

The Clinical Relevance and Therapeutic Benefit of Established Active Ingredients Incorporated into Advanced Foam Vehicles: Vehicle Characteristics Can Influence and Improve Patient Outcomes

James Q. Del Rosso DO,^a Leon Kircik MD,^b Joshua Zeichner MD,^c Linda Stein Gold MD^d

^aJDR Dermatology Research/Thomas Dermatology, Las Vegas, NV; Touro University, Henderson, NV

^bIcahn School of Medicine at Mount Sinai, New York, NY

^cIcahn School of Medicine at Mount Sinai, New York, NY

^dHenry Ford Hospital, Detroit, MI

ABSTRACT

Topical delivery of therapeutic agents for skin diseases is a major advantage in dermatology. However, the efficacy and tolerability of topically applied therapies is dependent on several characteristics, including percutaneous penetration and permeation of active ingredient and lack of side effects, especially local tolerability reactions. Importantly, the ultimate performance of a topical product includes collectively the effects of the active ingredient and the impact that specific additives have on vehicle characteristics, such as penetration, permeation, epidermal barrier properties, relative irritancy, allergenicity potential, and patient acceptance/preference of the vehicle formulation used. Foam vehicles have evolved over time with the emergence of a menu of alcohol-based and aqueous-based variations that provide various advantages depending on clinical circumstances and the disease being treated. Aqueous-based foams have gained widespread acceptance and preference, especially due to favorable skin tolerability and the cosmetic elegance of the products. In this manuscript, data are presented supporting the efficacy, tolerability, and safety, of specific aqueous-based foam vehicles for calcipotriene used to treat plaque psoriasis, and for tazarotene used to treat acne vulgaris. Discussions include both vehicle-based properties that are relevant to clinical practice, and outcomes from the large-scale pivotal clinical trials that review efficacy and safety results and patient reported outcomes. The latter also discusses several practical subject assessments about use of the foam vehicle.

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INTRODUCTION

The accessibility of skin as a target organ in cutaneous disease allows for topical therapy to sustain a pivotal role in disease management. It is well established that vehicle characteristics can have a major impact on whether or not topical therapy is effective and/or tolerable.¹⁻⁴ The basic formulation, including vehicles such as cream, ointment, solution, foam, and spray, can directly influence the efficacy of a given product, and may also have profound effects on patient preference and compliance.¹⁻⁵ It is also important to recognize that both the individual selection and combinations of specific excipient ingredients have significant effects on several characteristics of topical formulations. These include release, delivery, penetration, and permeation of active ingredient in skin; cutaneous tolerability; product texture and cosmetic acceptance; ease of application and spreadability; lack of residue after application; and potential effects on the epidermal barrier such as changes in transepidermal water loss and water content/gradient in the stratum corneum.¹⁻⁸

How Can Differences in Vehicle Formulations Affect Clinical Performance?

There are several examples that can be shown to exemplify how differences in topically applied vehicle formulations can influence clinical outcomes when treating skin diseases. For example, common conventional generalizations for several years were that incorporation of a given topical corticosteroid (TCS) in an ointment would provide greater potency than a cream, and that a TCS cream is more potent than a lotion.^{1-3,6,9} These generalizations remain true in some cases where older vehicle formulations and excipient ingredients are utilized. However, advances in formulation technology can augment potency through use of certain excipients that facilitate delivery of active ingredients into skin, with some lotions, foams, solutions, creams, and sprays providing higher potency rankings than in the past.^{6,9-14} For example, a fixed amount of clobetasol propionate 0.05% (CP) formulated in an alcohol-based foam applied to human skin provided greater percutaneous penetration (flux

measured as %dose/cm/h) compared to CP solution, CP cream, CP emollient cream, and CP lotion using a Franz chamber assay model.¹¹ Other examples are the differences in potency rankings based on vasoconstrictor assay with betamethasone dipropionate 0.05% (BD) when incorporated in specific vehicles that utilize different bases and admixtures of excipients.^{15,16} High concentrations of propylene glycol are often utilized to produce augmented potency formulations of TCS, including some ointments, creams, and lotions ranked as ultra-high potency TCS.^{2-4,14,17}

