

Cortexolone 17α-propionate (Clascoterone) Is a Novel Androgen Receptor Antagonist that Inhibits Production of Lipids and Inflammatory Cytokines from Sebocytes In Vitro

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ABSTRACT

Cortexolone 17α-propionate (clascoterone) is a novel topical androgen antagonist that is being analyzed for its ability to treat acne. The pathogenesis of acne is attributed to multiple factors, including altered sebum production, inflammatory processes, dysregulation of the hormone microenvironment, and the proliferation of the skin commensal bacteria, *Propionibacterium acnes (P. acnes)*. Androgens induce the proliferation and differentiation of sebocytes, (cells that comprise the sebaceous gland), help regulate the synthesis of the lipids that are incorporated into sebum and stimulate the production of cytokines that are found in inflammatory acne lesions. Several studies have established that clascoterone is a potent antiandrogen that is well tolerated and has selective topical activity. Its potency as an acne therapeutic is currently being analyzed in a large phase 3 clinical trial. The study described herein elucidates for the first time the mechanism of action of clascoterone. Clascoterone was found to bind the androgen receptor (AR) with high affinity in vitro, inhibit AR-regulated transcription in a reporter cell line, and antagonize androgen-regulated lipid and inflammatory cytokine production in a dose-dependent manner in human primary sebocytes. In particular, when compared to another AR antagonist, spironolactone, clascoterone was significantly better at inhibiting inflammatory cytokine synthesis from sebocytes. Therefore, clascoterone may be an excellent candidate to be the first topical antiandrogen to treat acne.

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INTRODUCTION

The pathogenesis of acne is attributed to a combination of changes in the skin. Many of these changes are dominantly regulated by the sebaceous gland and include increased sebum production, altered lipid composition of sebum, and inflammation.[1-3] Insulin-like growth factor-1 (IGF-1), which increases during puberty, stimulates lipogenesis in sebaceous glands and potentiates androgen signaling by inducing 5α-reductase activity and activation of the AR.[4] The AR is expressed in the cells of the sebaceous gland (sebocytes), and androgenic hormones have been shown to increase the proliferation and differentiation of sebocytes.[5-7] The AR is both a major regulator of the synthesis of a complex group of lipids and is involved in signaling pathways that lead to the production of inflammatory cytokines.[6,8] Both *P. acnes* and the potent androgen dihydrotestosterone (DHT) can stimulate sebocytes to secrete these cytokines.[8-10] Comparing gene expression profiles of skin obtained from acne patients and those without acne shows that the majority of upregulated genes are involved in inflammatory processes.[11] Consistent with this is the abundance of the inflammatory cytokines IL-1β and IL8 in human acne lesions.[12]

Although several new anti-acne agents that target various processes relevant to acne pathogenesis have completed or are currently in Phase 1 and 2 clinical trials,[13] altering sebocyte signaling remains one of the most attractive therapeutic option for treating acne. Currently, the most commonly used sebo-suppressive treatment involves the use of isotretinoin administered orally.[14] Another sebo-suppressive acne therapeutic currently in use is the oral androgen inhibitor spironolactone, which is only effective in females and can cause health problems in males.[15,16] Finally, the acetyl coenzyme A carboxylase (ACC) inhibitor olumacostat glasaretil (OG) was being developed as an acne treatment based on its ability to inhibit the rate-limiting step of lipid synthesis in sebocytes.[17] However, OG failed to meet the designated endpoints in a recent Phase 3 clinical trial.[18]

Despite considerable evidence for the role of excess androgens in the pathophysiology of acne, to date there is no topical androgen inhibitor prescribed to treat acne. Cortexolone 17α-propionate (clascoterone) is a novel AR inhibitor with strong topical antiandrogenic activity and anti-inflammatory properties.[19] A pilot study comparing topical creams containing either clascoterone or tretinoin in acne patients demonstrated that clascoterone was well tolerated, more effective than tretinoin at reducing acne lesions, and worked 50% faster than

tretinoin.[20] It is hypothesized that clascoterone's mechanism of action is through direct inhibition of AR signaling, but this has yet to be proven. In this report, direct binding of clascoterone to the AR is demonstrated in vitro, and clascoterone's ability to inhibit lipid synthesis and inflammatory signaling downstream of the AR is analyzed in cultured human primary sebocytes.

MATERIALS AND METHODS

Materials

The AR reporter cell line kit was purchased from Indigo Biosciences (State College, PA) and was used per manufacturer's protocol. Human primary sebocytes, their growth medium, and collagen coated culture plates were purchased from Zen-Bio, Inc. (Research Triangle Park, NC). Complete media proprietary to Zen-Bio was developed to optimize sebocyte proliferation and maintain sebocytes in an undifferentiated state. It contains serum free base medium, penicillin, streptomycin, amphotericin B, bovine pituitary extract, and human recombinant epidermal growth factor. Cytokine Bead Array and Cytofix/Cytoperm were purchased from Becton Dickinson (Franklin Lakes, NJ). The anti-human AR antibody (rabbit mAB D6F11, PE-conjugated) was purchased from Cell Signaling Technology (Santa Cruz, CA, cat #84285). OG and spironolactone were purchased from Sigma (St. Louis, MO). Clascoterone and DHT were gifts from Cosmo S.p.A.

