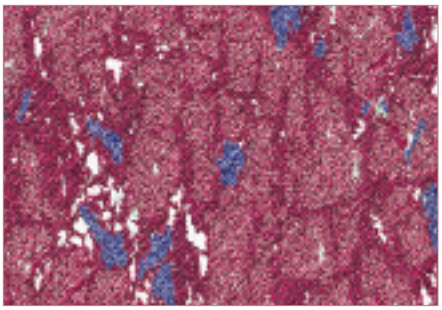

Topical Corticosteroid Therapy for Psoriasis—A Review of Clobetasol Propionate 0.025% Cream and the Clinical Relevance of Penetration Modification

by JAMES Q. DEL ROSSO, DO, FAOCD, FAAD

Dr. Del Rosso is with JDR Dermatology Research/Thomas Dermatology in Las Vegas, Nevada and Touro University Nevada in Henderson, Nevada.

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ABSTRACT

Topical corticosteroids (TCs) have played a central role, over the past several decades, as a treatment for many dermatologic disorders. A number of factors, including potency, anticipated efficacy, vehicle formulation, and patient preference, directly influence the success or failure of any TC. In this article, the author reviews and discusses the current literature on various aspects of TCs for the treatment of plaque psoriasis, including an overview of product selection tendencies of patients, conventional use and formulations of topical clobetasol propionate (CP) 0.05%, and the use of special additives (e.g., penetration enhancers) to increase CP potency. The author highlights data from recent studies that evaluated a new CP cream formulation that incorporates half the concentration of traditional CP (0.025%) without the loss of super-potency (Class I) status and without the use of traditional potency enhancement with propylene glycol.

KEY WORDS: Clobetasol propionate, plaque psoriasis, Topical corticosteroid

Ever since topical hydrocortisone was first introduced, in 1952, as a treatment for eczematous dermatitis, topical corticosteroids (TCs) have maintained a central position in the therapeutic armamentarium for several dermatologic disorders, including psoriasis, atopic dermatitis (AD), contact dermatitis, seborrheic dermatitis, and other inflammatory dermatoses.[1–5] For several years, when highlighting the presence of an indication approved by the United States (US) Food and Drug Administration (FDA) for a TC brought to the US marketplace, product labeling has included the following description: "topical corticosteroids are indicated for the relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses" (CRDs).[6] The list of CRDs could include psoriasis, AD, allergic contact dermatitis, irritant contact dermatitis, dyshidrotic eczema, lichen planus, cutaneous lupus, granuloma annulare, and others.[1,4,5] The diverse biologic properties of TCs appear to contribute directly to their positive therapeutic effects in many skin disorders; these effects include anti-inflammatory properties, stabilization of cellular and lysosomal membranes, reduction in neutrophil and monocyte recruitment, decreased lymphocyte reactivity, modulation of Langerhans cell activity/expression, antiproliferative/antimitotic effects, vasoconstrictive properties, and reduction in mast cell density and reactivity, including immunoglobulin E sensitization.[1,5,7] Nevertheless, the FDA has more recently disbanded the use of the broad CRD category and now restricts disease-state approval to the specific skin disorder evaluated in the pivotal large-scale, randomized, controlled clinical trials (RCTs) that are required during formal product development prior to submission to the FDA for approval.

The FDA-approved indication of a novel TC formulation now specifies the disease state and age group for which it is indicated (e.g., "topical treatment of plaque psoriasis in patients 18 years of age and older").[8] As a result, newer and more potent TC formulations are usually studied in adult subjects with plaque psoriasis. Less often, or especially with lower-potency TCs, some pivotal trials are designed to test the medication in subjects with AD that include adolescent and pediatric age groups.

In addition to the potency and anticipated efficacy of a given TC, vehicle formulation and patient preference are major factors that directly influence the success or failure of TC therapy. The formulation determines the pharmacokinetic (PK) properties of the TC product (e.g., skin penetration, active ingredient release/skin delivery, skin tolerability), and the vehicle characteristics affect whether the patients like the feel of the product (i.e., cosmetic acceptability) and will adhere with application

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

instructions.[1–5,7,9–16] It cannot be assumed that generic formulations containing the same concentration of active ingredient are equivalent to brand formulations that incorporate a different vehicle composition and/or formulation technology, as PK effects, clinical efficacy, skin tolerability, and patient satisfaction and adherence might differ substantially between the two.[1,2,8–10,14,17–22]

In this report, the author provides an overview of managing plaque psoriasis with TCs, discusses product selection tendencies, addresses conventional use and formulations of topical clobetasol propionate (CP) 0.05%, reviews the use of special additives (e.g., penetration enhancers) to increase CP potency, and highlights results from a recent study on a new CP cream formulation.