Not All Foam Vehicles Are Created Equal

The development of different foam vehicles and their associated clinical characteristics have evolved over time. Foams were first popularized in dermatology with the emergence of a specified technology (Versafoam®) used to develop a platform of foam vehicles that were substantiated by research that demonstrated optimized cutaneous penetration of active ingredient (usually a TCS) using a freshly-harvested ex vivo human skin model.^{11,18} These foams were initially marketed in the United States with the release of “quick break” *hydroethanolic-based* foams, such as betamethasone valerate 0.12% foam and clobetasol propionate 0.05% foam studied in plaque psoriasis; these foams quickly liquified upon contact with the skin and tended to be drying and cause local tolerability issues due to the high content of ethanol.¹⁹⁻²¹

Hydroethanolic foams were followed by the development of *emollient foams* that incorporated “barrier friendly” excipients such as petrolatum, with ethanol removed as an excipient; these modifications allowed for “slow break foams” that did not immediately dissolve on skin contact, were easily spread into the skin manually, were not associated with a drying effect due to absence of ethanol, and exhibited a decreased potential for skin application site reactions such as stinging and burning.^{10,22} The lower potential for application site reactions is particularly relevant in patients with eczematous, xerotic, excoriated, and/or acutely inflamed skin. Formulation differences between foams and the clinical characteristics of the underlying skin disease being treated can both influence which foam vehicle is preferred and is thus more likely to lead to improved adherence with use.^{1,3,5,13,23}

Although the initial focus with development of foam vehicles usually incorporated TCS as the active ingredients, advances in foam technology led to the development of *aqueous-based foams* and *aqueous-based emulsion foams*, which are devoid of ethanol as an excipient.²⁴⁻²⁷ These foam formulations are similar, exhibiting lack of drying effect and favorable skin tolerability, with some modifications of their excipients that allow for optimal compatibility with different active ingredients. Specifically, tazarotene is incorporated into an aqueous-based foam and calcipotriene is incorporated into an aqueous-based

TABLE 1.

Selected Foam Formulations Showing Differences in Formulation Category, Excipients, and Active Ingredients ^{20-27,32,33}			
	Formulation	Does NOT Contain	Example Product
VersaFoam®-AF	✓ Aqueous-based	× Ethanol × Propylene Glycol × Fragrance	Fabior® (tazarotene) Foam, 0.1%
VersaFoam®-AEF	✓ Aqueous-based emulsion	× Ethanol × Preservatives × Fragrance	Sorilux® (calcipotriene) Foam, 0.005%
VersaFoam®-HF	✓ Hydroethanolic	× Light mineral oil × Fragrance	Olux® (clobetasol propionate) Foam, 0.05%
VersaFoam®-EF	✓ Petrolatum-based emulsion	× Ethanol × Fragrance	Olux-E® (clobetasol propionate) Foam, 0.05%

Note: No comparative head to head studies have been completed with these products.

emulsion foam.²⁴⁻²⁷ As with the other foams described above, these aqueous-based foam vehicles do not contain fragrances, which reduces the risk of allergic contact dermatitis.¹⁹⁻²⁷ Another advantage associated with both types of aqueous foams and emollient-based foams is low potential for cutaneous irritation. This is due to the absence of short-chain alcohols such as ethanol, and inclusion of excipients that exhibit a low risk for contact irritancy and/or contact allergy. Although head-to-head studies are lacking overall, data from studies with topical calcipotriene 0.005% completed in the same disease state (plaque psoriasis, scalp psoriasis), all demonstrate efficacy in pivotal studies, with a lower rate of cutaneous irritation reported with foam vehicle (2% [body]; 4% [scalp]) than with ointment or cream (10-15%) or with scalp solution (23%).^{24,28-30} Interestingly, the foam vehicle of azelaic acid (AzA) 15%, which utilizes a different vehicle platform that is ethanol-free and highly lipid based, appears to exhibit a more favorable skin tolerability profile than what has been reported with AzA 15% gel, based on results from pivotal trials of adult subjects with predominantly moderate papulopustular rosacea.³¹