Clascoterone Binding to the AR In Vitro

A cell-free in vitro system of recombinant protein consisting of the human wt AR ligand binding domain (LBD) and fluorescently labeled DHT was used to determine the affinity of clascoterone along with positive control unlabeled DHT and low binding control Dichlorodiphenyldichloroethylene (DDE) (Invitrogen/Life Technologies). It is a fluorescence polarization-based competitive binding assay. Clascoterone was assayed at 10 concentrations in triplicate in two independent assays.

AR Expression in Human Sebocytes

Cells were fixed in 2% paraformaldehyde/ 0.1%Tween20 for 15 min at 4°C, washed twice in phosphate buffered saline (PBS) and incubated with a fluorescently tagged antibody to human AR for 1 hour at room temperature. Cells were washed in PBS then analyzed flow cytometrically using MacQuantanalyzer 10 (Miltenyi, Germany) followed by data analysis using FlowJo software (Ashland, OR).

DHT-Stimulated Lipid Accumulation in Human Sebocytes

Sebocytes (500,000) were seeded in collagen I coated flasks in complete medium then incubated in a 37°C humidified chamber and 5% CO_2. Media was changed after 24 hours and then every 2-3 days until the cells reached 70-80% confluence. Cells were trypsinized and transferred to collagen I-coated 96-well flat bottom plates (10,000 cells per well in 200µL complete media). The following day, cells were stimulated with DHT in the presence or absence of clascoterone or the test compounds/acne treatments OG or spironolactone, in complete media. DHT + 0.1% DMSO served as the no compound control. Two days later, they were treated again as on the first day. A third and final treatment was performed 4 days after the first treatment. On the final day cells were harvested by trypsinization, washed with PBS and incubated with Nile Red (NR, 1µg/ml) in the dark for 5 min at room temperature. The fluorescence intensity of each sample was measured immediately by flow cytometry at an excitation wavelength of 488 nm and emission wavelength of 550 nm. Dead cells were gated out of the analysis based on the forward and side scatter profiles so that only mean fluorescence intensity (MFI) of NR from live cells is reported.

Cytokine Analysis Using Bead-Based ELISA Assay

Culture supernatants harvested on days 3, 5, and 7 were analyzed for the presence of IL8, IL1ß, and IL6. Cytokines were measured using bead-based ELISA kits (Cytokine Bead Array kit) with the manufacturer's protocol modified for a 96-well format and flow cytometrically analyzed.

AR Activity Assay

The AR reporter assay kit utilizes mammalian cells that co-express the full-length human AR and a luciferase reporter gene controlled by an AR-responsive promoter. The kit was used per manufacturer's protocol. Cells were seeded in 96 well plates in media containing 400 pM testosterone in the presence or absence of either clascoterone or enzalutamide. Negative controls were no cells and DMSO only. After incubation for 24 hours at 37°C, 5% CO_2, media were aspirated and replaced with luminescence detection reagent (LDR). Luminescence was quantified on a ClarioStar plate reader.