TCs IN THE MANAGEMENT OF PLAQUE PSORIASIS

Selection. Clinicians often involve TCs early in the management of plaque psoriasis, especially when limited body surface area (BSA) is affected; however, TCs are used for all severities of disease, and several factors—such as patient age, affected anatomic locations, extent of BSA involvement, prior therapies utilized, and other concurrent treatments—affect the potency of agents and the vehicles that are selected.[1–5,7,11,23–26] The literature supports the use of primarily super-potency (Class I) or high potency (Class II) TCs for the treatment of plaque psoriasis, especially to achieve adequate control of a disease flare or persistent psoriatic lesions.[23,26]

Class I TCs are superior to Class II TCs in achieving clearance or near-clearance of psoriatic plaques.[23,26] Limitations of use include general avoidance on certain body locations (e.g., face, inguinal/genital region), necessary application to an extensive BSA, especially over prolonged durations of therapy, and use of Class I TCs in children.[1–5,7,11,23–26] From a practical perspective, specific vehicles might be more applicable to certain body sites due to specific factors, such as ease of application, spreadability, emolliency, lack of residue, and ease of wash-off. Examples of such sites include the scalp, hair-bearing areas, palms, soles of the feet, and large surfaces when diffusely affected (e.g., back). Data suggest that patients prefer to use a vehicle that spreads well and disappears easily into skin, which they reportedly perceive these features to correlate with better efficacy.[1–3,23–26]

A retrospective chart review by Pearce et al [27] evaluated prescribing patterns of 650 patients with psoriasis who attended a group dermatology practice within a large academic medical center.[27] Overall, in 79 percent of patients, a TC was prescribed. Interestingly, 58 percent of patients who received a TC for psoriasis treatment received a super-potent (Class 1) TC agent. In 11 percent of cases, a Class I TC was prescribed along with a systemic agent, a pattern that reflects the well-established concept of combination therapy for psoriasis, especially in cases of greater severity.[1,26,27] Pearce et al also elucidated that approximately one-third of the patients who were then prescribed systemic therapy for psoriasis also received Class I TC therapy.[27] A separate review of RCTs supports, overall, the idea that Class I and Class II TCs are the most effective treatment options, compared to other TCs, for plaque psoriasis, reporting appropriate limitations of use, including short duration of continuous use, avoidance of certain body sites (e.g., face, groin region), and avoidance/extreme caution regarding use in the pediatric population.[26] There is also corroborative evidence that combination-therapy regimens, including the use of higher-potency TCs, are more effective overall than monotherapy approaches for plaque psoriasis.[23,24,26,28]

Take-home point. TCs are the "cornerstone" of most topical regimens for psoriasis.[1–3,7,23,26,27] Class I TC agents are commonly utilized by dermatologists, demonstrate high levels of efficacy, and exhibit greater potential to clear or nearly clear individual psoriatic plaques more effectively than other topical therapies (e.g., TCs, other agents).[23–27] Avoidance of adverse effects (AEs) requires proper use and treatment adherence by patients, as well as regular monitoring of response by a knowledgeable clinician. Long-term management of plaque psoriasis using TCs requires individualized adjustments to the therapeutic approach.[1–3,5,7,11,23,26]

Long-term use. Less data are available on the efficacy and safety of TCs for long-term management of plaque psoriasis.[1–3,11,24–26] An obvious real-world challenge encountered by clinicians when managing chronic and recurrent skin diseases such as psoriasis is balancing the sustained suppression of psoriatic disease with the avoidance of both local and/or systemic AEs of TCs.

As previously stated, Class I TCs provide the greatest opportunity to clear or significantly improve individual plaques of psoriasis, including efficacy that is markedly superior to Class II TCs.[23,26,36] However, chronic, continuous therapy is not recommended due to the potential for AEs.[1–5,11,26] The predominant Class I TC used in dermatology has been CP 0.05% (FDA approved in November 1996 [NDA 19322/S15]), which is currently formulated in several vehicles, all with generic availability (e.g., cream, ointment, emollient cream, solution, hydroethanolic foam, emollient foam, lotion). CP is most often prescribed as a cream or ointment. Halobetasol propionate 0.05% is another commonly used Class I TC, also formulated in several vehicles, with generic availability.[1–3,5,7,13,14,26,36]

With very few exceptions, FDA-approved labeling with a Class I TC states that continuous treatment beyond two consecutive weeks is not recommended, with a total application dosage not to exceed 50g per week.[6,8,37] These recommendations are put in place to reduce the risk of AEs. Application of more than 50g of CP 0.05% cream or ointment over a one-week period has been shown to induce either a reduction in 9:00AM serum cortisol levels or decreased peak insulin stress testing results, and increasing the total weekly application to more than 100g resulted in profound suppression of morning serum cortisol levels.[1]

In an attempt to sustain the long-term control of plaque psoriasis and to reduce the risk of AEs, intermittent regimens of topical CP therapy have been suggested based on reasonably good study outcomes. Combination topical approaches with a vitamin D analog (i.e., calcipotriene) or tazarotene have also been recommended due to favorable outcomes. These intermittent regimens allow for more prolonged treatment to better control plaque psoriasis.[1–3,36,38–43]

Take-home point. Limitations on the use of TCs in FDA-approved labeling, especially in regard to Class I agents, are based on data submitted to the FDA from preclinical research and pivotal clinical trials and serve to reduce the risk of AEs rather than limit the therapeutic benefits of these therapies.[6,8,43] When properly prescribed by knowledgeable clinicians, Class I TCs continue to be an important component of the topical management of plaque psoriasis.[1–3,23–28] Published recommendations on the use of TCs for the long-term management of plaque psoriasis are designed to optimize

efficacy and safety and sustain remission and/or control of the disease.[1–3,23,24,26,37–42]