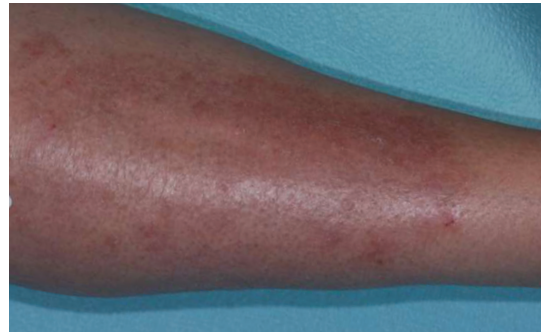
To summarize, based on the available evidence, the hallmarks of all foam formulations incorporating Versafoam® technology are penetration of active ingredient through the stratum corneum with permeation into epidermis and dermis, ease of spread with lack of residue, adaptability to both hair-bearing and non-hair-bearing anatomic skin areas, and high acceptance among patients utilizing these therapies.^{10,11,13,18,24-27,32,33} Table 1 depicts specific foam formulations incorporating different active ingredients and excipients that contribute to the clinical attributes of each product. The next sections of this article will discuss data on calcipotriene 0.005% foam for plaque psoriasis and tazarotene 0.1% foam for acne vulgaris followed by “take home” concluding suggestions on clinical applications.

FIGURE 1. Clinical response to calcipotriene 0.005% foam applied twice daily for 8 weeks to plaque psoriasis affecting the anterior leg.²⁷

BASELINE (Moderate Severity)



WEEK 8 (Almost Clear)

**Calcipotriene 0.005% Foam for Plaque Psoriasis**

Calcipotriene is a structural analog of vitamin D3, exhibiting similar keratinocyte receptor binding capacity but with 100-fold lower potency of effect on calcium metabolism, likely due to its more rapid cutaneous metabolism.^{34,35} Improvement of psoriasis after topical application of calcipotriene appears to relate to inhibition of keratinocyte proliferation, improved keratinocyte differentiation and modulation of T lymphocyte proliferation.^{34,35} Calcipotriene for psoriasis has been used successfully as monotherapy and also sequentially with TCS, contributing to reduced TCS side effects and longer periods of disease remission.³⁴⁻³⁷

Calcipotriene Foam Studies

Calcipotriene 0.005% foam (CalcipF) is approved by the Food and Drug Administration (FDA) for topical treatment of plaque psoriasis of the scalp and body in patients ≥ 18 years of age; a thin layer is to be applied into affected areas twice daily (BID).²⁴ Studies were performed in both body psoriasis and scalp psoriasis using conventional inclusion/exclusion/washout criteria and safety assessments including laboratory testing.²⁷ The CalcipF was packaged in aluminum cans pressurized with a propane/butane propellant, with vehicle foam identically packaged except for absence of the active ingredient. Notably, twenty-one adolescent subjects (ages 12-17 years) were includ-

ed collectively in the body and scalp studies, with this number of subjects too low for the FDA to grant approval down to age 12 years. As discussed earlier, CalcipF is an aqueous-based emulsion foam that is devoid of ethanol, preservatives, and fragrances.²⁴ Patient assessments of clinically relevant foam characteristics will be discussed later in this article.

Body Plaque Psoriasis

Two 8-week, randomized, controlled, double-blind trials (RCTs) were completed in subjects ≥ 12 years of age treated with CalcipF BID (n=437) or vehicle BID (n=222) with mild to moderate body plaque psoriasis affecting the trunk and/or extremities (N=659); 71% were rated as moderate and 29% as mild based on Investigator Static Global Assessment (ISGA).²⁷ The mean body surface area (BSA) affected was 6.3% (range, 2%-20%). Target lesions were also assessed. Both genders were equally represented (54% male; 46% female). The primary efficacy endpoint was percent subjects achieving ISGA of clear or almost clear with a ≥ 2 -grade improvement at end of treatment (EOT/week 8).

Primary endpoint success in Study 1 was achieved by 14% and 7% of subjects in the CalcipF group and vehicle group, respectively ($P=0.058$), which included a higher number of baseline ISGA mild subjects (31.8%). In Study 2, endpoint success was

FIGURE 2. Clinical response to calcipotriene 0.005% foam applied twice daily for 8 weeks to plaque psoriasis affecting the posterior elbow.²⁷

BASELINE (Moderate Severity)



WEEK 8 (Almost Clear)



FIGURE 3. Clinical response to calcipotriene 0.005% foam applied twice daily for scalp psoriasis affecting $\geq 10\%$ of scalp surface area.