Data Analysis

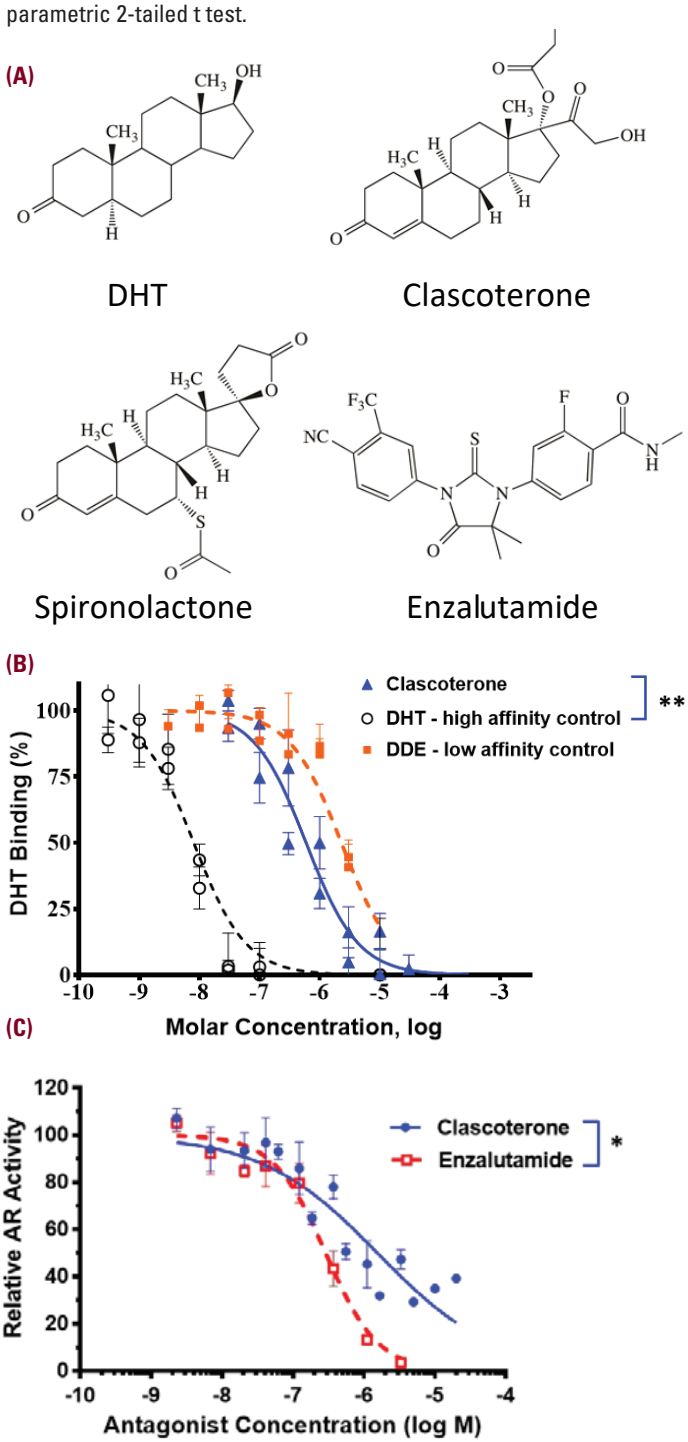
Data were analyzed using GraphPad Prism version 7.03 software (La Jolla, CA). Dead cells were excluded from analysis by gating them out of flow cytometric analyses based on forward and side scatter profiles.

RESULTS

Clascoterone Binds the AR and Antagonizes Testosterone-Stimulated Transcriptional Activity

The structure of clascoterone shares the fused-four ring backbone with DHT and the AR inhibitor spironolactone (Figure 1A). The other control, enzalutamide, is a non-steroidal AR inhibitor that is FDA approved as a treatment for androgen-dependent prostate cancer. To determine the affinity of clascoterone for the AR in vitro, a recombinant protein system utilizing the AR-LBD and fluorescently labeled DHT was used. Unlabeled DHT was used as a high affinity positive control and DDE was used as a low affinity control (Figure 1B). The mean IC_{50} for clascoterone binding to the AR was calculated as 6.24×10^{-7}. Meanwhile, those of DHT and DDE were 8.06×10^{-9} M and 2.58×10^{-6} M,

FIGURE 1. Characterization of clascoterone binding and activation of the AR in vitro. (A) Structures of tested compounds (B) Binding of clascoterone, DHT or DDE to recombinant AR LBD. The mean IC_{50} and SD were calculated from two independent experiments, each in triplicates and were determined to be 6.24 x 10^{-7} M, 8.06 x 10^{-9} M and 2.58 x 10^{-6} M for clascoterone, DHT and DDE, respectively. $^{**}P<0.005$ DHT vs clascoterone, based on multiple t tests with Holm-Sidak method correction (C) AR transcriptional activity in reporter cells. Data points are the mean +SD for 3 independent experiments, $^{*}P<0.05$, based on parametric 2-tailed t test.