Adverse effects. Local AEs associated with TCs include telangiectasias, atrophy, persistent erythema, purpura, rosacea-like facial eruptions/perioral dermatitis, acneiform eruptions, folliculitis, tinea incognito, skin tolerability reactions (e.g., stinging, burning), and allergic contact dermatitis.[1–5,11,25,26] Reports of systemic AEs, such as hypothalamic-pituitary axis (HPA) suppression, growth retardation in children, increased intraocular pressure, and cataract formation are relatively uncommon. However, these AEs might occur more often than suspected clinically due to the possibility of remaining clinically undetected for prolonged periods of time.[1,26,29–35] The literature suggests extra caution should be taken in the following circumstances: facial application of TCs due to potential cutaneous and ocular side effects, continuous peripubertal use due to potential growth suppression, and application to large BSAs over a prolonged period of time, or under occlusion due to the potential for HPA suppression.[1–5,26,29–35] Ocular side effects, such as increased intraocular pressure and cataract formation, are associated with long-term application of TCs to periorbital skin.[1,31]

Good judgment and proper follow-up on the part of the clinician are necessary when treating patients with TCs to optimize results and minimize AEs. Most cases of HPA suppression are subclinical and detectable only by laboratory testing, with many resolving after discontinuation of TC therapy, especially if continuous use has not been exceptionally prolonged (i.e., months to years).[1] Nevertheless, multiple cases of TC-induced HPA suppression with adverse clinical sequelae have been reported, often involving the prolonged use of an agent of at least medium potency; HPA suppression is less likely observed in association with the use of a low-potency TC, although cases might occur with chronic and widespread use.[1,32–35] Sporadic cases of TC-induced HPA suppression that manifest with adverse clinical sequelae can occur when TC therapy is unknowingly or erroneously administered over a prolonged duration without proper monitoring by a knowledgeable clinician.[1]

Take-home points. It is important that clinicians select a TC of adequate potency to treat plaque psoriasis, then monitor and adjust the regimen to sustain results while avoiding AEs. Controlling the amount of TC prescribed, specifying the frequency and duration of use, restricting the number of allowed refills, and patient education through reinforcement of proper medication use at each visit will yield optimal therapeutic outcomes of TC therapy in psoriasis.

SAFETY AND EFFICACY DATA FOR A LOWER-CONCENTRATION CP CREAM FORMULATION

There are several factors that influence the efficacy, safety, and PK characteristics of a CP 0.025% cream (Impoyz; Encore Dermatology, Malvern, Pennsylvania) that was recently approved by the FDA. CP 0.025% cream is a Class I TC topical formulation that is applied twice daily for treatment of moderate-to-severe plaque psoriasis in patients 18 years of age or older.[43–45] Unlike prior CP formulations, CP 0.025% cream formulation is free of propylene glycol, short-chain alcohols (e.g., ethanol), and sorbitan sesquioleate, a sorbitol-based emulsifier that is a common contact allergen used in many TC formulations, including CP 0.05% ointment.[6,43–46] Several studies have examined the clinical, PK, and HPA suppression characteristics of CP 0.05%, compared to other available CP formulations containing 0.05% of the active drug and different vehicle compositions.[6,13,14,43,45]

Phase III study design. In two seperately performed, identically designed, 15-day, Phase III, randomized, controlled trials, 543 patients with moderate-to-severe plaque psoriasis were randomized to receive either the CP 0.025% cream (n=354) or the vehicle cream (n=178) for 14 days. The study included adult subjects (average age: 49.5–50.6 years; 49.4–63.1% male). Patients applied their assigned formulation twice daily for 14 days.[43,47] Enrolled subjects were rated by Investigator Global Assessment (IGA) at baseline as moderate (80.7–86.5% had IGA score rating of 3) or severe (13.5–19.3% had IGA score rating of 4) among the study groups. The mean BSA affected in both the active and placebo groups ranged from 6.8 to 9.2 percent (>3% BSA was required in all study groups). The primary efficacy endpoint defined *endpoint success* as the percent of subjects achieving clear (IGA score rating of 0) or almost clear (IGA score rating of 1) with more than a two-grade improvement from baseline.. Skin tolerability and safety was assessed in all treated subjects. Well-established and protocol-approved inclusion criteria, exclusion criteria, and washout periods were used, with institutional review board approval of all study materials and sites and all investigators and staff adherent with recognized clinical study ethics guidelines.