BASELINE (Moderate)



WEEK 8 (Almost Clear)



achieved by 27% of subjects in the CalcipF group and 16% in the vehicle group ($P=0.016$), with 26.9% of subjects rated as ISGA mild at baseline.²⁷ The percent of mild severity subjects at baseline can influence study outcomes as differentiation between topical products by ISGA assessments is primarily revealed among subjects with greater severity of disease. CalcipF-treated subjects showed better response rates than subjects treated with vehicle foam for most secondary outcomes, including ratings of erythema, scaling, and plaque thickness of the baseline target lesion, and assessment of response in subjects with a baseline ISGA rating of moderate severity.²⁷

Figures 1 and 2 depict individual responses by EOT in subjects treated with CalcipF applied BID as monotherapy for body plaque psoriasis during the RCTs.

CalcipF was safe and well-tolerated with an overall rate of adverse events (AEs) similar to those noted in the vehicle group.²⁷ Application-site reactions (ASRs) occurred in approximately 1–2% of subjects in each group. Treatment was discontinued because of AEs in approximately 2% of subjects in both groups, with most due to ASRs. No concerning systemic safety signals emerged in either study group.²⁷

Scalp Psoriasis

An 8-week RCT was completed in subjects ≥ 12 years of age treated with CalcipF BID ($n=181$) or vehicle foam BID ($n=182$) for scalp psoriasis of moderate ISGA severity affecting $\geq 10\%$ of scalp surface area.³⁸ Both genders were well represented (60% male; 40% female). The primary efficacy endpoint was percent subjects achieving ISGA clear or almost clear at EOT (week 8), which automatically required ≥ 2 -grade improvement.

Primary endpoint success was achieved by 41% in the CalcipF group and 24% in the vehicle group ($P=0.001$).³⁸ No systemic safety signals were observed. The incidence of ASRs in both

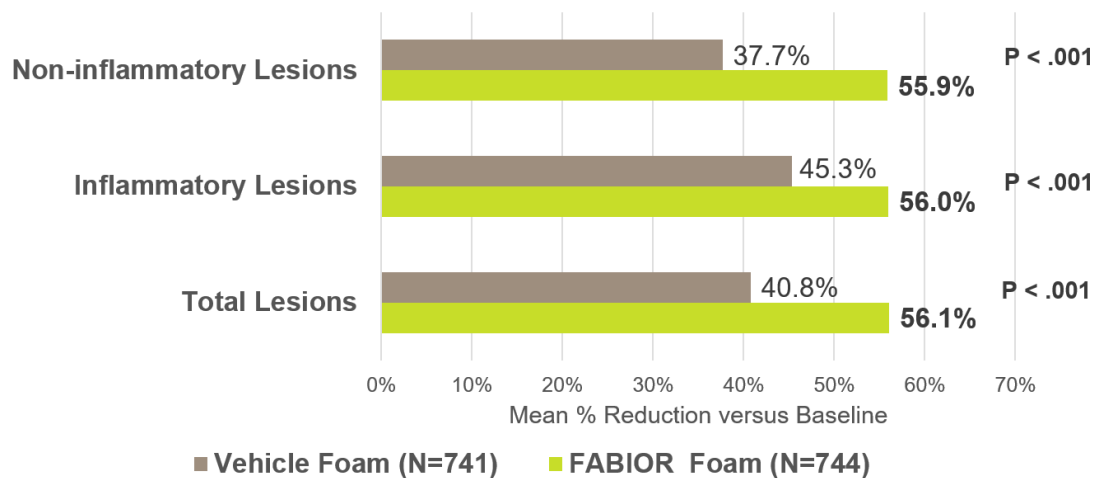
study groups were similar to those observed in the RCTs with body psoriasis. Application site pain (ie, stinging, burning), pruritus, and erythema occurred in 4%, 4%, and 3% of CalcipF-treated subjects, and in 3%, 4%, and 0% of vehicle-treated subjects, respectively.³⁸ Figure 3 shows an example of a subject treated with CalcipF BID for scalp psoriasis (data on file).

