The Treatment of Inflammatory Facial Dermatoses With Topical Corticosteroids: Focus on Clocortolone Pivalate 0.1% Cream

Leon H. Kircik MD FAAD[a] and James Q. Del Rosso DO FAOCD[b]
[a]Indiana University School of Medicine, Indianapolis, IN
Mount Sinai Medical Center, New York, NY; DermResearch, PLLC, Louisville, KY
[b]Valley Hospital Medical Center, Las Vegas, NV; Touro University College of Osteopathic Medicine, Henderson, NV
Las Vegas Skin & Cancer Clinics, Dermatology and Cutaneous Surgery, Las Vegas and Henderson, NV

ABSTRACT

Objective: Study results evaluating the efficacy and safety of clocortolone pivalate 0.1% cream in the treatment of adults, young children, and infants with inflammatory facial dermatoses are reported in this article. Clocortolone pivalate 0.1% cream, indicated for the relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses, is a mid-potency topical corticosteroid (Class 4) that has been studied and used extensively to treat a variety of corticosteroid-responsive inflammatory dermatoses, many of which often involve facial skin in both adults and children.

Methods: Clocortolone pivalate 0.01% cream was applied to affected facial skin in subjects presenting with seborrheic dermatitis, contact dermatitis, atopic dermatitis, or psoriasis. Application was completed three times daily for 21 days. Assessments of erythema, edema, transudation, lichenification, scaling, pruritus and/or pain were completed at baseline and Days 4, 7, 14, and 21. Overall therapeutic response was assessed at all follow-up visits. Forty-nine subjects were entered, ranging in age from 1 month to 88 years of age. Thirty-eight subjects completed the studies, with 11 subjects lost to follow-up after the first visit. Individuals between the ages of 13 and 19 years were pre-emptively excluded to avoid potential application of a corticosteroid to acne-affected or acne-prone skin.

Results: Treatment with clocortolone pivalate 0.1% cream resulted in decreases in erythema, edema, transudation, lichenification, scaling, and pruritus/pain in 76% of treated study subjects. The overall therapeutic response in approximately two-thirds of the subjects (68%) was rated as good to excellent. There were 7 adverse events noted over the course of the study that were judged to be related to treatment, all of which were cutaneous and localized to the site of application (acneiform eruptions, burning, and folliculitis).

Conclusion: Clocortolone pivalate 0.1% cream was effective in relieving the signs and symptoms of corticosteroid-responsive inflammatory dermatoses involving facial skin, including seborrheic dermatitis, contact dermatitis, atopic dermatitis, and psoriasis. Overall, the safety profile was favorable and devoid of any treatment-related serious adverse events.

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INTRODUCTION

Seborrheic dermatitis and atopic dermatitis are well recognized as common facial dermatoses. Both irritant and allergic contact dermatitis may involve any anatomic location, with facial involvement sometimes noted depending on the contactants involved and patterns of cutaneous exposure. Facial psoriasis is perceived to be relatively uncommon by comparison, however, facial skin may be affected in 17% to 46% of patients with psoriasis.[1] Atopic dermatitis flares may sometimes be localized to the eyelids and/or the post auricular region, with or without involvement of other facial areas.[2]

The most commonly encountered skin disorders that fall under the umbrella of corticosteroid-responsive dermatoses are seborrheic dermatitis, psoriasis (plaque type), and eczematous dermatoses such as atopic dermatitis and contact dermatitis, As these entities are very common, therapies for these disorders are well established and widely published. However, data are more limited on the treatment of only facial involvement for most of these disorders. Even with larger clinical trials, subset analyses evaluating efficacy and safety with treatment of the face alone is not typically reported. Therapeutic response and adverse event profiles related to specific treatments of facial skin involve unique challenges, as the patient's desire for a more rapid response is usually greater, and visible adverse reactions are more psychologically bothersome to many patients, especially those that may be persistent.

Facial skin is different from other body locations in a number of ways.[3] The skin on the face is thinner and pilosebaceous units are much more numerous. Due to regular exposure of facial skin to environmental factors, climatic changes, and many contactants, such as products used for personal hygiene, skin care,

FIGURE 1. Percentage of subjects with improvement at day 28.