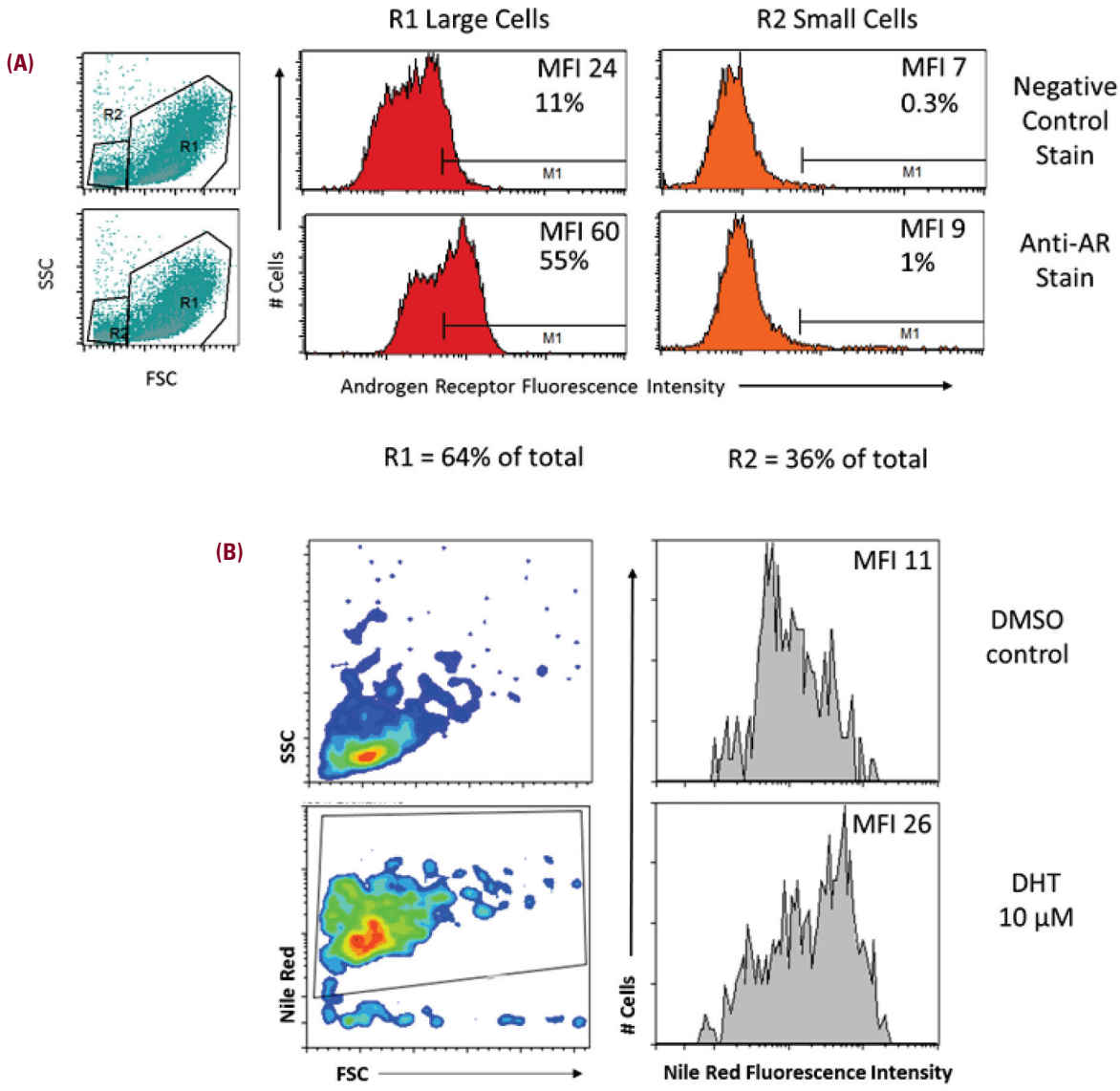
respectively ($P<0.005$ clascoterone vs DHT). These data show that clascoterone binds to the AR with approximately 100-fold lower affinity than DHT, but 4-fold higher affinity than DDE. To evaluate clascoterone antagonism of AR biologic activity in cell culture, the ability of clascoterone to inhibit testosterone-stimulated transcriptional activity from reporter cells was measured. Cells were treated for 24 hours with 400 pM testosterone in the presence of either clascoterone or enzalutamide. The IC_{50}s were calculated to be 1.6 x 10^{-6} M and 2.9 x 10^{-7} M for clascoterone and enzalutamide, respectively, making clascoterone 5-fold less effective at antagonizing testosterone-induced AR activity than enzalutamide in this system (Figure 1C).

Clascoterone Inhibits DHT-Induced Lipid Synthesis in Primary Sebocytes from Human Donors

We confirmed expression of AR in primary sebocytes from three donors using a fluorescently labeled anti-AR antibody detected flow cytometrically. Only the large cells, which compromise 64% of the total number of cells, express the AR (Figure 2A, scatter dot plots in green). These are the fully differentiated, mature sebocytes which we've confirmed to produce lipids based on NR staining of sebocytes from multiple donors. Of the large cells, 55% express high levels of AR protein, while the remaining 45% express low or undetectable levels (Figure 2A, lower panel in red). Based on the percentage of AR positive large cells, the relative number of cells expressing AR is 5-fold relative to control isotype antibody-stained cells, while the relative expression level based on the MFI is 2.5-fold. To determine whether DHT can induce lipid synthesis in donor sebocytes, cells were treated with 10μM DHT three times over a period of 7 days, stained with NR and analyzed flow cytometrically. The MFI for cells treated with DHT was 2.4-fold higher than those treated with DMSO, indicating that DHT induced lipid synthesis in these primary human sebocytes (Figure 2B). These data are representative of four independent studies.