Tazarotene 0.1% Foam for Acne Vulgaris

Tazarotene (Taz) is a topical retinoid, available initially as both 0.1% and 0.05% gel and cream formulations, that has been evaluated extensively for treatment of acne vulgaris (AV) and plaque psoriasis.^{34,39,40} After application to skin, Taz is rapidly converted to tazarotenic acid, which is biologically active via binding to specific retinoic acid receptors, resulting in several suggested modes of action.^{34,39} These include regulation of cellular proliferation, differentiation and dermal matrix degradation, and modulation of various pathways and signals involved in cutaneous inflammation.^{34,39,40} More recently, Taz 0.1% has been formulated in an aqueous-based foam containing non-comedogenic light mineral oil, devoid of ethanol, fragrances, propylene glycol, and parabens, that has been shown to be effective for once daily (QD) treatment for AV of the face and/or upper trunk.^{24,33} Lower systemic exposure of tazarotenic acid was also shown in a comparative bioavailability study after widespread application of Taz foam to face, chest, upper back, and shoulders as compared to Taz gel.²⁶ In the pivotal studies, TazF was packaged in aluminum cans pressurized with a propane/butane propellant; the vehicle foam was packaged identically except for absence of the active ingredient.^{25,33}

Acne Vulgaris

Taz 0.1% foam (TazF) is FDA-approved for topical treatment of AV in patients ≥ 12 years of age; a thin layer is to be applied QD to the face and/or upper trunk in the evening, with concomitant use of moisturizer if needed.^{25,33} Two 12-week RCTs were completed in subjects with baseline Investigator Global Assessment

FIGURE 4. Mean % reduction in lesion counts with tazarotene 0.1% foam versus vehicle foam at end of treatment (week 12) compared to baseline. (Pooled data from two Phase III studies; N=1485).

(IGA) ratings of moderate or severe facial AV treated with TazF QD (n=744) or vehicle foam QD (n=741). Subjects were enrolled after confirming eligibility based on inclusion and exclusion criteria, including prior treatment washout periods, and with completion of conventional safety assessments and laboratory testing at baseline and throughout the study.³³ Subjects applied study drug to the face with efficacy and safety outcomes assessed throughout the study, but were also allowed to treat upper truncal AV if present. Most randomized subjects presented with moderate severity (80%) with the remainder rated as severe (20%); mean lesion counts at baseline were 31.9 inflammatory (papules, pustules, ≤2 nodules), 47.8 non-inflammatory (comedonal), and 79.8 total AV lesions. Gender representation was essentially equal (51% male, 49% female), with 58% of subjects being adolescent (ages 12-17 years). Racial distribution was 77% White, 15% African-American, 4% Asian, and 4% oth-

er. The primary efficacy endpoint was the percent of subjects achieving IGA of clear or almost clear with ≥2-grade improvement at EOT (week 12); percent reductions in lesion counts were also evaluated.³³

Primary efficacy success achieved at week 12 was 28.2% in TazF-treated subjects and 14.7% in vehicle-treated subjects ($P<.001$).³³ Figure 4 depicts mean % reductions in individual lesion counts, with significant decreases noted in both inflammatory and non-inflammatory (comedonal) lesions ($P<.001$ for both).³³ Figure 5 shows the EOT outcome achieved in a subject treated with TazF.

Local ASRs associated with TazF occurred early with peak incidence at week 2, followed by progressive improvement to baseline, consistent with what is anticipated historically with topical retinoid use.³³ ASRs such as dermatitis, erythema, sting-

