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 ORIGINAL ARTICLE

Hypothalamic-Pituitary-Adrenal Axis Response in Patients With Acne Vulgaris Treated With Clascoterone

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ABSTRACT

Background: Clascoterone cream 1% is a topical androgen receptor inhibitor approved to treat acne vulgaris in patients ≥12 years of age. This report provides details of patients who developed laboratory signs of hypothalamic-pituitary-adrenal (HPA) axis suppression without clinical signs of adrenal suppression during the clascoterone development program.

Methods: Two open-label, multicenter, Phase 2 trials evaluated HPA axis suppression in patients with moderate-to-severe acne vulgaris. Study 1 (NCT01831960) enrolled cohorts of adults ≥18 years of age and adolescents ≥12 to <18 years of age. Study 2 (NCT02720627) enrolled adolescents 9 to <12 years of age. Patients applied clascoterone twice daily at maximum-exposure dosages for 14 days. Adrenal suppression was evaluated via cosyntropin stimulation test (CST) at baseline and day 14. Patients with an abnormal CST result (serum cortisol level ≤18 µg/dL) had a follow-up CST approximately 4 weeks later. Blood was collected for pharmacokinetic analysis. Other safety assessments included adverse events (AEs), physical examination/vital signs, and electrocardiography.

Results: Overall, 5/69 clascoterone-treated patients had an abnormal CST result on day 14, including 1/20 adults, 2/22 patients aged ≥12 to <18 years, and 2/27 patients aged 9 to <12 years. All patients had normal cortisol levels at follow-up testing approximately 4 weeks later. No relationship was observed between abnormal CST results and clascoterone plasma concentrations or the amount of study drug applied. No clinically relevant AEs or clinically significant changes in safety measures were observed in patients with adrenal suppression.

Conclusion: Clascoterone induced laboratory evidence of mild, reversible HPA axis suppression under maximum-use exposure.

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INTRODUCTION

Acne vulgaris is a common, chronic skin disease characterized by open or closed comedones and inflammatory lesions.[1] The pathogenesis of acne is multifactorial, and key factors include follicular hyperkeratinization, microbial colonization with *Cutibacterium acnes*, sebum production, innate and acquired immunity, diet, and genetic and nongenetic factors.[1] Puberty is associated with an increase in androgen levels and sebum production, and these events correlate directly with the development of acne.[2]

Clascoterone cream 1% is an androgen receptor inhibitor indicated for the topical treatment of acne vulgaris in patients ≥12 years of age at a recommended dosage of approximately 1 g applied twice daily.[3] Clascoterone was found to be safe and effective in 2 identical Phase 3 trials with treatment for up to 12 weeks and a long-term extension trial with treatment for up to 9 months in patients ≥9 years of age with facial acne vulgaris.[4,5] In vitro, clascoterone inhibits the binding of dihydrotestosterone (DHT) to the androgen receptor and decreases DHT-stimulated production of sebum components and inflammatory cytokines.[6,7]

Steroids and steroidal molecules have the potential to interfere with the endogenous hypothalamic-pituitary-adrenal (HPA) axis, which regulates cortisol secretion in a tightly controlled negative feedback loop.[8,9] Prolonged adrenal suppression by steroid treatment can lead to atrophy of the adrenal glands and functional deficiency in the HPA axis, and failure of adequate preventative measures may lead to unnecessary morbidity and even death.[8,9] Corticosteroid treatments such as dexamethasone and triamcinolone acetonide are associated with HPA axis suppression[1,10]; in contrast, treatment with the mineralocorticoid antagonist spironolactone can activate the HPA axis.[11] In preclinical studies, clascoterone was rapidly metabolized by skin and plasma esterases to cortexolone, a natural intermediate of corticosteroid synthesis with only weak glucocorticoid activity, and systemic exposure to clascoterone and cortexolone in human patients applying topical clascoterone cream was limited even after maximum-use exposure for 2 weeks.[12-14] Due to the steroidal structures of clascoterone and cortexolone, the potential of topical clascoterone to suppress the HPA axis was evaluated in 2 maximum-use Phase 2 trials; based on the results, monitoring for adrenal suppression was not required for the Phase 3

trials. Laboratory signs of HPA axis suppression developed in 5 patients during the Phase 2 maximum-use trials of clascoterone. Here, we describe those cases and review the risk of HPA suppression with the recommended dosing of clascoterone cream 1%.