To investigate the effect of clascoterone on DHT-stimulated lipid production, sebocytes were treated with different concentrations of DHT in the presence or absence of 50μM clascoterone. Positive and negative controls were cells treated with 0.1μM spironolactone or vehicle (DMSO), respectively. DHT dose-dependently induced lipid accumulation in donor sebocytes from 1.3 to 2.4-fold higher than vehicle alone (Figure 3A). Clascoterone at 50μM was able to inhibit lipid synthesis from sebocytes that have been exposed to a wide range of DHT concentrations. This activity is similar to spironolactone. The parallel curves (blue and orange lines) indicate that the difference between lipid levels in sebocytes treated with DHT plus DMSO versus those treated with DHT plus clascoterone was consistent across all concentrations of DHT tested. These results are statistically significant for all tested concentrations ($P<0.05$).

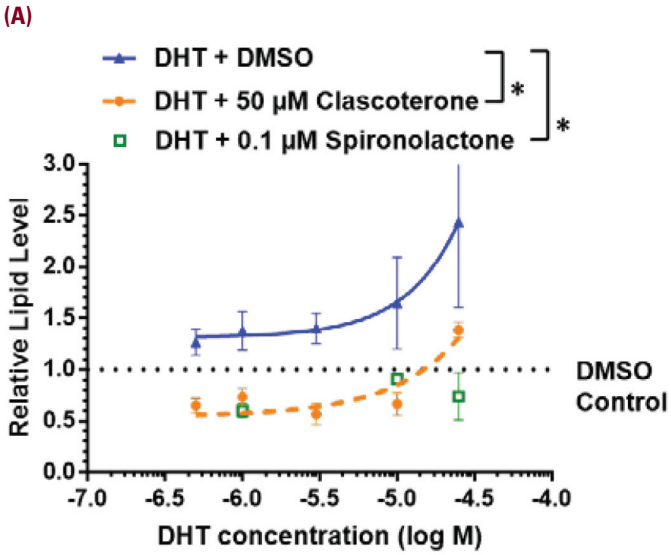
FIGURE 2. DHT induces lipid synthesis in cultured primary human sebocytes. (A) Representative histogram of primary human sebocytes stained with an antibody against the AR or an isotype negative control. R1 and R2 in the dot plots represent large and small cells, respectively, based on the forward (FSC) and side (SSC) scatter dot plots. The corresponding AR histogram plots for large and small cells are shown in red and orange, respectively. (B) Sebocytes treated with 10μM DHT for 7 days were analyzed by NR staining and flow cytometry. The histogram shown is representative of 4 independent experiments and shows a 2.4-fold increase in intracellular lipid levels (MFI 26/11= 2.4).

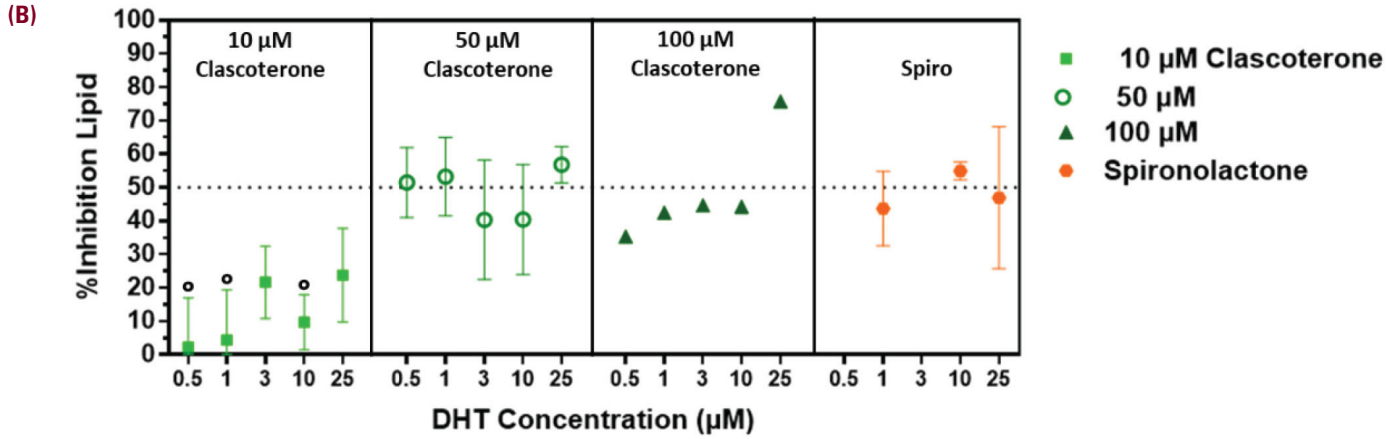


Additionally, clascoterone was titrated for each of the DHT concentration used (Figure 3B). Percent inhibition was calculated based on the percentage of NR positive cells after treatment with DHT plus DMSO alone. Almost all data points are statistically significant compared to the DMSO control except for 3 data points as indicated by °. The data demonstrate that regardless of DHT concentration, 50 and 100μM clascoterone resulted in an approximately 50% reduction in DHT-induced intracellular lipid levels, similar to spironolactone's activity.