Phase III study outcomes. At Day 8 (results for both studies) endpoint success was achieved in 15.7 percent (n=178) and 14.2 percent (n=176) of the CP 0.025% cream-treated subjects and in 5.6 percent (n=89) and 1.6 percent (n=89) of the vehicle-treated subjects (secondary efficacy endpoint; $p<0.001$). At Day 15, endpoint success was achieved in 30.2 percent (n=178) and 30.1 percent (n=176) of subjects treated with CP 0.025% cream and in 9.0 percent (n=89) and 9.7 percent (n=89) of the vehicle-treated subjects, for both studies, (primary efficacy endpoint; $p<0.001$) (Figure 1).[43,47] The reduction in BSA at the end of the study (Day 15) relative to baseline was greater in the CP 0.025% cream-treated group than in the vehicle-treated group ($p<0.001$ in both studies): -28.9 percent (n=178) and -25.1 percent (n=176) versus 6.1 percent (n=89) and -7.4 percent (n=89). Figures 2 and 3 depict patients from the Phase III RCTs, demonstrating visible clinical improvement following 14 days of active treatment; however, neither patient achieved endpoint success according to the study protocol definition: both cases were rated as mild (IGA score rating of 2 points) at Day 15 (end of study).

Figures 4 and 5 represent two cases of successful treatment from real-world clinical practice using the regimen of treatment given twice-daily for 14 days as described in the Phase III RCT protocol.

The AEs reported in more than one percent of actively treated subjects was application site discoloration. AEs reported in less than one percent of actively treated subjects included rash, telangiectasia, and atrophy (by clinical assessment).[43,47]

Maximum use safety study design. A safety study was completed in adult subjects with moderate-to-severe plaque psoriasis involving 20 to 50 percent of BSA who used either CP 0.025% cream twice daily for 14 days days (n=26) or CP 0.05% cream (Temovate; Lupin Pharmaceuticals, Mumbai, India) twice daily for 14 days (n=24).[43,47] Applications to the face, axillae, groin, and scalp were excluded. Average patient age was 50.9 years and 43.5 years in the CP 0.05% and CP 0.025% cream groups, respectively. The majority of subjects

were men (63.6–70.8%) with predominantly moderate IGA severity (68.2–79.2%) and a mean BSA of 26.5 to 27 percent at baseline. The study objectives were evaluation of potential HPA suppression, as well as analysis of systemic drug absorption—measured through CP plasma concentration after two weeks of continuous therapy with both active cream formulations—and the comparison of CP plasma concentrations in both study groups under maximal use conditions. In cases where HPA effect was confirmed at Day 15, a follow-up visit was arranged for Day 43 to confirm HPA recovery. All randomized subjects underwent normal HPA testing (adrenocorticotropic hormone [ACTH] test) and dehydroepiandrosterone sulfate level assessment at screening, and no clinical signs of HPA axis dysfunction were noted (e.g., Cushingoid features, Addisonian features).[43,47]

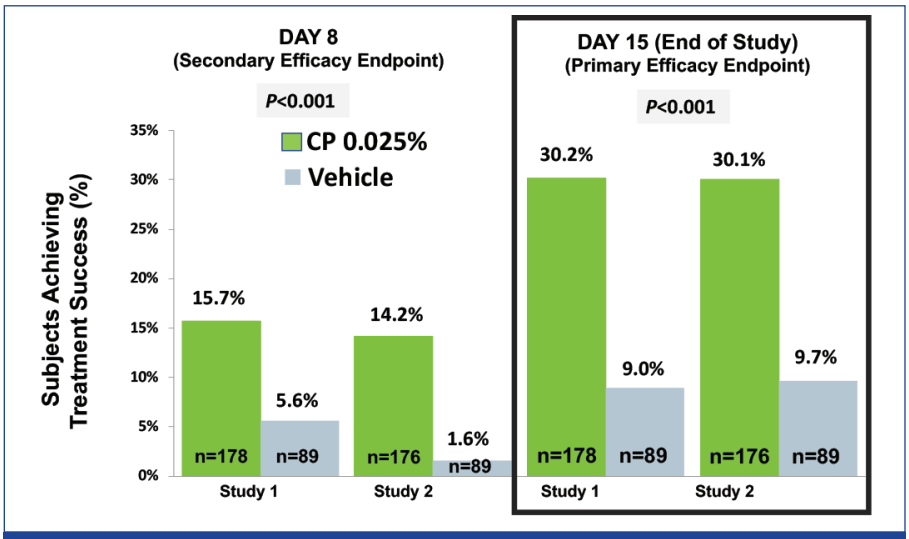

FIGURE 1. Primary efficacy endpoint results for clobetasol propionate 0.025% cream vs. vehicle cream twice daily for 14 days in adults with moderate-to severe plaque psoriasis

Maximal use safety study HPA axis suppression results. At Day 15, the percent of subjects with HPA axis suppression (determined by abnormal ACTH stimulation test results) was 36.4 percent in the group treated with CP 0.05% cream (n=22) and 12.5 percent in the group treated with CP 0.025% cream (n=24).[43,47] Although the comparative difference in results was not statistically significant ($p<0.086$), the numerical results demonstrated a threefold greater increase in HPA suppression among subjects treated with CP 0.05% cream, compared to CP 0.025% cream group, under maximum use conditions (Figure 6).[43,47] The lack of statistical significance is likely related to the small study population size in each study arm.

