarche and initially progresses during puberty in conjunction with an increase in the production of sex hormones, particularly androgens.[2,9] Although reproductive organs are the primary site of androgen synthesis, the sebaceous gland contains androgen-synthesizing enzymes that enable the local biosynthesis of androgens such as dihydrotestosterone (DHT) from androgenic precursors.[10] The cutaneous effects of androgens are mediated via binding to androgen receptors expressed in the skin and sebaceous glands,[11,12] thereby inducing the downstream transcription of genes that regulate sebum production.[3,13] Androgen-mediated increased sebum production is a key driver of the acne pathogenesis cascade.[7] Free fatty acids released from sebum triglycerides promote keratinocyte differentiation,[14,15] and androgens can also modulate keratinocyte differentiation directly by stimulating the production of growth factors from dermal fibroblasts, thereby contributing to comedogenesis in AV.[16] Sebum also provides a favorable environment for the growth of *Cutibacterium acnes*, triggering local inflammatory responses.[17] Due to their significant roles in regulating sebaceous gland activity and sebum production, androgens are an important therapeutic target for the treatment of AV. Hormonal therapies used in the treatment of AV generally work by hindering the biological activity of androgens by decreasing androgen synthesis (eg, oral contraceptives) and/or blocking the activity of androgens at androgen receptors (eg, oral contraceptives, clascoterone, and spironolactone).[6]

WHAT ARE THE CURRENT RECOMMENDATIONS FOR THE USE OF HORMONAL THERAPIES FOR AV?

The American Academy of Dermatology recommends a multimodal topical treatment consisting of therapies targeting different aspects of acne pathogenesis for the management of AV, with systemic therapy typically added to the regimen for moderate-to-severe cases that are not adequately controlled by topical therapy alone.[6] The spectrum of hormonal treatments available for patients with AV includes topical (clascoterone) and systemic (spironolactone, oral contraceptives) agents[6]; however, systemic hormonal agents are generally limited to use in female patients due to the potential for feminizing effects and other adverse effects in males, including gynecomastia, impotence, and decreased libido.[2] Clascoterone cream 1% is a first-in-class topical antiandrogen therapy[8,18] and is the only topical hormonal agent approved by the FDA for acne treatment as of 2025. Other topical antiandrogen agents, including topical spironolactone, are also under clinical evaluation and may ultimately provide additional options for targeted hormonal acne treatment (Table 1).

WHAT CLINICAL EVIDENCE SUPPORTS THE USE OF TOPICAL HORMONAL AGENTS IN THE TREATMENT OF ACNE VULGARIS?

Clascoterone. Clascoterone cream 1% is approved for the topical treatment of acne vulgaris in patients aged 12 years or older.[8] In vitro, clascoterone competes with DHT for binding to androgen receptors in the skin to prevent androgen-mediated sebum and inflammatory cytokine production;[4,5] however, the precise mechanism of action of clascoterone in the treatment of AV is unknown.[8] According to an interim report at 12 weeks from a recent study, casual facial sebum measurements obtained with a sebumeter decreased by approximately 27% following 12 weeks of treatment with clascoterone cream 1% in 40 patients with AV, providing new evidence for sebum reduction as a component of the mechanism of action of clascoterone for acne treatment.[26] The full study will evaluate changes in sebum measurements following treatment with clascoterone cream 1% through 52 weeks.[26]

The pharmacokinetic properties of clascoterone were evaluated in an open-label Phase II study of 20 adult (aged 18 years or older) and 22 adolescent (12–17 years old) patients with AV. Patients applied approximately 6g of clascoterone cream 1% (or 4g in adolescents with a body surface area $<1.6m^2$) twice daily for 2 weeks,[27] up to 6 times the recommended dose of 1g twice daily in the approved product labeling.[8] Clascoterone plasma concentrations reached steady-state levels by 96 hours after application, with mean maximum plasma concentrations of 4.4ng/mL and 4.6ng/mL in adolescents and adults, respectively, an approximately 1.8- to 2.1-fold increase compared with the first dose.[27] In vitro, clascoterone is rapidly metabolized to the primary metabolite cortexolone, which has minimal physiological activity.[28,29] Plasma concentrations of cortexolone were measured in the Phase II study and generally remained below the lower limit of quantitation (0.5ng/mL).[27] Collectively, this evidence demonstrates the limited systemic exposure to clascoterone or its metabolite following topical application.[27]