To confirm the results from Figure 3B, sebocytes from four additional donors were obtained, and clascoterone's ability to inhibit the production of lipids downstream of the AR was analyzed. Spironolactone was used as a positive control, while OG was analyzed in these donors concurrently. The concentration of all compounds used was the highest that was determined to be non-toxic to the cells (50μM clascoterone, 3μM OG, and 3μM spironolactone) in the presence of 10μM DHT. The data from donors 1, 2, and 3 treated with 10μM DHT and either 50μM clas-

FIGURE 3. Inhibition of DHT-stimulated lipid synthesis by clascoterone in primary human sebocytes. (A) Sebocytes were treated as indicated for 7 days. Lipid accumulation was assessed in 3 different sebocyte donors following flow cytometry of NR stained cells and is expressed relative to the vehicle-alone control (0.1% DMSO). Data are presented as the mean lipid accumulation ± SD of four independent experiments. All values for the positive control DHT vs the negative control DMSO are significant ($P<0.005$), based on multiple t tests with Holm-Sidak method correction, as well as comparison of DHT+DMSO vs clascoterone or DHT+DMSO vs spironolactone ($^*P<0.05$), based on parametric 2-tailed t test (B) Clascoterone was titrated with 5 DHT concentrations (as indicated). Data are presented as the mean % lipid inhibition ± SD for four independent experiments using sebocytes from 3 donors. ($P<0.05$ for all data points vs DMSO except for 3 points as indicated by °, based on Wilcoxon signed rank 2-tailed t test). The lipid inhibition by clascoterone at both 50 and 100μM are not significantly different from inhibition by spironolactone, based on parametric 2-tailed t test. For (C), the data are presented as % inhibition of lipid production by 50μM clascoterone, 3μM OG, 3μM Spiro in the presence of 10μM DHT. % inhibition was calculated based on the percent of NR positive cells after treatment with 10 μM DHT + 0.1% DMSO (no compound control). OG was not tested in donors 1, 2, and 3. Solid black lines indicate mean %inhibition in tested donors. The *P* values vs the DHT control were only significant for clascoterone and spironolactone ($*P<0.05$) based on Wilcoxon signed rank 2-tailed t test.





coterone or 3μM spironolactone were included so that there are seven relevant data points for clascoterone and spironolactone and four data points for OG. As would be expected from cells derived from a heterogeneous group of patients, there is high variability in response to the test compounds amongst sebocyte donors (Figure 3C). For example, amongst the seven donors tested, the lower limit for clascoterone inhibition of DHT-induced lipid production was 15% inhibition in Donor 6 and the higher limit was 69% in Donor 4. Importantly, the inhibition of lipid production is comparable between clascoterone, OG and spironolactone within the same donor, although *P* values versus the vehicle-only control were significant only for clascoterone and spironolactone inhibition of DHT-induced lipid synthesis ($P<0.05$). This is likely due to the lower number of donors tested with OG. These data show that clascoterone is

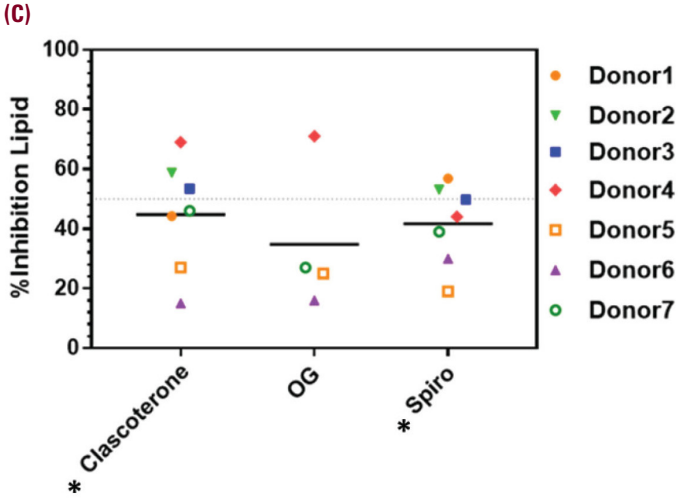
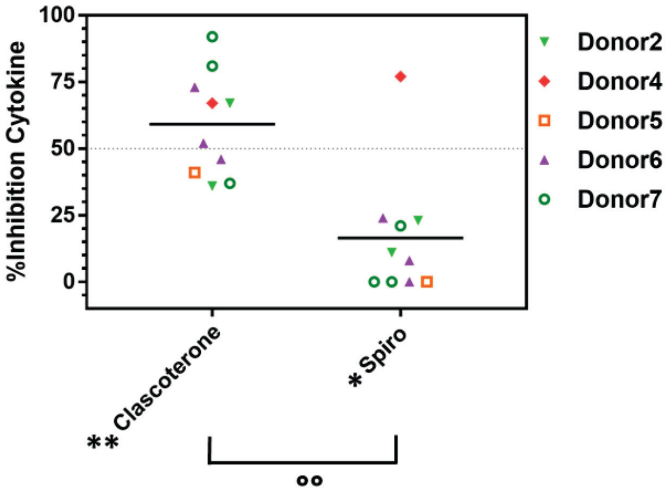


TABLE 1.