Maximal use safety study systemic absorption (plasma concentration) results. After completion of two weeks of continuous use for plaque psoriasis, the CP plasma concentration was 152.5pg/mL in subjects treated with CP 0.05% cream (n=22) and 56.3pg/mL in those treated with CP 0.025% cream (n=24), reflecting a 2.7-fold increase in plasma CP level in the CP 0.05% cream-treated subjects (p=0.014) (Figure 7).

Nonpowered efficacy evaluation. The maximal use safety study was not powered to statistically evaluate efficacy differences between CP 0.025% cream twice daily (n=23) and CP 0.05% cream twice daily (n=22) after two weeks of use in adults with moderate-to-severe plaque psoriasis affecting 20 to 50 percent of the BSA.[43,47] However, in both study groups, 50 percent of the subjects improved to a severity rating of mild (IGA score rating of 2) by Day 15. Considering the large mean BSA of 26.5 to 27 percent recorded at baseline, both groups exhibited similar results in the achievement of clear (IGA score rating of 0) or almost clear (IGA score rating of 1) skin after two weeks of treatment; reported results were 16.7 percent in the CP 0.025% cream group and 18.1 percent in the CP 0.05% cream group.[43,47] Although not a formal head-to-head comparison, these data provide some support for comparable efficacy between both formulations, despite the presence of half of the usual concentration of active ingredient in the CP 0.025% cream. Because this was a maximal use safety study, one would not expect to see complete clearance of all psoriatic plaques that compose a BSA involvement of 26 to 27 percent. However, in a more conventional study evaluating the use of a TC for plaque psoriasis, the BSA would more likely range

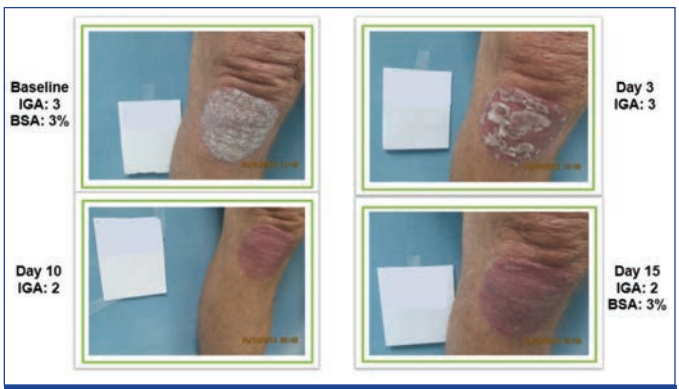

FIGURE 2. Plaque psoriasis on right knee of 53-year-old woman at baseline, Day 3, Day 10, and Day 15 after 2 weeks of twice-daily treatment with clobetasol propionate 0.025% cream; Investigator Global Assessment improved by 1 point

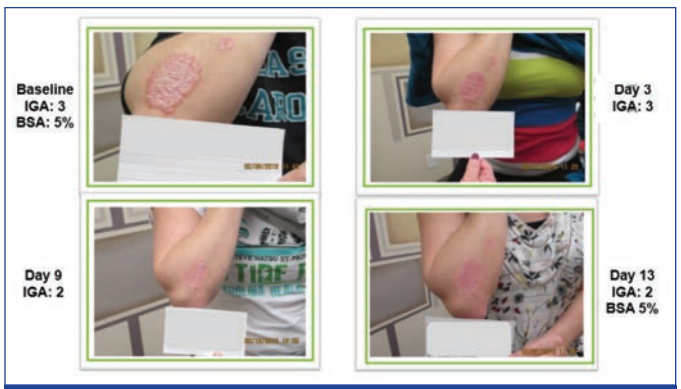

FIGURE 3. Plaque psoriasis on right elbow of 26-year-old woman at baseline, Day 3, Day 9, and Day 15 after 2 weeks of twice-daily treatment with clobetasol propionate 0.025% cream; Investigator Global Assessment improved by 1 point

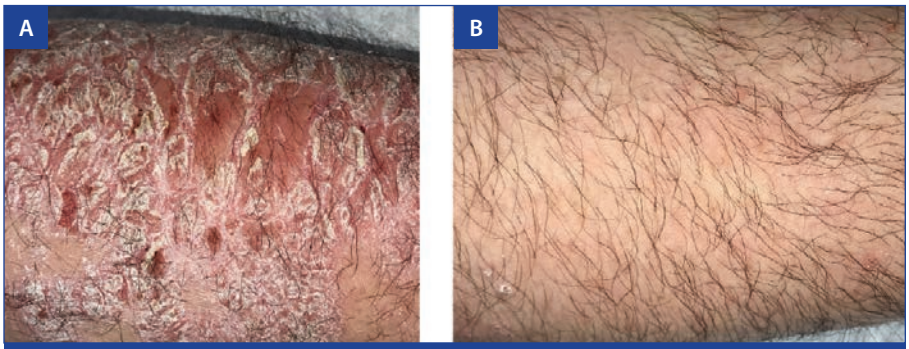

FIGURE 4. Plaque psoriasis on left forearm of 47-year-old man at A) baseline and B) Day 15 after 2 weeks of twice-daily treatment with clobetasol propionate 0.025% cream

Photo courtery of Harold Farber, MD

from 3 to 6 percent, with a greater likelihood of achieving complete or near complete clearance of all the treated psoriatic plaques.