Clascoterone cream 1% had favorable efficacy and safety in early Phase I and II studies. In a pilot comparative study evaluating clascoterone cream 1% versus placebo and tretinoin 0.05% cream for 8 weeks in 77 male patients with AV, clascoterone led to significantly greater reductions versus placebo in total lesion count (TLC; $p=0.0017$), inflammatory lesion count (ILC; $p=0.0134$), and acne severity index (ASI; $p=0.009$).[30] Compared with tretinoin, clascoterone resulted in significantly greater reductions in ILC at Week 6 ($p=0.0374$), with comparable reductions in ASI and TLC at all time points evaluated.[30] Clascoterone was also evaluated in a 12-week Phase IIb randomized controlled trial (RCT) in 363 patients with acne in which patients were randomized to clascoterone 0.1% twice daily (n=72), clascoterone 0.5% twice daily (n=76), clascoterone 1% once daily (n=70), clascoterone 1% twice daily (n = 70), or vehicle (n=75).[31] At Week 12, clascoterone cream 1% dosed twice daily led to the highest rates of treatment success and the largest reductions from baseline in lesion counts compared with vehicle and the other treatment cohorts. The frequency of adverse events was similar in patients treated with clascoterone cream 1% twice daily (13 patients, 18.6%) and vehicle (17 patients, 22.7%), and clascoterone was well tolerated.[31]

The efficacy and safety of clascoterone cream 1% for the treatment of acne were evaluated in two randomized, double-blind, vehicle-controlled, Phase III trials of 1440 patients 9 years or older with moderate-to-severe facial acne vulgaris.[18] The trials included 1421 patients aged 12 years or older (the approved population) with a mean age of 19.7 years, of whom 62% were female and 91% were White.[8] Following 12 weeks of twice-daily treatment, patients using clascoterone cream 1% had significantly higher rates of Investigator's Global Assessment (IGA) score treatment success and larger reductions in lesion counts compared with those receiving vehicle.[18] Clascoterone had a safety profile similar to the vehicle, with the most common adverse events being nasopharyngitis, headache, and oropharyngeal pain.[18] The most common new or worsening local skin reactions