MATERIALS AND METHODS

Study Design

Study 1 (clinicaltrials.gov NCT01831960; 171-7175-202) was an open-label, multicenter trial of clascoterone cream 1% in separate cohorts of adults and adolescent patients with acne vulgaris (Cohort 1 [≥18 years of age] and Cohort 2 [≥12 to <18 years of age]); the study was previously published, including an overall summary of HPA suppression data.[13] Study 2 (clinicaltrials.gov NCT02720627; CB-03-01/28) was an open-label, multicenter trial of clascoterone cream 1% in adolescent patients 9 to <12 years of age with acne vulgaris. The study protocols, consent forms, participant recruitment materials, and other relevant documents were submitted to an institutional review board for review and approved prior to study initiation. The trials were conducted in accordance with Title v21 of the US Code of Federal Regulations, the International Conference on Harmonisation guidelines, current Good Clinical Practice principles, the Declaration of Helsinki, and local regulatory requirements. All patients and their parents or guardians provided written informed consent before enrollment.

Study Population

The eligibility criteria for Study 1 were previously described.[13] Briefly, male and female patients with moderate-to-severe facial acne vulgaris (Investigator's Global Assessment [IGA] Grade 3 or 4) and obvious acne on the chest and/or back were eligible. Patients were enrolled in 2 separate cohorts: Cohort 1, including patients ≥18 years of age, and Cohort 2, including patients ≥12 to <18 years of age. For Study 2, male and female patients 9 to <12 years of age with moderate-to-severe facial acne vulgaris (IGA Grade 3 or 4) and obvious acne on the trunk (ie, shoulder, upper chest, and/or back) were eligible. Patients were excluded from either study if they were pregnant, lactating, or planning to become pregnant during the study; had a body mass index—for-age percentile >95% or >32.0 kg/m^2 (Study 1, Cohort 1); had previously used systemic antibiotics within 2 weeks, topical anti-acne medication containing retinoids, or systemic spironolactone within 4 weeks, or systemic retinoid therapy within 3 months of baseline; or topical corticosteroids (including inhaled and intranasal corticosteroids) within 2 weeks or systemic corticosteroids (including intramuscular and intralesional injections) within 4 weeks of the cosyntropin stimulation test (CST).

Treatment

In Study 1, adult patients and adolescent patients with a body surface area >1.6 m^2 applied 6 g of clascoterone cream 1% to their entire face, shoulders, upper chest, and upper back twice daily for 14 days. Patients <18 years of age with a body surface area ≤1.6 m^2 applied 4 g of clascoterone cream 1% twice daily. In Study 2, patients applied 2 g of clascoterone cream 1% to their entire face and trunk twice daily for 14 days.

Assessments

In both studies, a CST was performed at baseline and again on day 14, within 1 hour of the same time of day as the baseline CST. Any patient with an abnormal CST result, defined as a serum cortisol level ≤18 µg/dL 30 minutes post stimulation, at day 14 returned approximately 4 weeks later for a follow-up CST. The serum cortisol assays were analyzed at ACM Global Central Laboratory (Rochester, NY). All tubes of returned cream were weighed to determine the amount of test article used. Blood samples for pharmacokinetic analysis were collected at various time points, including pre-dose on day 14, and approximately 12 hours after the evening application on the prior day, in both studies. All plasma samples were frozen after collection and analyzed by MicroConstants (San Diego, CA). Local and systemic adverse events (AEs) were recorded throughout the study, and physical examination, vital signs, and electrocardiograms were performed at baseline and day 14.

Statistical Analyses

Individual patient-level data are provided, and no statistical analysis was performed.

RESULTS

Study Population

A total of 42 patients (Cohort 1, n = 20; Cohort 2, n = 22) were enrolled in Study 1; all completed the study and were evaluable for HPA suppression.[13] A total of 27 patients were enrolled in Study 2; all completed the study, and 23 were evaluable for HPA suppression.