Take-home point. The efficacy, skin tolerability, and safety of CP 0.025% cream were well-supported by two pivotal RCTs and a maximal use safety study.[43,47] Although the safety study results might seem purely academic on initial cursory review, the clinical relevance of the reduced risk of HPA suppression and decreased systemic corticosteroid absorption should not be underestimated. The ability to achieve efficacy results similar to that of Class I TC products but offer lower risk of HPA suppression and significant reduction in cumulative corticosteroid plasma levels reduces risk of AEs without losing the efficacy typically seen with topical CP therapy for psoriasis. With CP 0.025% cream, this is achieved without the incorporation of the two most common contact allergens found in many TC formulations: propylene glycol, a penetration enhancer and preservative, and sorbitan sesquioleate, an emulsifier.[43,46–49] In addition, the lack of propylene glycol and short-chain alcohols (e.g., ethanol), both of which exhibit a broad range of antimicrobial effects, in the CP 0.025% cream also reduces unnecessary alteration of the cutaneous microbiome.[43,47,50–52]

VEHICLE COMPONENTS AND SUPER-POTENCY RATINGS IN TC PRODUCTS

Propylene glycol (PG). There are several properties that contribute to the potency ranking of TC formulations, including the TC molecule itself, concentration, and vehicle properties and content.[1,2] The excipients included in a topical formulation, including TCs, contribute significantly to the potency, tolerability, safety, and cosmetic acceptability of the final product.[1,2,10,13–15,44,45,53–55]

The development of super-potent TCs began, most notably, with augmented betamethasone dipropionate formulations.[56] The excipient ingredient that contributed markedly to increased penetration—and, hence, potency—of the active TC (including CP and other TCs) was PG, serving as a penetration enhancer in concentrations as high as 70 percent.[56,57] Interestingly, as far back as 1993, PG was an ingredient in approximately 60 percent of TC products and is the most common contact allergen found in TC formulations available in the marketplace.[48,49,57]

Structurally a dihydric alcohol, PG is highly hygroscopic and readily miscible with water, essential oils, and acetone.[57] Depending on the concentration used, PG is incorporated in many topical prescription products, cosmetics, hand lotions, and body lotions as a solvent, lubricant, humectant, preservative, and/or penetration enhancer.[57] Penetration enhancement facilitated by chemicals, such as PG, can alter stratum corneum structure and function by disrupting intercellular lipids and/or proteins and by increasing the partitioning of active ingredient and solvents used in the vehicle.[53] Thus, potential downsides of the double-edged sword of penetration enhancement of a TC with PG include direct induction of epidermal barrier dysfunction caused by PG and decreased SC lipid synthesis caused by the TC.[53,58] Other disadvantages of PG include unintended alteration of the cutaneous microbiome with antibacterial and antifungal properties at concentrations of more than 25 percent, along with the ability to induce both allergic and irritant reactions—usually seen

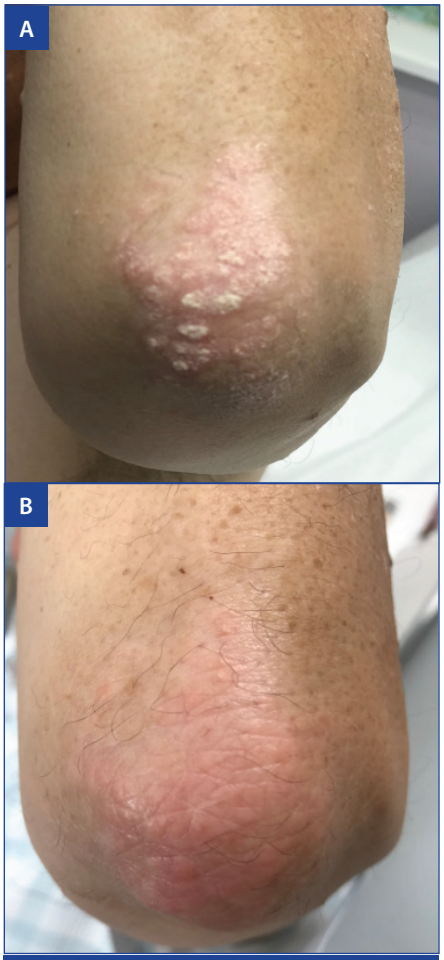

FIGURE 5. Plaque psoriasis on left elbow of 49-year-old man at A) baseline and B) Day 15 after 2 weeks of twice-daily treatment with clobetasol propionate 0.025% cream

Photo courtesy of Todd Plott, MD

with concentrations of greater than 10 percent.[57] Cutaneous allergy to PG has been correlated with several reports of allergic contact dermatitis (ACD) to TC formulations, otitis externa, and hand dermatitis, as well as cases of irritant contact dermatitis (ICD).[48,49,57,59] Data from the North American Contact Dermatitis Group (2015–2016) demonstrated a positive patch test rate of four percent, which is an increase from the 1 to 2 percent rate noted in the 1980s and early 1990s.[48,49,57,59] This increase might reflect the widespread use of PG in many topical formulations, including more than 60 percent of TC products.[57,59]