TABLE 1. Summary of clinical studies evaluating topical antiandrogen therapies

CITATION	STUDY DESIGN	Intervention (enrolled M/F)	TREATMENT REGIMEN	PATIENT CHARACTERISTICS	KEY FINDINGS	LIMITATIONS
Hebert et al[18]	RCT	Clascoterone cream 1% (258/464); vehicle cream (282/436)	BID, 12 weeks	Moderate-to-severe facial acne (IGA score of 3 or 4)	**Efficacy:** Statistically significant rates of treatment success[a] and reductions in lesion counts at Week 12 vs. vehicle ($p<0.001$) **Safety:** TEAE frequency was similar between clascoterone and vehicle, and most were mild or moderate in severity	Concomitant acne therapies were not used
Walton et al[19]	R	3% spironolactone powder finely ground (4/7); 5% spironolactone cream (7/4); 3% potassium canrenoate solution (5/4)	BID, 2 months	Moderately severe facial acne[b]; age not reported	**Efficacy:** No statistically significant changes in sebum excretion rate following 2 months of treatment with topical spironolactone 3% powder ($p>0.6$) or 5% cream ($p>0.1$)	Vehicle design limitations and solubility issues
Afzali et al[20]	RCT	5% spironolactone gel (8/30); placebo (6/34)	BID, 6 weeks	Mild-to-moderate acne; aged 11 to 30 years	**Efficacy:** Statistically significant reductions in total lesion count in spironolactone-treated vs. placebo-treated patients following 6 weeks of treatment ($p=0.007$). Differences in ASI were not statistically significant between spironolactone- and placebo-treated patients at Week 6 ($p=0.05$)	Small number of male patients evaluated, short study duration, absence of objective biometric assessments
Kelidari et al[21]	R	Spironolactone-NLC 1% (3/27); spironolactone-ALC 5% (2/28)	BID, 8 weeks	Mild-to-moderate acne[c]; aged 8 years or older	**Efficacy:** Both formulations led to significant reductions relative to baseline in noninflammatory lesion scores at Week 8 (both $p<0.01$), with significant increases in skin hydration observed with spironolactone-NLC ($p=0.002$) and reductions in sebum measurements with spironolactone-ALC ($p=0.01$) at Week 8 **Safety:** Dryness and itching were the most common symptoms reported in patients treated with spironolactone-NLC (2.7%) and spironolactone-ALC (15%), respectively	Small number of male patients evaluated
Ayatollahi et al[22]	OL	5% spironolactone cream (5/10)	BID, 8 weeks	Mild-to-moderate acne; aged 18 to 35 years	**Efficacy:** Statistically significant reductions relative to baseline in the numbers of total ($p<0.05$), inflammatory ($p=0.004$), and noninflammatory lesions ($p<0.001$) following 8 weeks of treatment **Safety:** No adverse effects were reported during the treatment period **Skin characteristics:** No statistically significant changes from baseline were observed in skin hydration, sebum index, or TEWL at Week 8 (all $p>0.05$)	Small sample size, short follow-up period
Noaimi and Al-Saadi[23]	RB	2% spironolactone solution (9/26); 1.5% clindamycin solution (8/25)	BID, 12 weeks	Mild-to-moderate facial acne	**Efficacy:** Statistically significant reductions in the number of comedones from baseline to Week 12 in spironolactone-treated ($p=0.0001$) but not clindamycin-treated patients ($p>0.05$); significant, comparable reductions in papules and pustules in both cohorts (all $p=0.0001$); reductions in ASI with spironolactone were statistically significantly greater vs. clindamycin ($p<0.05$) **Safety:** Mild adverse effects reported in patients using spironolactone (itching, 5.7%; burning, 11.4%) and clindamycin (itching, 9.1%; burning, 18.2%)	Absence of objective biometric assessments
Gharib et al[24]	RCT	5% spironolactone gel (3/11); 5% dapsone gel (2/12)	BID, 12 weeks	Mild-to-moderate acne; aged 17 to 24 years	**Efficacy:** Therapeutic response[d] was significantly greater in patients using spironolactone vs. dapsone ($p=0.034$); there was no significant difference between treatments in ASI ($p>0.05$) **Safety:** Frequency of adverse effects was significantly lower in patients using spironolactone vs. dapsone ($p=0.021$)	Small sample size, small number of male patients evaluated
Nassar et al[25]	RCT	1% flutamide gel (1/26); placebo (3/24)	BID, 8 weeks	Mild-to-moderate acne; aged 16 to 27 years	**Efficacy:** Statistically significant reductions relative to baseline in the numbers of papules ($p<0.05$) and pustules ($p<0.001$) but not comedones or total lesions following 8 weeks of treatment with flutamide, with no statistically significant differences relative to baseline in lesion counts in placebo-treated patients **Safety:** 12 (44.4%) patients treated with flutamide reported mild adverse effects, including scaling (7.4%), stinging (22.2%), erythema (7.4%), and dryness (25.9%), compared with 6 (22.2%) patients treated with placebo. No systemic adverse effects, including hot flashes, decreased libido, or impotence, were observed in patients treated with flutamide	Small number of male patients evaluated

[a]Treatment success was defined as an IGA score of 0 or 1 and at least a 2-point reduction in IGA score from baseline.[18]
[b]Defined as grade 1–3, assessed as described by Cunliffe and Burk, 1984.[19]
[c]Defined as a score of 1–30 on the GAGS scale.[21]
[d]Therapeutic response was calculated based on the percentage improvement in ASI from the first visit and was rated as poor, moderate, good, or excellent.[24]

ALC: alcohol gel; ASI: acne severity index; BID: twice daily; F: female; GAGS: Global Acne Grading System; IGA: Investigator's Global Assessment; M: male; NLC: nanolipid carrier gel; OL: open label; R: randomized; RB: rater (or investigator) blinded; RCT: randomized controlled trial; TEAE: treatment-emergent adverse event; TEWL: transepidermal water loss

were erythema and scaling/dryness.[18] There was no clinical evidence of systemic adverse effects related to androgen suppression reported in the Phase III clinical trials.[18] In an open-label long-term extension study, the efficacy and safety of clascoterone were maintained for up to 9 additional months of treatment in patients with facial AV, with a progressive increase in efficacy over time and with no new safety signals reported.[32,33] Clascoterone cream 1% also led to improvement in truncal IGA score through 9 months in patients who opted to treat truncal acne.[32]