CST Results

Across both studies, 5 patients treated with clascoterone had an abnormal CST result at day 14: three from Study 1 and two from Study 2. These included 1 adult patient (Study 1, Cohort 1), 2 adolescent patients ≥12 to <18 years of age (Study 1, Cohort 2), and 2 adolescent patients 9 to <12 years of age (Study 2). Baseline demographic and clinical characteristics of these patients are presented in Table 1. All patients were female and White, with moderate IGA scores at baseline. Details of the CST results are shown in Table 2. At baseline, post-CST cortisol levels for all 5 patients were >18.0 µg/dL (range, 18.2–32.8), although Patient 5 had a borderline result at baseline (18.2 µg/dL). After treatment with clascoterone cream 1%, post-CST cortisol levels in these patients shifted to ≤18 ug/dL at the day 14 assessment (range, 14.9–18.0). Patients with abnormal CST results were followed up for at least 4 weeks after completion of the treatment period at day 14. All affected patients' post-CST cortisol levels at the follow-up test had returned to >18.0 µg/dL (range, 19.5–30.5). Affected patients in Study 1 used 105.8 to 167.9 g total of clascoterone, while affected patients in Study 2 used 50.7 and 56.0 g of clascoterone (Table 2).

Pharmacokinetics of Clascoterone Cream 1% in Patients With Normal and Abnormal CST Results

Predose plasma clascoterone concentrations on day 14 were available for both studies. In all age groups, morning trough plasma concentrations of clascoterone in patients with HPA axis suppression based on CST results were within the range of values observed in patients without HPA axis suppression, and no correlation was observed between plasma concentration and HPA axis suppression (Figure 1). The steady-state trough plasma concentration of clascoterone was below the limit of quantitation (<0.25 ng/mL) in many patients, including all patients ≥12 to <18 years of age (Study 1, Cohort 2).

TABLE 1.

Baseline Demographic and Clinical Characteristics of Patients With HPA Axis Suppression

Parameter	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Age, y	22.4	14.7	14.8	10	10
Sex	Female	Female	Female	Female	Female
Race	White	White	White	White	White
Ethnicity	Not Hispanic or Latino	Not Hispanic or Latino	Not Hispanic or Latino	Not Hispanic or Latino	Not Hispanic or Latino
Weight, kg	68.0	62.1	50.2	43.1	41.6
Height, cm	167.6	161.0	152.4	153.5	152.0
BMI, kg/m^2	24.3	24.0	21.8	18.3	18.0
Baseline IGA score	Moderate	Moderate	Moderate	Moderate	Moderate
Inflammatory lesions	34	21	24	33	35
Noninflammatory lesions	27	41	24	43	20

BMI, body mass index; HPA, hypothalamic-pituitary-adrenal; IGA, Investigator's Global Assessment.

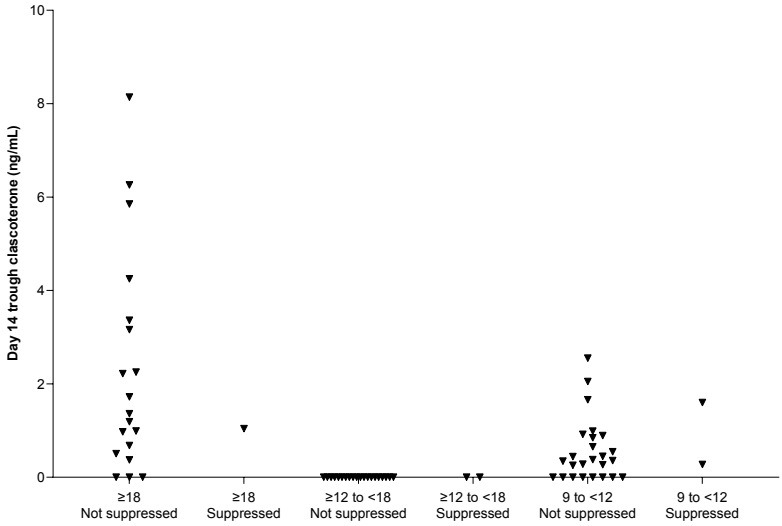
TABLE 2.

Baseline and Posttreatment CST Values for Patients With Abnormal Results

Parameter	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Baseline cortisol, µg/dL	32.8	23.1	26.2	19.5	18.2[a]
Day 14 cortisol, µg/dL	17.7	17.0	14.9	18.0	16.1
Follow-up cortisol, µg/dL	23.4	19.5	22.3	23.0	30.5
Total test article used, g	167.9	158.6	105.8	50.7	56.0

[a]Borderline value. CST, cosyntropin stimulation test.