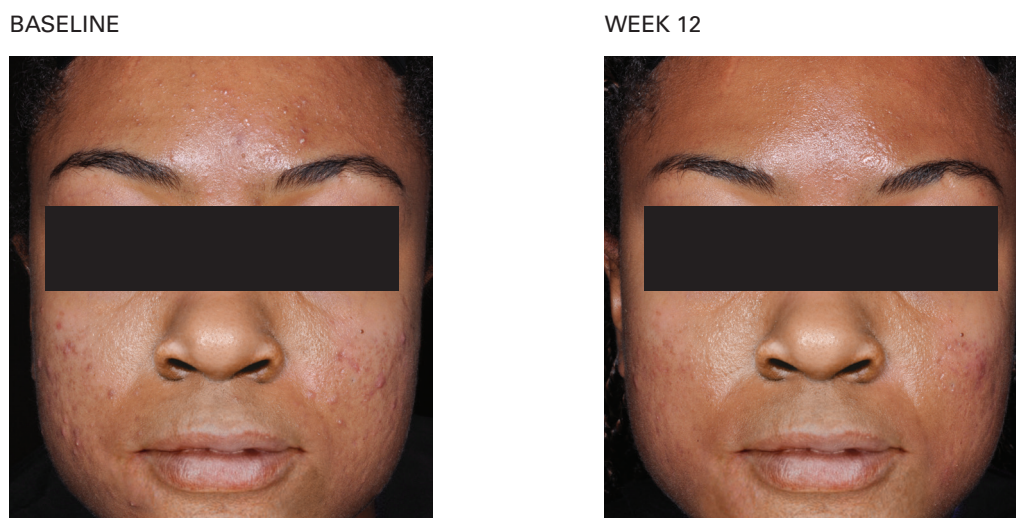
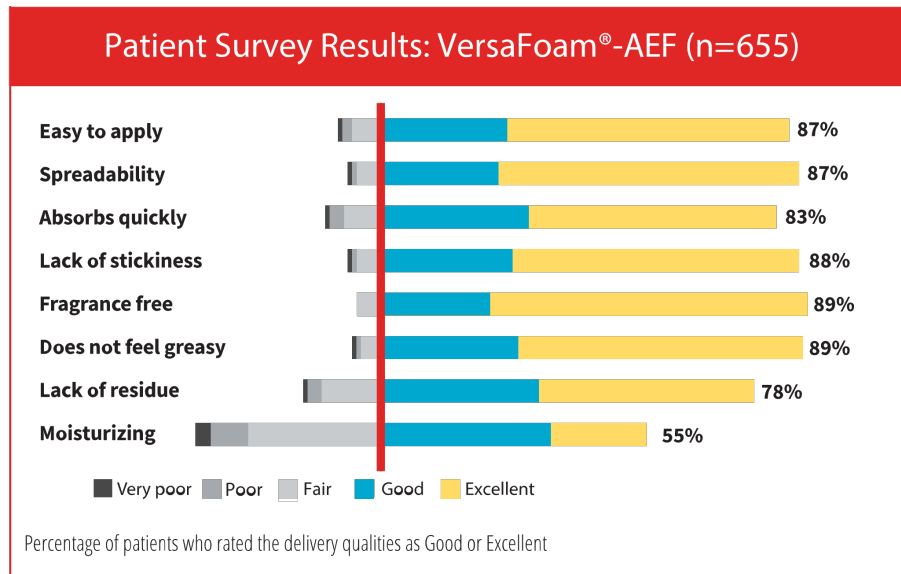
FIGURE 5. Subject with acne vulgaris treated with tazarotene 0.1% foam once daily for 12 weeks.

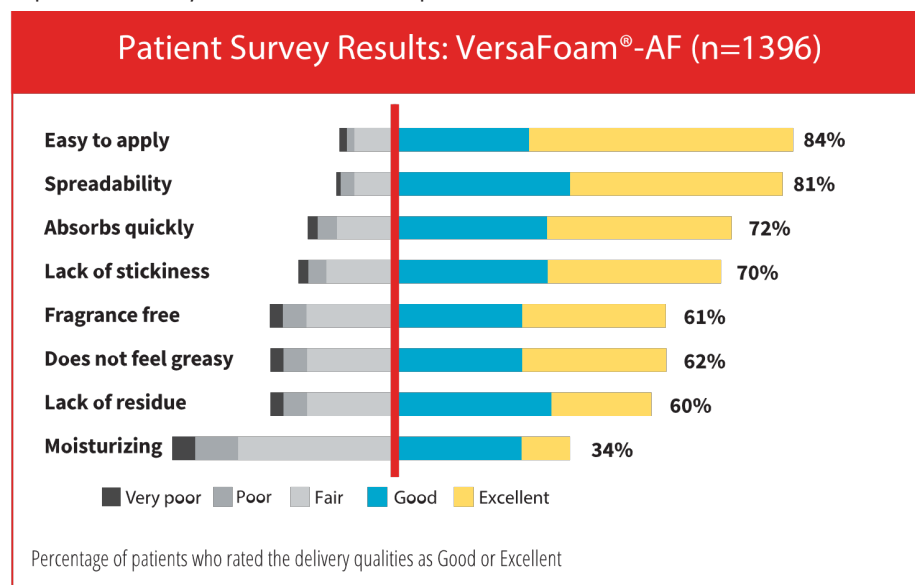
FIGURE 6. Patient perceptions of delivery characteristics with aqueous emulsion foam used with calcipotriene 0.005% foam.⁴¹

ing, burning, exfoliation, and itching occurred over a range of 1% to 7% in TazF-treated subjects compared to up to 1% in vehicle-treated subjects; similar tolerability outcomes were shown in both genders and across all age groups and races among enrolled subjects. Importantly, study discontinuation occurred in only 2.7% of TazF-treated subjects compared to 0.13% of vehicle-treated subjects. No systemic safety signals were noted.³³