Recent clinical evidence also indicated that clascoterone cream 1% does not adversely affect the epidermal barrier, which is commonly observed in patients with AV[34] and often exacerbated by common topical acne medications.[35,36] Among 50 participants with acne-prone skin who applied clascoterone cream 1% twice daily in a randomized split-face study, the side of the face treated with clascoterone exhibited an increase in skin moisturization with no change in transepidermal water loss (TEWL), a measure of epidermal permeability, following 2 weeks of treatment compared with the untreated side of the face.[37]

Topical spironolactone. Spironolactone is an oral aldosterone receptor antagonist that is used off-label for treatment of AV in select female patients.[6] Spironolactone inhibits androgen signaling through multiple mechanisms, including competing with testosterone and DHT for binding to androgen receptors.[6,38] There is also evidence that spironolactone inhibits 5α-reductase, an enzyme responsible for converting testosterone into DHT, and increases levels of steroid hormone-binding globulin, thereby reducing the local bioavailability of testosterone and DHT.[6,38] Several different topical formulations and concentrations of spironolactone have been evaluated in clinical studies for AV treatment.

An early study by Walton et al[19] compared the effects of 3 topical spironolactone preparations (3% cream, 5% cream, and 3% solution containing the active spironolactone metabolite canrenone) in 31 patients with moderate-to-severe acne (Table 1), which revealed no statistically significant reductions in sebum excretion rate following 2 months of treatment with any of the preparations tested. Other measures of treatment efficacy, such as reductions in lesion counts, were not evaluated in the study. In a more recent study by Ayatollahi et al,[22] treatment with a topical 5% spironolactone cream twice daily for 8 weeks in 15 patients with mild-to-moderate acne resulted in significant reductions in lesion counts and acne global grading score ($p<0.05$; Table 1).[33] There were no adverse effects reported and no significant differences in skin hydration or TEWL before and after treatment with topical spironolactone. Additionally, spironolactone did not affect the skin sebum index,[22] which is consistent with earlier results.[19]

Afzali et al[20] evaluated the efficacy and safety of 5% spironolactone gel in a double-blind study of 78 patients with mild-to-moderate acne, of whom 38 received spironolactone and 40 received placebo. There was no statistically significant difference in ASI between patients treated with spironolactone and those treated with placebo ($p>0.05$); however, spironolactone did lead to significantly greater reductions in TLC versus placebo following 6 weeks of treatment ($p=0.007$). Adverse reactions were reported with similar frequency between the two treatment arms.

There is growing interest in using lipid nanoparticles and other novel topical delivery systems for optimized formulations of spironolactone, although few have been evaluated in clinical studies.[35-39] Spironolactone-loaded nanostructured lipid carrier gel (SP-NLC) was compared with a spironolactone alcoholic gel (SP-ALC) in a randomized double-blind study of 76 patients with mild-to-moderate acne.[21] After 8 weeks of treatment, both formulations resulted in statistically significant reductions versus baseline in the numbers of noninflammatory and total lesions, but there was no change in ILC or ASI. Notably, significant reductions in sebum levels were reported after 8 weeks in patients receiving SP-ALC,[21] contrasting with studies evaluating spironolactone cream formulations.[19,22]

In a recently published comparative study,[24] there was no significant difference in ASI between patients treated twice daily with 5% spironolactone gel (n=14) versus 5% dapsone gel (n=14; $p>0.05$) for 12 weeks. However, the overall frequency of adverse effects was significantly lower in patients treated with spironolactone (5 patients, 35.7%) versus dapsone (11 patients, 78.6%; $p=0.021$). In particular, itching was significantly more common following treatment with dapsone versus spironolactone ($p=0.003$). In another study of 73 patients with mild-to-moderate facial acne, spironolactone 2% solution had significantly greater efficacy versus 1.5% clindamycin solution for the reduction of the number of comedones and improvement in ASI.[23] Mild local adverse effects (itching, burning) were reported with similar frequency in both cohorts.