FIGURE 1. Individual day 14 plasma trough concentrations of clascoterone in patients with normal and abnormal CST results by age group.



CST, cosyntropin stimulation test.

TABLE 3.

Summary of Key Safety Data for Patients With Abnormal CST Results

Parameter	Visit	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Adverse events[a]	--	None	Upper respiratory infection	None	None	None
Local skin reactions[b,c]	Baseline	None	None	None	None	None
	Day 14	None	None	None	None	None
Systolic/diastolic blood pressure, mmHg	Baseline	117/62	109/76	109/79	95/60	125/73
	Day 14	127/64	110/74	121/86	90/60	112/65
ECG	Baseline	Normal	Normal	Normal	Normal	Normal
	Day 14	Normal	Normal	Normal	Normal	Normal
Heart rate, beats/min	Baseline	70	60	69	96	60
	Day 14	82	66	82	88	63
PR duration, msec	Baseline	172	136	147	127	129
	Day 14	178	140	156	137	134
QRS duration, msec	Baseline	94	90	87	79	74
	Day 14	88	78	89	80	73
QT duration, msec	Baseline	375	428	386	354	391
	Day 14	359	414	368	373	399

[a]An abnormal CST result was recorded as an adverse event for all patients. [b]Local skin reactions included assessment of telangiectasia, skin atrophy, striae rubrae, erythema, edema, scaling/dryness, stinging/burning, and pruritus of the face or torso/trunk. [c]Baseline local skin reaction data were evaluated after clascoterone cream 1% application at the baseline visit for Study 1 (Patients 1 to 3) or day 1 for Study 2 (Patients 4 to 5). CST, cosyntropin stimulation test; ECG, electrocardiogram.

Safety

All 5 abnormal CST results were documented as AEs. One additional AE of upper respiratory infection was reported for a patient from Study 1 with an abnormal CST result (Table 3). This event was not serious and was not considered related to the study drug. None of the 5 patients with an abnormal CST result had local skin reactions at baseline, and no change was observed on day 14 after treatment with clascoterone cream. There were no remarkable changes in vital signs in patients with an abnormal CST result, and electrocardiogram results for these patients were normal at baseline and day 14.

DISCUSSION

Pooled data from two Phase 2, open-label trials of twice-daily treatment with clascoterone cream 1% for 2 weeks in 69 patients with moderate-to-severe acne vulgaris were analyzed to provide details of the 5 patients with laboratory evidence of adrenal suppression. At follow-up evaluation approximately 4 weeks after treatment withdrawal, cortisol levels had returned to normal in all patients. No clear relationship was observed between abnormal CST results and clascoterone plasma concentrations or the amount of study drug applied. No clinically relevant AEs were reported and no clinically significant changes in safety measures, including physical examination, vital signs, and electrocardiogram results, were observed in patients with adrenal suppression.

Across the two Phase 2 trials, HPA axis suppression associated with clascoterone cream 1% was assessed under maximum-use conditions in patients with acne vulgaris. Based on the recommended dosing of clascoterone cream 1% at approximately 1 g applied twice daily,[3] the maximum amount of clascoterone cream that would be applied over a 14-day period by a patient who was 100% compliant is 28 g. In contrast, patients in Study 1 applied 4 to 6 g of clascoterone twice daily, depending on age and body surface area, and patients in Study 2 applied 2 g of clascoterone twice daily. Over the 14-day treatment period, the 3 patients with abnormal CST results in Study 1 applied 105.8 to 167.9 g of clascoterone, and the 2 patients in Study 2 applied 50.7 and 56.0 g of clascoterone. Thus, the amount of clascoterone applied in these studies was approximately 2- to 6-fold higher than the recommended dosing. There was no clear relationship between adrenal suppression and clascoterone exposure; patients in Study 1 with normal CST results applied a mean of 153.5 g of clascoterone (range: Cohort 1, 141.0–195.0 g; Cohort 2, 54.7–178.7 g), which is within the range (105.8–167.9 g) used by patients with abnormal results.[13]

All 5 patients with abnormal CST results were female, White, and not Hispanic or Latino. The only differentiating feature was age. Across the 2 trials, 1/20 adult patients (from Study 1, Cohort 1; 5.0%), 2/22 patients ≥12 to <18 years of age (Study 1, Cohort 2; 9.1%), and 2/23 evaluable patients 9 to <12 years of age (Study 2; 8.7%) had abnormal CST results. This suggests that adolescents may be slightly more susceptible to developing laboratory signs of adrenal suppression during clascoterone treatment, although the potential significance of this difference is unclear given the maximum-use exposure in this study and the small number of patients evaluated.