Patient Assessments of Characteristics of Aqueous Foam Formulations

Subjects in both the two CalcipF phase III studies (n=655) and two TazF phase III studies (n=1396) rated the qualities of their re-

spective aqueous foam formulations.⁴¹ The results demonstrate that most subjects were highly satisfied with several delivery qualities of both foam vehicles. Figure 6 and Figure 7 show patient survey results of delivery qualities with the calcipotriene aqueous emulsion foam and the tazarotene aqueous foam, respectively. Subjects in both studies who completed these surveys did not know if they were using the active foam or the vehicle foam due to the double-blind methodology used in these pivotal studies.⁴¹ The sum effect of these favorable foam delivery characteristics is likely to be improved adherence with treatment among many patients.

FIGURE 7. Patient perceptions of delivery characteristics with aqueous foam used with tazarotene 0.1% foam.⁴¹

Take Home Observations and Concluding Remarks

- It is important that CalcipF and TazF be stored appropriately away from excessive heat. As the propellant in these foams is flammable, the patient is to avoid proximity to flames, fire, and smoking during dispensing and application of the foam.^{24,25}
- Foam formulations were first used as vehicles for TCS for disease states that often affected large body surface areas. Additionally, some foams were associated with skin dryness and irritation due to their hydroethanolic base. As a result, the positioning of foam vehicles in the minds of clinicians has unfortunately led to use limited to widespread disease due to spreadability, and/or avoidance of facial use due to concerns about irritation or lack of familiarity with proper methods of application. The favorable tolerability and delivery properties of the aqueous foams provides greater adaptability for localized or widespread use, including facial application.
- To improve facial application of a foam vehicle and avoid waste, it is suggested that a small amount be applied to the top of the foam cannister cap. The lead author recommends that the tip of the finger be used to transfer the foam by spot application to six points on the face: right forehead, left forehead, right mid cheek, left mid cheek, chin, and lower nose dorsum. The fingers can then be used to confluenty connect the spots of application by gentle circular motion to provide even and diffuse facial application, with avoidance of the eyelids and lips.
- The risk of calcipotriene use during pregnancy is not fully established and should be used only if the potential benefit justifies the potential risk.²⁴
- Patients should avoid exposure to natural sunlight, artificial ultraviolet (UV) light, or application prior to phototherapy when using CalcipF due to instability and breakdown of calcipotriene upon exposure to UV light.^{24,42} Calcipotriene may also be broken down and inactivated when applied concurrently with acidic pH products such as salicylic acid, lactic acid, and some TCS.⁴³
- The risk of clinically relevant hypercalcemia is very low with topical calcipotriene use.^{34,35} Product labeling with calcipotriene suggests avoidance of use in patients with known hypercalcemia.^{24,28-30}
- Topical tazarotene is contraindicated in pregnancy. Females of child-bearing potential should be instructed to use adequate birth control measures when using tazarotene.^{25,39-41}
- Patients should be instructed regarding potential for visible

and/or symptomatic ASRs when using a topical retinoid for AV, including TazF. Gentle skin care including moisturizer use may be needed to ameliorate local skin reactions.³⁹⁻⁴¹

- Space limitations preclude the ability to cover all of information in product labeling and pivotal study publications. It is recommended that the reader review the package inserts for CalcipF and TazF, including storage recommendations, application instructions, patient information, and important safety information.^{24,25}

DISCLOSURE

Drs. Del Rosso, Kircik, and Stein Gold have served as advisors and speakers for Mayne Pharma. Dr. Zeichner has served as a consultant for Mayne Pharma.

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AUTHOR CORRESPONDENCE

James Q. Del Rosso DO

Email:..... jqdelrosso@yahoo.com