In a systematic review of the 5 clinical trials described above that evaluated topical formulations of spironolactone including 5% cream, 5% gel, 2% solution, 3% powder, and 1% nanogel in a total of 195 patients, topical spironolactone led to statistically significant reductions in ASI and/or TLC in 4 of the 5 studies.[43] The patients included adolescents and adults aged 11 to 40 years, most of whom were women (n=152).[43] Topical spironolactone had a generally favorable safety profile with few adverse reactions reported.[43] However, the systemic safety of topical spironolactone is not well characterized because clinical studies to date included few male patients. Additionally, there are no published data on the pharmacokinetic profile of topical spironolactone, and it is therefore not known how much systemic exposure occurs after topical application.

Topical flutamide. The antiandrogen actions of flutamide are mediated via competition with DHT for binding to androgen receptors in the skin.[25] Systemically administered flutamide is approved for the treatment of prostate cancer but is not currently approved for acne.[44] A topical formulation of flutamide was evaluated in a RCT of 54 patients with mild-to-moderate acne.[25] Flutamide 1% gel twice daily for 8 weeks versus placebo resulted in significant reductions from baseline in the number of papules and pustules but not in the number of comedones or total lesions.[43] Adverse effects were reported in 12 of 27 (44.4%) patients receiving flutamide gel, including scaling (7.4%), stinging (22.2%), erythema (7.4%), and dryness (25.9%). The overall frequency of adverse effects with flutamide was numerically but not statistically significantly higher than the frequency reported with placebo (22.2%).[25] No systemic adverse effects (eg, decreased libido, impotence) were reported in patients using flutamide.[25] However, it is not known how much systemic exposure occurs after topical application, as the study did not include pharmacokinetic assessments.

WHAT ARE THE THERAPEUTIC DIFFERENCES BETWEEN CLASCOTERONE AND TOPICAL SPIRONOLACTONE?

Although clascoterone and spironolactone

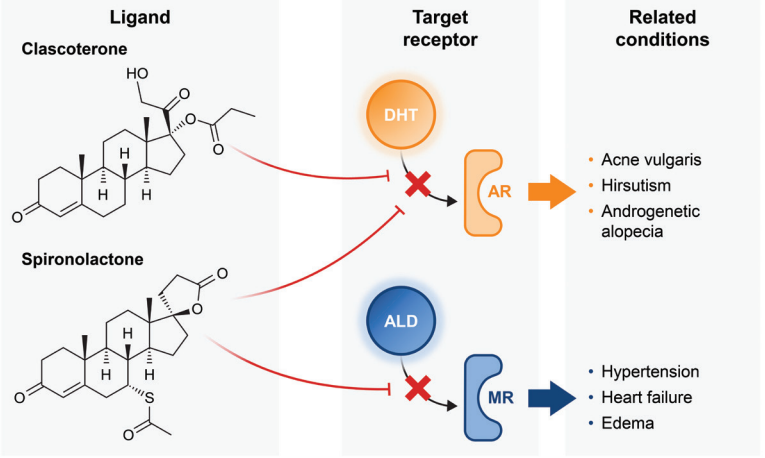

FIGURE 1. Mechanisms of action of clascoterone and spironolactone.
ALD: aldosterone; AR: androgen receptor; DHT: dihydrotestosterone; MR: mineralocorticoid receptor

have similar chemical structures with a 4-ring backbone similar to that of DHT,[29,45] these compounds differ somewhat in their mechanisms of action (Figure 1) and are not considered to be substitutable with each other for clinical use.[46] Whereas both clascoterone and spironolactone competitively inhibit DHT binding to androgen receptors within sebaceous glands,[4,5,38] spironolactone also exhibits activity at aldosterone (ie, mineralocorticoid) receptors, by which it additionally regulates blood pressure and potassium levels.[2,45] Systemically administered spironolactone is associated with an increased risk of hyperkalemia, particularly in patients with impaired renal function or those using concomitant drugs that increase potassium,[45] although evidence suggests minimal risk of hyperkalemia in young, healthy patients.[47,48] There are currently insufficient pharmacokinetic data to determine whether topical spironolactone is safe for use in patients for whom systemic spironolactone is contraindicated or those at elevated risk for adverse effects associated with systemic spironolactone. Additional data are needed on the safety profiles of topical spironolactone and flutamide, particularly the potential for systemic adverse reactions. Additionally, compounded topical spironolactone products prescribed to patients for acne treatment may differ from each other and from published formulations. Clinicians and patients should be informed of the potential differences between topical spironolactone products and clascoterone when considering optimal treatment options.