Diethylene glycol monoethyl ether (DEGEE). Due to the various disadvantages associated with the use of PG in TCs, there has been a dedicated effort to develop vehicles

that optimize TC potency without the use of PG, especially at high concentrations. There has also been an effort to avoid or limit the use of short-chain alcohols (e.g., ethanol) due to adverse application-site reactions (e.g., dryness, stinging, burning) and unintended alteration of the cutaneous microbiome secondary to direct antimicrobial effects.[52,60] A major advancement and predominant contributor to the potency of CP 0.025% cream is the use of pharmaceutical-grade diethylene glycol monoethyl ether (DEGEE), an agent that provides penetration modification by increased active ingredient penetration and/or limiting systemic uptake of dissolved active ingredient.[45] Available data show that DEGEE is a safe and well-tolerated solvent that is miscible with water and stratum corneum lipids; is systemically nontoxic; has not been associated with ACD; has negligible antimicrobial effects; exhibits favorable cosmetic eloquence, emolliency, and spreadability; and provides an expanded intracutaneous depot for certain active ingredients without enhancing diffusivity (i.e., systemic exposure).[44,45,53–55,61,62]

The use of DEGEE is widespread in topical formulations, including more than 500 cosmetic products as of 2011, and more recently, has been used in topical prescription vehicles (e.g., dapsone gel), with concentrations ranging from 5 to 40 percent.[45] Reports prior to the 1990s on AEs were related to use of industrial-grade DEGEE, which is, at best, less than 98-percent pure. Importantly, these AEs have been averted by the use of pharmaceutical-grade DEGEE, which exhibits greater than 99.9-percent purity.[45,53] DEGEE serves to increase solubility and intracutaneous deposition of many active ingredients, without promoting systemic exposure, including TCs. Other chemicals that have been successfully studied with DEGEE using different research models include minoxidil, tretinoin, tacrolimus, testosterone, diclofenac, finasteride, and acyclovir.[44,45,53–55,61,62] In some cases, DEGEE functions cooperatively as a cosolvent.[53] Ultimately, DEGEE, as a penetration modifier, differs from conventional penetration enhancers, such as PG and ethanol. The properties that make DEGEE so valuable in vehicle technology are its abilities to increase solubility of compounds in suitable solvents, including poorly soluble agents, provide immediate dissolution and suspension of active ingredient (i.e., reservoir effect), and increase cutaneous retention of active ingredient (i.e., expanded intracutaneous depot) while limiting systemic exposure.[44,45,53] Other favorable characteristics of DEGEE include a lack of irritancy and allergenicity, noncarcinogenicity/nonmutagenicity, negligible systemic toxicity, and the absence of antimicrobial activity.[45,53] Table 1 depicts a thorough overview of the properties of DEGEE that support its use as an excipient/solvent in topical formulations. Another excipient included in the CP 0.025% cream vehicle, cyclomethicone NF (decamethylcyclopentasiloxane) is an astringent emollient and spreading agent that provides some occlusivity while leaving the skin feeling smooth and lubricated and not sticky or oily.[60,63]

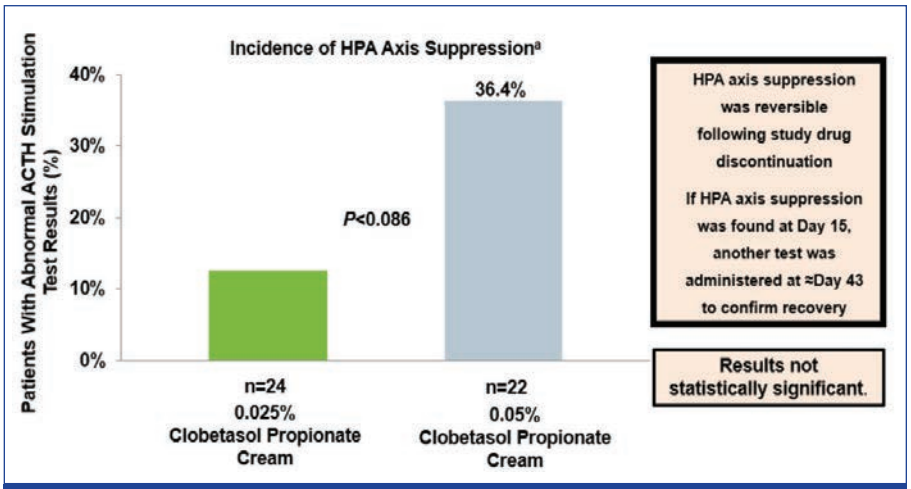

FIGURE 6. Incidence of hypothalamic-pituitary axis (HPA) suppression in maximal use safety study of clobetasol propionate 0.025% cream vs. 0.05% cream twice daily for 14 days; mean body surface area (BSA) 26.5–27%