Specific evaluation of clinical symptoms of HPA axis suppression was not required by the US Food and Drug Administration (FDA) and was not performed in the two 12-week, Phase 3, randomized clinical trials of clascoterone cream or in the 9-month long-term extension study.[4,5] Based on the authors' clinical experience, clinical symptoms of HPA axis suppression are rare but may include fatigue, nausea, muscle weakness, loss of appetite, and abdominal pain. Across the two Phase 3 trials and the long-term extension, 1 patient in the long-term extension reported fatigue.[4,5] While this event was severe and noted as a serious AE, it was determined not to be related to the test article.[5] No other AEs relevant to HPA axis suppression were reported in these trials.

One limitation of this analysis was the short-term nature of the treatment period, even with the use of higher-than-recommended dosages. As concomitant anti-acne medications were prohibited to facilitate evaluation of the effects of clascoterone treatment, the studies were unable to assess the effect of clascoterone on HPA axis suppression when multiple acne treatments are used, which may limit generalizability to real-world use. Furthermore, although these were maximum-use studies and included pediatric patients, the trials did not evaluate any other conditions subsequently listed in the FDA-approved labeling for clascoterone cream 1% as having the potential to augment the systemic absorption of clascoterone, such as the use of occlusive dressings.

In conclusion, laboratory signs of HPA axis suppression were observed in 5 patients across two Phase 2, open-label, maximum-use trials of clascoterone cream 1%. In all patients, cortisol levels returned to normal after study drug withdrawal, and no clinically relevant changes in any other safety measures were reported. In the Phase 3 trials, patients applied approximately 1 g of clascoterone cream 1% twice daily, which is the dose that is recommended in the approved labeling for clascoterone cream 1%; no laboratory monitoring of HPA axis suppression was required in the Phase 3 trials, and no systemic AEs attributed to HPA axis suppression were reported.[4] Clascoterone cream 1% is approved for the topical treatment of acne vulgaris in patients ≥12 years of age, and no laboratory monitoring for HPA axis suppression is recommended per the approved labeling.[3]

DISCLOSURES

Dr Bhatia is an advisor, consultant, and investigator for AbbVie, Almirall, Arcutis, Biofrontera, Boehringer Ingelheim, Brickell, Bristol Myers Squibb, Dermavant, Eli Lilly, EPI Health, Ferndale, Galderma, Genentech, InCyte, ISDIN, Johnson & Johnson, La Roche-Posay, LEO Pharma, Novartis, Ortho Dermatologics, Patagonia, Pfizer, Procter & Gamble, Regeneron, Sanofi, Stemline, Sun Pharma, and Verrica. Dr Eichenfield is a former study investigator, a former compensated advisor to Cassiopea, and a current employee of the University of California San Diego, which received compensation from Cassiopea S.p.A. for study participation; he has also served as an investigator, advisor, or consultant for Almirall, Dermata, Galderma, Ortho Dermatologics, and Pfizer. Dr Mazzetti is employed as the chief medical officer for Cassiopea S.p.A. and holds stock options in the company, is a board member of Cassiopea S.p.A., and has served as the chief medical officer of Cosmo Pharmaceuticals. Dr Moro is an employee of Cassiopea S.p.A. and holds stock options in the company. Dr Squittieri is an employee of Sun Pharmaceutical Industries, Inc. Dr Hebert is a former study investigator, a former compensated advisor to Cassiopea, and a current employee of the McGovern Medical School of The University of Texas Health Science Center in Houston, which received compensation from Cassiopea S.p.A. for study participation; she also received an honorarium for serving on the Cassiopea advisory board; all research grant funds were paid to her institution; she is also a consultant and speaker for Almirall, Arcutis, Galderma, InCyte, and Pfizer.

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