CONCLUSION

Topical hormonal therapies fulfill an important clinical need, as they can be used safely to address the hormonal pathophysiology of acne in a variety of patients, allowing healthcare professionals to tailor acne management in diverse populations. There has been substantial interest in developing topical hormonal therapies to address the androgen-driven component of acne with lower potential for systemic adverse reactions both before and after the approval of clascoterone cream 1% in 2020.[8] Evaluations supporting the approval of clascoterone comprised Phase I and Phase II studies in patients with AV, including a pharmacokinetic study demonstrating limited systemic exposure following topical application,[27,30,31] and two pivotal Phase III RCTs demonstrating clascoterone efficacy versus vehicle based on IGA success and lesion counts, along with favorable safety and tolerability.[18] Evidence from a recent report demonstrating reductions in casual sebum production following treatment with clascoterone cream 1% further describe the mechanism of action of clascoterone.[19]

Spironolactone is readily available for compounding, and multiple clinical studies to date have evaluated a range of topical spironolactone formulations and concentrations including 5% cream, 5% gel, 2% solution, 3% powder, and 1% nanogel.[43] Based on limited available evidence, topical spironolactone may potentially provide an effective option for topical hormonal therapy; however, given the relatively small study sizes and inconsistency of reported efficacy results among different formulations, pharmacokinetic studies and large-scale RCTs that include both female and male patients are needed to support its mainstream use in AV management. Similarly, topical flutamide may potentially provide an effective option for AV treatment, but clinical experience thus far is limited. Efficacy, safety, and other considerations (ie, patient characteristics and clinical history) should be taken into account when making decisions regarding topical hormonal treatment options for patients with AV.

ACKNOWLEDGMENTS

Manuscript preparation and editorial support were provided by Dana Lengel, PhD, of AlphaBioCom, a Red Nucleus company, and funded by Sun Pharma.

REFERENCES

1. Chen H, Zhang TC, Yin XL, Man JY, Yang XR, Lu M. Magnitude and temporal trend of acne vulgaris burden in 204 countries and territories from 1990 to 2019: an analysis from the Global Burden of Disease Study 2019. *Br J Dermatol*. 2022;186(4):673-683.
2. Elsaie ML. Hormonal treatment of acne vulgaris: an update. *Clin Cosmet Investig Dermatol*. 2016;9:241-248.
3. Barrault C, Garnier J, Pedretti N, et al. Androgens induce sebaceous differentiation in sebocyte cells expressing a stable functional androgen receptor. *J Steroid Biochem Mol Biol*. 2015;152:34-44.
4. Rosette C, Agan FJ, Mazzetti A, Moro L, Gerloni M. 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(5):412-18.
5. Rosette C, Rosette N, Mazzetti A, Moro L, Gerloni M. Cortexolone 17α-propionate (clascoterone) is an androgen receptor antagonist in dermal papilla cells in vitro. *J Drugs Dermatol*. 2019;18(2):197-201.
6. Reynolds RV, Yeung H, Cheng CE, et al. Guidelines of care for the management of acne vulgaris. *J Am Acad Dermatol*. 2024;90(5):1006.e1-1006.e30.
7. Del Rosso JQ, Kircik L. The cutaneous effects of androgens and androgen-mediated sebum production and their pathophysiologic and therapeutic importance in acne vulgaris. *J*