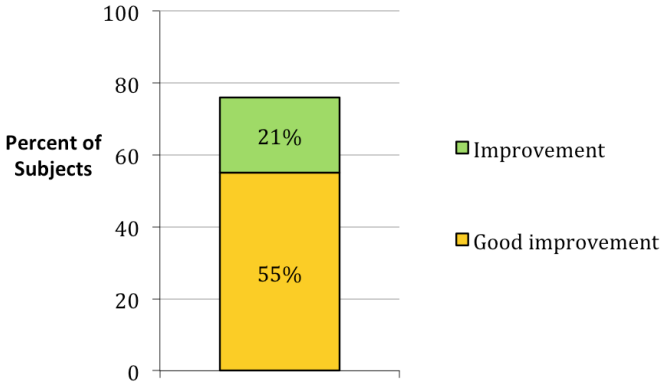
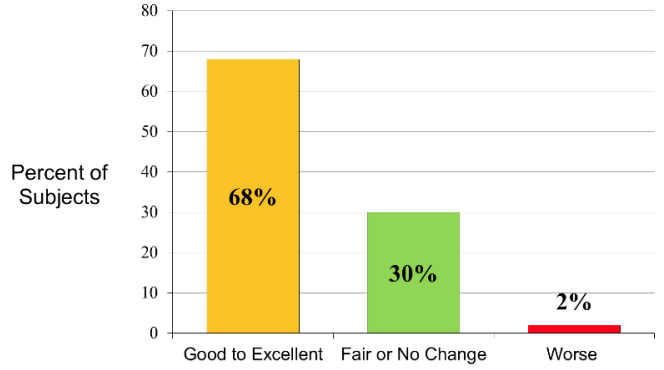


FIGURE 2. Percentage of subjects with improvement at day 21.



or cosmetic purposes, transepidermal water loss (TEWL) may be increased secondary to damage to the stratum corneum (SC) permeability barrier. The decreased hydration of facial skin SC may increase skin sensitivity resulting in reduced tolerability to applied products, including some topical corticosteroid (TC) formulations, and increased percutaneous penetration. An important clinical observation is that facial skin is more sensitive to the adverse effects of TC with a high predilection for atrophy, telangiectasia, persistent erythema and edema, rosaceaform eruptions, perioral dermatitis, and acneiform eruptions.[4]

Despite the common awareness in dermatology that TCs should be used cautiously when treating facial skin, hard data from clinical studies on the incidence of adverse reactions to individual TC formulations applied specifically to facial skin are not available.[2] One reason for this is the lack of detailed reporting requirements at the time when many TCs were studied years ago. Additionally, the study designs needed to truly assess for TC-induced adverse reactions on facial skin are much different and more prolonged than protocols used to evaluate for efficacy and tolerability. In this article, the results of a study evaluating the treatment of inflammatory facial dermatoses with clocortolone pivalate 0.1% cream is reported. Clocortolone pivalate 0.1% cream, indicated for the relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses, is a mid-potency TC (Class 4). The chemical structure of clocortolone pivalate is similar to flumethasone pivalate (Locorten), a TC that is approved for use in Canada. Both flumethasone and clocortolone pivalate are fluorinated, although the structural details of clocortolone pivalate are distinctly different with the fluorine atom in the 6α position and the chlorine atom in the 9α position of the core nucleus. This positioning of the halogen atoms provides Class 4 efficacy for clocortolone pivalate, with a favorable efficacy and safety profile based on clinical studies in adults and children.[5] An overall discussion of TC use on the face is also included below based on literature review.

METHODS

Forty subjects <12 years of age and >19 years of age were enrolled in this open-label study. The age exclusion between 13 and 19 years of age was mandated within the final study protocol to avoid acne-affected and acne-prone skin as a potential complicating factor that could affect study evaluations. All enrolled subjects were diagnosed with one of four inflammatory dermatoses involving the face (Table 1), including seborrheic dermatitis, contact dermatitis, atopic dermatitis, and psoriasis. Subjects were excluded if they had applied a TC to facial skin within one month prior to the study. Concurrent medications during the study that could influence efficacy, skin tolerability, and/or other safety outcomes were prohibited. All subjects used clocortolone pivalate 0.1% cream (Cloderm® Cream, Promius Pharma, LLC) 3 times daily (morning, afternoon, evening) for 21 days.