Clascoterone Inhibits DHT-induced Cytokines in Sebocytes. Inhibition Values of the 3 cytokines tested in the 5 donors plotted in Figure 4. (-) denotes cytokine was not detectable.

%Inhibition Cytokine	Donor2			Donor4			Donor5			Donor6			Donor7		
	IL8	IL6	IL1ß	IL8	IL6	IL1ß	IL8	IL6	IL1ß	IL8	IL6	IL1ß	IL8	IL6	IL1ß
Clascoterone	--	67	36	67	--	--	41	--	--	52	73	46	37	92	81
Spironolactone	--	23	11	77	--	--	0	--	--	8	0	24	21	0	0

FIGURE 4. Clascoterone inhibits DHT-induced inflammatory pathways in cultured sebocytes. Culture supernatants from the experiments described in Figure 3C were analyzed for IL8, IL6, and IL1ß levels. %Inhibition was calculated relative to the no compound control (10μM DHT + 0.1% DMSO). Data points are the mean of the triplicate wells from sebocyte culture of the indicated donor. Solid black lines indicate the mean inhibition in all seven donors. *P* values for clascoterone and spironolactone vs DMSO are significant ($^{*}P<0.05$, $^{**}P<0.005$) based on Wilcoxon signed rank 2-tailed t test. *P* values for spironolactone vs clascoterone are significant ($^{\circ\circ}P<0.005$), based on parametric 2-tailed t test.



a moderately potent inhibitor of lipid production downstream of the AR in cultured primary human sebocytes.

Clascoterone Inhibits DHT-Induced Activation of Inflammatory Pathways in Sebocytes

To test for cytokine secretion in these sebocytes, the cell culture media that was collected on days 3, 5, and 7 from cells treated and analyzed for lipid production (Figure 3B) was tested for the presence of IL8, IL6, and IL1β utilizing bead-based ELISA assays (Figure 4). The concentration of all compounds used was the highest that was determined to be non-toxic to the cells (50μM clascoterone, and 3μM spironolactone) in the presence of 10μM DHT. Percent inhibition was calculated relative to the DHT plus DMSO control. The *P* values for clascoterone and spironolactone vs DMSO were significant, and clascoterone inhibited DHT-stimulated cytokine production consistently better than spironolactone ($P<0.005$). Table 1 details the specific cytokines plotted in Figure 4, as a list of %inhibition of detectable cytokines from each donor. Overall, the data demonstrate that clascoterone is a moderately potent inhibitor of proinflammatory pathways.

DISCUSSION

Clascoterone is a novel androgen antagonist with strong potential for use as a topical acne treatment. To date, there is no registered topical antiandrogenic treatment for acne. While direct inhibition of DHT binding to the AR in sebocytes is the proposed mechanism of action of clascoterone, it has not yet been proven. The present study demonstrates that clascoterone binds to the AR with high affinity in a cell-free competitive binding assay and inhibits DHT-stimulated signaling downstream of the AR in cultured cells. Clascoterone had a strong antagonistic effect on the production of lipids and activation of inflammatory pathways downstream of the AR in cultured human primary sebocytes. These results suggest that clascoterone directly competes with DHT for binding to the AR to attenuate signaling necessary for acne pathogenesis.

Although the NR stain used in these studies does not discriminate between different lipid types, the inhibition of lipid production is comparable between clascoterone, OG, and spironolactone within the same donor.

OG inhibits ACC, an enzyme which plays a key role in the synthesis of the fatty acids that are incorporated into sebaceous glands and is downstream of several signaling pathways, including the AR.[21] However, a Phase 3 clinical trial with OG failed to meet the designated endpoints. Spironolactone is an orally administered, FDA-approved, antiandrogen used to treat high blood pressure and heart failure. However, it has been prescribed off-label for several years to treat adult female patients with acne. It is a direct inhibitor of both AR signaling and androgen production, and has been shown to reduce sebum production in vivo.[22] There have been no publicized placebo-controlled studies to determine the efficacy of oral spironolactone in treating acne, but several retrospective analyses have demonstrated that it is an excellent therapeutic in the treatment of adult female acne.[23] One such study included male patients, but treatment was stopped after several men developed gynecomastia.[16,23] Significantly, the previous clinical studies of clascoterone were in men[20] while spironolactone is only deemed safe for use to

treat acne in women. Although both compounds inhibit signaling downstream of AR activation, and both have comparable lipid inhibitory activities, clascoterone demonstrated a greater ability to antagonize DHT-stimulated cytokine secretion in primary human sebocytes in culture.