Dermatolog Treat. 2024;35(1):2298878.
8. WINLEVI (clascoterone cream 1%). Prescribing information. Sun Pharmaceutical Industries, Inc.; 2025.
9. Heng AHS, Chew FT. Systematic review of the epidemiology of acne vulgaris. *Sci Rep*. 2020;10(1):5754.
10. Thiboutot D, Bayne E, Thorne J, et al. Immunolocalization of 5alpha-reductase isozymes in acne lesions and normal skin. *Arch Dermatol*. 2000;136(9):1125-1129.
11. Bläuer M, Vaalasti A, Pauli SL, Ylikomi T, Joensuu T, Tuohimaa P. Location of androgen receptor in human skin. *J Invest Dermatol*. 1991;97(2):264-268.
12. Liang T, Hoyer S, Yu R, et al. Immunocytochemical localization of androgen receptors in human skin using monoclonal antibodies against the androgen receptor. *J Invest Dermatol.* 1993;100(5):663-666.
13. Davey RA, Grossmann M. Androgen receptor structure, function and biology: from bench to bedside. *Clin Biochem Rev*. 2016;37(1):3-15.
14. Kim YJ, Lee SB, Lee HB. Oleic acid enhances keratinocytes differentiation via the upregulation of miR-203 in human epidermal keratinocytes. *J Cosmet Dermatol*. 2019;18(1):383-389.
15. Li WH, Zhang Q, Flach CR, Mendelsohn R, Southall MD, Parsa R. In vitro modeling of unsaturated free fatty acid-mediated tissue impairments seen in acne lesions. *Arch Dermatol Res*. 2017;309(7):529-540.
16. Kumtornrut C, Yamauchi T, Koike S, Aiba S, Yamasaki K. Androgens modulate keratinocyte differentiation indirectly through enhancing growth factor production from dermal fibroblasts. *J Dermatol Sci*. 2019;93(3):150-158.
17. Nagy I, Pivarcsi A, Koreck A, Széll M, Urbán E, Kemény L. Distinct strains of Propionibacterium acnes induce selective human beta-defensin-2 and interleukin-8 expression in human keratinocytes through toll-like receptors. *J Invest Dermatol*. 2005;124(5):931-938.
18. Hebert A, Thiboutot D, Stein Gold L, et al. Efficacy and safety of topical clascoterone cream, 1%, for treatment in patients with facial acne: two Phase III randomized clinical trials. *JAMA Dermatol*. 2020;156(6):621-630.
19. Walton S, Cunliffe WJ, Lookingbill P, Keczkes K. Lack of effect of topical spironolactone on sebum excretion. *Br J Dermatol*. 1986;114(2):261-264.
20. Afzali BM, Yaghoobi E, Yaghoobi R, Bagherani N, Dabbagh MA. Comparison of the efficacy of 5% topical spironolactone gel and placebo in the treatment of mild and moderate acne vulgaris: a randomized controlled trial. *J Dermatolog Treat*. 2012;23(1):21-25.
21. Kelidari HR, Saeedi M, Hajheydari Z, et al. Spironolactone loaded nanostructured lipid carrier gel for effective treatment of mild and moderate acne vulgaris: a randomized, double-blind, prospective trial. *Colloids Surf B Biointerfaces*. 2016;146:47-53.
22. Ayatollahi A, Samadi A, Bahmanjahromi A, Robati RM. Efficacy and safety of topical spironolactone 5% cream in the treatment of acne: a pilot study. *Health Sci Rep*. 2021;4(3):e317.
23. Noaimi A, Al-Saadi SR. Treatment of acne vulgaris by topical spironolactone solution compared with clindamycin solution. *Cureus*. 2021;13(8):e17606.
24. Gharib K, Samir M, Mohamed G, Rageh MA. Efficacy and safety of topical spironolactone versus topical dapsone in the treatment of acne vulgaris. *Arch Dermatol Res*. 2024;316(10):732.
25. Nassar A, Sayed AE, Samy A, Essam R. Efficacy and safety of topical flutamide 1% gel as an adjunctive therapy in the treatment of patients with acne vulgaris. *J Cutan Med Surg*. 2023;27(5):472-475.
26. Draelos ZD, Kyerematen KK, Squittieri N. Reduction in facial sebum production following treatment with clascoterone cream 1% in patients with acne vulgaris: 12-week interim analysis. Presented at Fall Clinical Dermatology; October 24–27, 2024; Las Vegas, NV, USA.
27. 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 IIa study. *J Drugs Dermatol*. 2019;18(6):563.
28. Celasco G, Moro L, Bozzella R, et al. Biological profile of cortexolone 17alpha-propionate (CB-03-01), a new topical and peripherally selective androgen antagonist. *Arzneimittelforschung*. 2004;54(12):881-886.
29. Ferraboschi P, Legnani L, Celasco G, et al. A full conformational characterization of antiandrogen corexolone-17α-propionate and related compounds through theoretical calculations and nuclear magnetic resonance spectroscopy. *Med Chem Commun*. 2014;5:904.
30. Trifu V, Tiplica GS, Naumescu E, et al. Cortexolone 17alpha-propionate 1% cream, a new potent antiandrogen for topical treatment of acne vulgaris. A pilot randomized, double-blind comparative study versus placebo and tretinoin 0.05% cream. *Br J Dermatol*. 2011;165(1):177-183.
31. Mazzetti A, Moro L, Gerloni M, Cartwright M. A Phase IIb, 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.
32. Eichenfield LF, Hebert AA, Gold LS, et al. Long-term safety and efficacy of twice-daily topical clascoterone cream 1% in patients greater than or equal to 12 years of age with acne vulgaris. *J Drugs Dermatol*. 2023;22(8):810-816.
33. Eichenfield L, Hebert A, Gold LS, et al. Open-label, long-term extension study to evaluate the safety of clascoterone (CB-03-01) cream, 1% twice daily, in patients with acne vulgaris. *J Am Acad Dermatol*. 2020;83(2):477-485.
34. Zhou L, Liu X, Li X, et al. Epidermal barrier integrity is associated with both skin microbiome diversity and composition in patients with acne vulgaris. *Clin Cosmet Investig Dermatol*. 2022;15:2065-2075.
35. Aschoff R, Moller S, Haase R, Kuske M. Tolerability and efficacy of clindamycin/tretinoin versus adapalene/benzoyl peroxide in the treatment of acne vulgaris. *J Drugs Dermatol*. 2021;20(3):295-301.
36. Zhou L, Chen L, Liu X, et al. The influence of benzoyl peroxide on skin microbiota and the epidermal barrier for acne vulgaris. Dermatol Ther. 2022;35(3):e15288.
37. Draelos ZD, Kyerematen K, Squittieri N. Improvement in skin moisturization and lack of barrier damage following treatment with clascoterone cream. *J Drugs Dermatol*. 2025;24(4):397-402.
38. Akamatsu H, Zouboulis CC, Orfanos CE. Spironolactone directly inhibits proliferation of cultured human facial sebocytes and acts antagonistically to testosterone and 5 alpha-dihydrotestosterone in vitro. *J Invest Dermatol*. 1993;100(5):660-662.
39. Albash R, Badawi NM, Hamed MIA, et al. Exploring the synergistic effect of bergamot essential oil with spironolactone loaded nano-phytosomes for treatment of acne vulgaris: in vitro optimization, in silico studies, and clinical evaluation. *Pharmaceuticals (Basel)*. 2023;16(1):128.