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A baseline evaluation was completed to ensure enrollment of the subject based on inclusion and exclusion criteria required in the protocol. Efficacy and safety assessments were completed at Days 4, 7, 14, and 21. Assessment of the level of improvement based on evaluation of specific clinical features was documented at each follow-up visit using the following ranking system: Good Improvement, Improvement, No Improvement. Improvement ratings were determined by the levels of change in erythema, edema, transudation (exudation) lichenification, and scaling, and subjective assessments of the degree of relief from pruritus and/or pain. An additional independent assessment

TABLE 1.

Facial Inflammatory Dermatoses in Patients Who Completed the Trial (n=38)	
Diagnosis	**Number of Subjects**
Seborrheic Dermatitis	19
Contact Dermatitis	6
Atopic Dermatitis	6
Psoriasis	3
Sunburn	1
Alopecia Areata	1
Wind-Exposure Dermatitis	1
Miliaria Rubra	1

parameter, the overall therapeutic response was collectively based on the above parameters, rapidity of onset of a response, and the maximum degree of lesion clearing using the following rating system: Excellent, Good, Fair, No Change, or Worse.

Safety was assessed both from reporting by study subjects and through updated history and clinical assessments completed at each study visit.

RESULTS

The demographic characteristics of the subjects enrolled is shown in Table 2. The majority of subjects were Caucasian females. The age of enrolled ranged from 1 month to 88 years.

Thirty-eight subjects were included in the final efficacy analyses. Eleven subjects failed to return after the baseline visit (lost to follow-up).

At the end of treatment, 29 subjects (76%) were rated as improved when their condition at the initial and final visits were compared. Determination of a ranking of Improvement was based on decreases in erythema, edema, transudation, lichenification, scaling, and relief of pruritus and/or pain (Figure 1). Twenty-five subjects (68%) had a good to excellent Overall Therapeutic Response (Figure 2). There were seven adverse events (AEs) reported during the study, judged by the investigator to be probably related to study drug (Table 3). All of these AEs were application site reactions, with one patient, five patients, and one patient exhibiting mild, transient burning upon study drug application, mild acneform eruptions, and folliculitis, respectively.

DISCUSSION

The results of this study show that clocortolone pivalate 0.1% cream, a mid-potency (Class 4) TC, was effective for the treatment of inflammatory facial dermatoses with very few side effects. Six of the seven AEs are known to occur with TC use, especially on facial skin, and resolve after discontinuation of therapy. The very low risk of cutaneous irritation with clocortolone pivalate 0.1% cream is not surprising as the formulation contains three agents that assist in maintaining SC permeability barrier integrity (white petrolatum, stearyl alcohol [long chain fatty acid emollient], and mineral oil) and is lanolin-free, propylene glycol-free, short-chain alcohol-free, and devoid of fragrances. This study is one of the few that was designed to determine the safety and efficacy of TC used to treat facial involvement with one of the common inflammatory dermatoses. Among inflammatory facial skin diseases, the most frequently studied is seborrheic dermatitis (SD).[6,7,8,9,10,11,12] These studies demonstrated the effectiveness and favorable safety profiles of several mid to low-potent TCs for facial SD when used appropriately over short durations of therapy. The TCs evaluated in these studies included desonide 0.05% lotion, hydrocortisone 1% ointment, desonide 0.05% hydrogel, desonide 0.05% cream, hydrocortisone acetate 1% cream, hydrocortisone 1% cream, and clocortolone 0.1% pivalate cream. However, TC cannot be used continuously for prolonged durations for SD or other dermatoses, with facial skin demonstrating a high propensity for TC-induced side effects.[13] This observation is illustrated in one more recent study of a low-potency TC in which 86% of patients with facial SD who had cleared after applying desonide 0.05% cream twice daily for 14 days relapsed at some point over the subsequent 14 days (post-treatment study phase) where no treatment was used.[9]