There is currently no topical acne treatment that has proven to be efficacious at inhibiting both lipogenic and pro-inflammatory signaling. With its demonstrated tolerabilty, local and non-systemic effects, and its inhibition of androgen-induced signaling pathways that contribute to lipid and cytokine synthesis, clascoterone profiles as an ideal candidate to be the first topical antiandrogenic acne treatment.

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C. Rosette and M. Gerloni contributed to research design, analysis, data interpretation and wrote the manuscript. F. Agan performed the research experiments. Luigi Moro and Alessandro Mazzetti critically revised the manuscript. All authors approved the submitted version.

DISCLOSURES

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REFERENCES

1. Makrantonaki E, Ganceviciene R, Zouboulis C. An update on the role of the sebaceous gland in the pathogenesis of acne. *Dermatoendocrinol.* 2011;3:41-49.
2. Williams HC, Dellavalle RP, Garner S. Acne vulgaris. *Lancet.* 2012;379:361-372.
3. Zouboulis CC, Jourdan E, Picardo M. Acne is an inflammatory disease and alterations of sebum composition initiate acne lesions. *J Eur Acad Dermatol Venereol.* 2014;28:527-532.
4. Melnik BC, Schmitz G. Role of insulin, insulin-like growth factor-1, hyperglycaemic food and milk consumption in the pathogenesis of acne vulgaris. *Exp Dermatol.* 2009;18:833-841.
5. Strauss JS, Kligman AM, Pochi PE. The effect of androgens and estrogens on human sebaceous glands. *J Invest Dermatol.* 1962;39:139-155.
6. 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.
7. Zouboulis CC. Sebaceous gland receptors. *Dermato-endocrinology.* 2009; 1:77-80.
8. Lee WJ, Jung HD, Chi SG, et al. Effect of dihydrotestosterone on the upregulation of inflammatory cytokines in cultured sebocytes. *Arch Dermatol Res.* 2010;302:429-433.
9. Nagy I, Pivarcsi A, Kis K, et al. Propionibacterium acnes and lipopolysaccharide induce the expression of antimicrobial peptides and proinflammatory cytokines/chemokines in human sebocytes. *Microbes Infect.* 2006;8:2195-2205.
10. Kim J. Review of the innate immune response in acne vulgaris: activation of Toll-like receptor 2 in acne triggers inflammatory cytokine responses. *Dermatology.* 2005;211:193-198.
11. Trivedi NR, Gilliland KL, Zhao W, et al. Gene array expression profiling in acne lesions reveals marked upregulation of genes involved in inflammation and matrix remodeling. *J Invest Dermatol.* 2006;126:1071-1079.
12. Kistowska M, Gehrke S, Jankovic D, et al. IL-1beta drives inflammatory responses to propionibacterium acnes in vitro and in vivo. *J Invest Dermatol.* 2014;134:677-685.
13. Zouboulis CC, Dessinioti C, Tsatsou F, et al. Anti-acne drugs in phase 1 and 2 clinical trials. Expert Opin Investig Drugs. 2017;26:813-823.
14. Layton A. The use of isotretinoin in acne. *Dermato-endocrinology.* 2009;1:162-169.
15. 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;5:37-50.
16. Sato K, Matsumoto D, Iizuka F, et al. Anti-androgenic therapy using oral spironolactone for acne vulgaris in Asians. *Aesthetic Plast Surg.* 2006;30:689-694.
17. Hunt DW, Winters GC, Brownsey RW, et al. Inhibition of sebum production with the acetyl coenzyme a carboxylase inhibitor olumacostat glasaretil. *J Invest Dermatol.* 2017;137:1415-1423.
18. Dermira. news release 2018, http://investor.dermira.com/news-releases/news-release-details/dermiras-two-phase-3-trials-evaluating-olumacostat-glasaretil. Accessed September 20, 2018.
19. 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;54:881-886.
20. 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 vs. placebo and tretinoin 0.05% cream. *Br J Dermatol.* 2011;165:177-183.
21. Melnik BC. Olumacostat glasaretil, a promising topical sebum-suppressing agent that affects all major pathogenic factors of acne vulgaris. *J Invest Dermatol.* 2017;137:1405-1408.
22. Goodfellow A, Alaghband-Zadeh J, Carter G, et al. Oral spironolactone improves acne vulgaris and reduces sebum excretion. *Br J Dermatol.* 1984;111:209-214.
23. Trivedi MK, Shinkai K, Murase JE. A Review of hormone-based therapies to treat adult acne vulgaris in women. *Int J Womens Dermatol.* 2017;3:44-52.

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