40. Ilic D, Cvetkovic M, Tasic-Kostov M. Emulsions with alkyl polyglucosides as carriers for off-label topical spironolactone - safety and stability evaluation. *Pharm Dev Technol*. 2021;26(3):373-379.
41. Salama A, Badran M, Elmowafy M, Soliman GM. Spironolactone-loaded LeciPlexes as potential topical delivery systems for female acne: in vitro appraisal and ex vivo skin permeability studies. *Pharmaceutics*. 2019;12(1):25.
42. Dereiah S, Ghori MU, Conway BR. A systematic review of spironolactone nano-formulations for topical treatment of skin hyperandrogenic disorders and chronic wounds. *Pharmaceutics*. 2024;17(1):27.
43. Rehan ST, Khan Z, Abbas S, et al. Role of topical spironolactone in the treatment of acne: a systematic review of clinical trials-does this therapy open a path towards favorable outcomes? *J Dermatol*. 2023;50(2):166-174.
44. Flutamide capsules USP, 125 mg. Full Prescribing Information. Miami, FL: Cipla USA Inc.; 2018.
45. Aldactone® (spironolactone) tablets for oral use. Full Prescribing Information. New York, NY: Pfizer Labs; 2024.
46. Approved Drug Products with Therapeutic Equivalence Evaluations. Orange Book. US Food and Drug Administration. Accessed October 8, 2024. https://www.fda.gov/drugs/drug-approvals-and-databases/approved-drug-products-therapeutic-equivalence-evaluations-orange-book.
47. Plovanich M, Weng QY, Mostaghimi A. Low usefulness of potassium monitoring among healthy young women taking spironolactone for acne. *JAMA Dermatol*. 2015;151(9):941-4.
48. Thiede RM, Rastogi S, Nardone B, et al. Hyperkalemia in women with acne exposed to oral spironolactone: A retrospective study from the RADAR (Research on Adverse Drug Events and Reports) program. *Int J Womens Dermatol*. 2019;5(3):155-57. JCAD