Flares of atopic dermatitis is frequently treated with TCs but only a few studies have been conducted to evaluate the outcomes of treatment specifically for facial lesions.[2] The effectiveness, safety, and patient acceptability of desonide 0.05% lotion, a low potency (Class 6) TC, was compared to its vehicle lotion for the treatment of facial atopic or seborrheic dermatitis.[6] In the desonide lotion group there were twelve patients with atopic dermatitis and twenty-eight with seborrheic dermatitis. Patients used the lotions twice daily for 3 weeks. Efficacy results for both diagnoses collectively revealed that 57% of patients cleared in the desonide lotion group and 11% cleared in the vehicle group. Cutaneous tolerability was rated as excellent for most patients in the desonide lotion group, with a mean global assessment score of 4.8 on a 5 point scale which ranged from Unacceptable (1) to Excellent (5). Two patients in the desonide lotion group experienced cutaneous adverse events ("rash" and pruritus). It is important to note that several TC compounds and vehicles are widely available as various brands, and most are available as generic formulations. As topical formulations with the same active ingredient and concentration may differ in their pharmacokinetic (PK) properties (ie, active drug release characteristics, percutaneous penetration) and "inert" ingredients, it is not automatically accurate to assume that the efficacy and tolerability results reported with a given brand formulation would be the same with other formulations, especially generic versions where efficacy, tolerability, and PK data are often (but not always) meager or nonexistent.

TABLE 2.

Demographics of Study Subjects	
	Number (%) of Subjects
Gender	
Male	20 (41%)
Female	29 (59%)
Race	
Caucasian	36 (74%)
Black	8 (16%)
Other	5 (11%)
Skin Type	
Normal	24 (49%)
Oily	23 (47%)
Dry	2 (4%)
Age Range	1 month to 88 years (excluding 13 to 19 years)

Another clinical trial[4] compared the efficacy and safety of tacrolimus 0.1% ointment versus fluticasone propionate 0.005% ointment an upper-end mid potency TC (Class 3) for treatment of atopic dermatitis on the face in adults. Approximately 280 patients with moderate or severe disease with at least 10% involvement of face, head, neck, lower anterior neck-upper chest juncture, and nape were enrolled in each group. Patients used the study medications twice daily for 3 weeks. In the fluticasone group, 79% of patients showed marked or excellent improvement or clearance for the facial region specifically as assessed by Physicians' Global Assessment of clinical response. From a subjective perspective, pruritus was reduced by 72% in the fluticasone ointment group vs 69.5% in the tacrolimus group after 7 days, based on use of a visual analog scale. In the fluticasone ointment group, 15% of patients reported application site AEs that were deemed as related to study medication, most frequently skin burning (2.9%) and pruritus (2.2%), with 3% of subjects withdrawing from the study due to an AE.

Treatment of eyelid dermatitis is especially challenging given concerns regarding increased intraocular pressure associated with TC application to the eyelid region.[14] Ocular hypertension has been reported with the use of corticosteroid ophthalmic drops,[15] and there have been multiple reports of ocular hypertension related to prolonged durations of TC application to eyelids and/or the periorbital area.[16,17] Conversely, in a recently conducted retrospective study looking at the correlation between the use of TCs in atopic dermatitis and the risk of glaucoma and cataracts,[18] there were no diagnoses of glaucoma. Two patients out of 88 had corticosteroid-induced cataracts, which were more likely caused by the use of systemic corticosteroids. It was concluded in this particular article that the application of TCs to the eyelids and periorbital region, even over long periods of time, was not related to the development of glaucoma or cataracts in this population of patients. Further research is needed in this area; however, it is not likely that any well-designed studies will be completed in the reasonably near future to definitively resolve the issue of TC application and glaucoma risk.

TABLE 3.

Adverse Events (n=7) Reported Among Enrolled Subjects Who Received Study Drug (N=49)	
Adverse Event	Number of Subjects
Mild Acneform Eruption	5
Folliculitis	1
Mild Transient Burning	1

There has been a conspicuous absence of clinical studies that specifically evaluate outcomes related to the treatment of facial contact dermatitis with a TC. In one older study from 1978, the use of hydrocortisone-17-butyrate, a lower end mid-potency TC (Class 5) was evaluated in patients with inflammatory dermatoses of the face and mucosa, including five patients with contact dermatitis. Data from this study are too limited on facial contact dermatitis to draw any definitive conclusions.