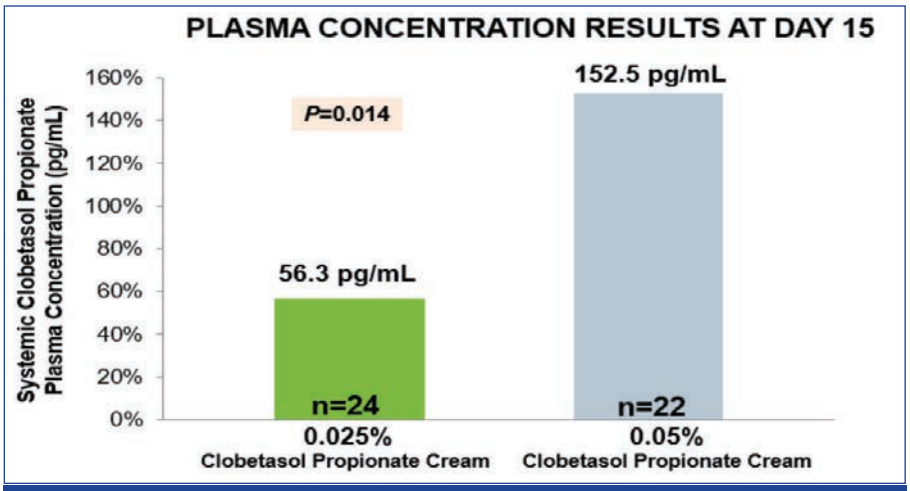

FIGURE 7. Serum clobetasol propionate levels: maximal use safety study of clobetasol propionate 0.025% cream vs. 0.05% cream twice daily for 14 days; mean body surface area (BSA) 26.5%–27%

Take-home points. Pharmaceutical-grade DEGEE provides important vehicle characteristic advantages over PG and ethanol. DEGEE provides a unique intracutaneous depot effect that prolongs retention of the active ingredient within skin, with the added benefit of lower systemic exposure.[44,45,53–55] Other advantages of DEGEE are depicted in Table 1 and include the relative absence of irritancy, allergenicity, adverse alteration of the skin microbiome, or toxicity.[45,53]

SUMMARY

Corticosteroids are the cornerstone of topical therapy for the management of plaque psoriasis. Among dermatologists, Class 1 TCs are prescribed in approximately 60 percent of patients with plaque psoriasis, with superiority over agents of lesser potency in achieving initial clearance or marked improvement. Class 1 TC use is adaptable to combination and/or intermittent therapy for

TABLE 1. Properties of DEGEEs relevant to use as a solvent in topical formulations[44,45,53–55,61,62]

CATEGORY	COMMENTS
Official United States Pharmacopeia name/ category	• DEGEE • Glycol ether solvent used for transdermal, ocular, and intranasal delivery • Pharmaceutical grade DEGEE with 99.9% purity; abolishes the adverse events previously associated with industrial-grade DEGEEs • May be listed as ethoxydiglycol by the International Nomenclature of Cosmetic Ingredients
Physical properties	• Colorless liquid • Stable under ordinary conditions • Hygroscopic • Compatible with commonly used solvents, including oleic acid, propylene glycol, and ethanol • Spreads easily without streaking
Biologic properties	• Nonirritating • Nonallergenic • Not carcinogenic, mutagenic, or genotoxic • Enhanced solubility and intracutaneous penetration of various topical ingredients (e.g., clobetasol propionate, mometasone furoate) with increased skin retention (e.g., dexamethasone, hydrocortisone) • Increased reservoir capacity of the stratum corneum for several active ingredients (intracutaneous depot effect) with decreased systemic exposure (body burden) • Systemic absorption of DEGEE after topical application without systemic toxicity (5%–40% DEGEE concentration in available products) • Negligible antimicrobial effects • Compatible with skin surface lipids (i.e., epidermis/stratum corneum, sebum)

DEGEE: diethylene glycol momoethyl ether

long-term management of psoriasis, regardless of severity. Application is sometimes directed at specific sites that are persistent and/or refractory to other therapies, such as systemic agents or phototherapy.

CP 0.025% is a Class 1 TC utilizing a specialized cream delivery vehicle that has demonstrated a 2.7-fold greater reduction in serum CP concentration and 2.9-fold lower percent of HPA suppression in subjects with moderate-to-severe plaque psoriasis following a two-week, twice-daily treatment period, compared to subjects using a branded CP 0.05% cream. The use of DEGEE as a solvent for CP 0.025% Class 1 TC provides penetration modification and formation of an intracutaneous depot (i.e., reservoir effect) without the use of PG or ethanol. DEGEE provides other formulation advantages, including some over PG and ethanol, including greater solubility of active ingredients with a relative decrease in systemic exposure, lack of irritancy or allergenicity, high level of cosmetic acceptability, easy spreadability, negligible antimicrobial effects, and the absence of carcinogenicity/ genotoxicity/mutagenicity. Absence of PG also markedly reduces the risk of ICD and ACD. Data from clinical studies of CP 0.025% cream have shown the formulation to have similar efficacy as a branded super-potent CP 0.05% cream in reducing clinical signs and symptoms of moderate-to-severe plaque psoriasis in a group of adult subjects following a two-week, twice-daily treatment period. CP 0.025% also demonstrated the additional benefits of lower CP serum levels and less HPA suppression, compared to the branded CP 0.05% cream. Larger, long-term studies are needed to confirm these findings.

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