There is a wide range of estimates on the incidence of facial psoriasis. For example, van de Kerkoff (2007) reported facial involvement in 17% to 46% of patients with psoriasis. An open-label study evaluated the use of TC therapy for facial and intertriginous psoriasis (N=20). Fluticasone 0.005% ointment was applied twice daily for 2 weeks then once daily for 2 consecutive days every week for 8 more weeks. Results revealed that more than 50% improvement was noted after 2 weeks in all cases of facial and intertriginous psoriasis.[19] Another interesting finding was that facial and intertriginous areas responded faster than nonfacial and nonintertriginous areas. There were no reports of skin atrophy or telangiectasias noted over the 10-week duration of the study.

CONCLUSION

Facial inflammatory and eczematous dermatoses warrant specific considerations when selecting therapy due to several factors, including the visibility of either the eruption or skin tolerability reactions related to treatment, the need to avoid persistent adverse sequelae, and the importance of maintain SC integrity. Unfortunately, there is a lack of clinical trials that specifically look at the evaluate TC therapy for corticosteroid-responsive facial dermatoses. Many trials exclude facial treatment, while others do not adequately carve out subset analyses based on anatomic location. In the few clinical studies that have been conducted, the use of mid-potency TCs for most cases of seborrheic dermatitis, atopic dermatitis, contact der-

matitis and psoriasis proved to be effective and safe over short courses of therapy for disease flares. In the study reported here, clocortolone pivalate 0.1% cream was effective and safe for the treatment of facial seborrheic dermatitis, atopic dermatitis, and psoriasis. The clocortolone pivalate molecule exhibits unique structural characteristics that impact upon efficacy and may also modify AEs in an advantageous manner. The distinctive halogen positioning and pivalate group produce a TC in the upper end of the mid-potency range. In addition, the cream formulation of clocortolone pivalate, contains three emollient ingredients (white petrolatum, mineral oil, stearyl alcohol) and is devoid of fragrance, propylene glycol, and lanolin, all factors that are favorable when treating inflamed or eczematous skin.

DISCLOSURES

Dr. Kircik serves as as advisor, investigator, consultant, and speaker for Bayer, Galderma, Promius, Stiefel, GSK, LeoPharma, Taro, and Valeant. Dr. Del Rosso has served as an advisor or consultant for: Allergan; Bayer Dermatology; Dermira; Galderma; LeoPharma; Medicis; Onset Therapeutics; Pharmaderm; Primus, Promius, Ranbaxy; Taro; TriaBeauty; Unilever; Valeant/Coria Dermatology, Warner Chilcott. Dr. Del Rosso has served as a speaker or a member of a speakers bureau for: Allergan; Bayer Dermatology; Galderma; LeoPharma; Medicis; Onset Therapeutics; Pharmaderm; Promius; Taro; TriaBeauty; Unilever; Valeant/Coria Dermatology, Warner Chilcott. Dr. Del Rosso has received grants for clinical research from: Allergan, Inc.; Amgen; Coria Laboratories, Ltd.; Galderma Laboratories, L.P.; Intendis Inc.; Medicis Pharmaceutical Corporation; Graceway Pharmaceuticals, LLC; Ortho Dermatology; Onset Therapeutics; Stiefel Laboratories Inc.; Triax Pharmaceuticals; Warner Chilcott. Dr. Del Rosso has no relevant stock ownership.

REFERENCES

1. van de Kerkhof PC, Murphy GM, Austad J, et al. Psoriasis of the face and flexures. *J Dermatog Treat.* 2007;18(6):351-60.
2. Draelos ZD. Use of topical corticosteroids and topical calcineurin inhibitors for the treatment of atopic dermatitis in thin and sensitive skin areas. *Curr Med Res Opin.* 2008;24:985-994.
3. Tagami, H. Location-related differences in structure and function of the stratum corneum with special emphasis on those of the facial skin. *Int J Cosmetic Sci.* 2008;30:413-434.
4. Doss N, Reitamo S, Dubertret L, et al. Superiority of tacrolimus 0.1% ointment compared with fluticasone 0.005% in adults with moderate to severe atopic dermatitis of the face: results from a randomized, double-blind trial. *Br J Dermatol.* 2009;161:427-434.
5. Del Rosso JQ, Kircik L, Clocortolone pivalate 0.1% cream, *JCAD*, July 2012.
6. Freeman S, Howard A, Foley P, et al. Efficacy, cutaneous tolerance and cosmetic acceptability of desonide 0.05% lotion (Desowen®) versus vehicle in the short-term treatment of facial atopic or seborrheic dermatitis. *Australas J Dermatol.* 2002;43:186-189.
7. Papp KA, Papp BA, Dahmer B, et al. Single-blind, randomized controlled trial evaluating the treatment of facial seborrheic dermatitis with hydrocortisone 1% ointment compared with tacrolimus 0.1% ointment in adults. *J Am Acad Dermatol.* Epub. 10.1016/j.jaad.2011.02.032.
8. Kircik LH. Treatment of scalp and facial seborrheic dermatitis with desonide hydrogel 0.05%. *J Clin Aesthetic Dermatol.* 2009;2:32-36.
9. Elewski B. An investigator-blind, randomized, 4-week, parallel-group, multicenter pilot study to compare the safety and efficacy of a nonsteroidal cream (Promiseb® Topical Cream) and desonide cream 0.05% in the twice-daily treatment of mild to moderate seborrheic dermatitis of the face. *Clinics in Dermatology.* 2009;27:S39-S40.
10. Firooz A, Solhpour A, Gorouhi F, et al. Pimecrolimus cream, 1%, vs hydrocortisone acetate cream, 1%, in the treatment of facial seborrheic dermatitis: a randomized, investigator-blind, clinical trial. *Arch Dermatol.* 2006;142:1066-1067.
11. Stratigos JD, Antoniou C, Katsambas A, et al. Ketoconazole 2% cream versus hydrocortisone 1% cream in the treatment of seborrheic dermatitis. A double-blind comparative study. *J Am Acad Dermatol.* 1988;19(5 Pt 1):850-853.
12. Nierman, MM. Safety and efficacy of clocortolone pivalate 0.1% cream, a new topical steroid in atopic dermatitis, contact dermatitis, and seborrheic dermatitis. Presented at North American Clinical Dermatological Society, March 1980. Data on file, Promius Pharma, LLC.
13. Bikowski J. Facial seborrheic dermatitis: a report on current status and therapeutic horizons. *J Drugs Dermatol.* 2009;8:125-133.
14. Kersey JP, Broadway DC. Corticosteroid-induced glaucoma: a review of the literature. Eye. 2006;20:407-416.
15. Nivenius E, van der Ploeg I, Jung K, et al. Tacrolimus ointment vs steroid ointment for eyelid dermatitis in patients with atopic keratoconjunctivitis. *Eye.* 2007;21:968-975.
16. Garrott HM, Walland MJ. Glaucoma from topical corticosteroids to the eyelids. *Clin Experiment Ophthalmol.* 2004;32:224-226.
17. Sahni D, Darley CR, Hawk JL. Glaucoma induced by periorbital topical steroid use – a rare complication. *Clin Exp Dermatol.* 2004;29:617-619.
18. Haeck IM, Rouwen TJ, Timmer-de Mik L, et al. Topical corticosteroids in atopic dermatitis and the risk of glaucoma and cataracts. *J Am Acad Dermatol.* 2011;64(2):275-281.
19. Lebwohl MG, Tan MH, Meador SL, et al. Limited application of fluticasone propionate ointment, 0.005% in patients with psoriasis of the face and intertriginous areas. *J Am Acad Dermatol.* 2001;44:77-82.

ADDRESS FOR CORRESPONDENCE

Leon H. Kircik MD
Physicians Skin Care, PLLC
1169 Eastern Parkway Suite 2310
Louisville, KY 40217
E-mail:.....wedoderm@yahoo.com