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Enstilar® (calcipotriene and betamethasone dipropionate): A new topical agent for the treatment of plaque psoriasis

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The World Health Organization recognizes psoriasis vulgaris as a chronic, painful and debilitating disease that negatively impacts a patient's quality of life in more ways than one. This disease is defined by chronic, inflammatory processes manifesting in painful, red and inflamed plaques on the skin, often covered by a silver scale. A systematic review of international population-based studies found wide variation in the global prevalence of psoriasis, with the incidence of psoriasis ranging from 0.91% to 8.5% in adults and up to 2.1% in children.[1] The etiology of psoriasis remains unclear; however, there appears to be a genetic predisposition to the disease.[2] Psoriasis vulgaris is associated with an increased risk for multiple serious comorbities such as cardiovascular disease, obesity, diabetes and psoriatic arthritis. Psoriasis vulgaris can have a large psychosocial impact on patients due to the stigma associated with large plaques on the skin, often leading to depression, anxiety and feelings of loneliness. In addition to psychosocial impacts, lost opportunities in professional life due to the stigma associated with psoriasis and high treatment expenses can add to the significant socioeconomic burden for patients.

Current non-curative treatment options include topical therapies, ultraviolet light, and systemic therapies. Topical therapies such as corticosteroids and vitamin D analogs remain the mainstay of treatment. However, compliance to topical therapies remains a large issue, as many of these therapies are given multiple times per day and can cause adverse effects, including dryness and burning of the skin. Two commonly-used topical medications, calcipotriene and betamethasone, are often employed, but issues exist regarding their co-administration, including non-compliance stemming from the burden of administering multiple products to the skin multiple times/day. New formulations have sought to overcome this limitation, including a novel formulation administered via aerosol foam (Enstilar®; Leo Pharma Inc; Parsippany, NJ) which was granted an FDA-approved indication for the topical treatment of plaque psoriasis in patients 18 years of age and older in October, 2015. The purpose of this article is to review the pharmacology, safety and efficacy of the aerosol formulation of calcipotriene and betamethasone dipropionate (Enstilar®) for the treatment of plaque psoriasis.

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Mechanism of Action

Enstilar® is composed of two active ingredients, betamethasone and calcipotriene. These two drugs work through different mechanisms to alleviate the symptoms of psoriasis. Betamethasone is a topical corticosteroid that exhibits anti-inflammatory, antipruritic and vasoconstrictive properties. Betamethasone's anti-inflammatory effects occur, in part through inhibition of macrophage and leukocyte activity at the site of inflammation. Corticosteroids also decrease the formation and release of prostaglandins, kinins, histamines, and liposomal enzymes. Calcipotriene is a synthetic analog of vitamin D3 and is similar to the naturally occurring active form of vitamin D3, calcitriol. Calcipotriene binds to vitamin D receptors on keratinocytes and inhibits cell proliferation and cell differentiation in psoriasis, which is thought to be the primary mechanism of action in treating this condition. Combined, these two drugs work to decrease inflammation and cell proliferation, improve appearance, and minimize clinical symptoms of psoriasis.[3]

Pharmacokinetics

Similar to most corticosteroids, betamethasone is metabolized primarily in the liver and subsequently excreted by the kidneys. The biological half-life of betamethasone is approximately 35 to 54 hours. After topical application of betamethasone ointment, up to 14% of the applied drug can be systemically absorbed. Calcipotriene is metabolized similar to other vitamin D3 derivatives through nonspecific enzymes such as oxidoreductase and 22,23-

Table 1 | Pharmacokinetic properties of calcipotriene/betamethasone aerosol foam.

Property	Betamethasone	Calcipotriene
Absorption		
C_{max}	52.2 pg/mL	55.9 pg/mL
AUC	36.5 pg*h/mL	82.5 pg*h/mL
Metabolism	By hydrolysis to betamethasone 17-propionate (B17P), betamethasone	Hepatically metabolized to MC1406, then MC1080 (primary metabolite), then calcitroic acid

AUC = area under the curve; **C_{max}** = maximum concentration

Table 2 | Summary of clinical trials for calcipotriene 0.005%/betamethasone dipropionate 0.064% aerosol foam.

Trial	Design	Treatments	Primary Endpoint	Results
Koo, et al. (2016)[5]	Phase II, multicenter, investigator-blinded study	• Calcipotriene/betamethasone aerosol foam (n=141) • Calcipotriene/betamethasone ointment (n=135) • Placebo aerosol foam vehicle (n=49) • Placebo ointment vehicle (n=51)	Proportion of patients at week 4 who achieved treatment success (clear or almost clear with at least a two-step improvement)	Week 4 treatment success: • Calcipotriene/betamethasone dipropionate aerosol foam 54.6% • Calcipotriene/betamethasone ointment, 43.0% • OR 1.7; (95% CI 1.1, 2.8; p=0.025)
PSO-FAST (2015)[6]	Randomized phase III double-blind trial	• Calcipotriene/betamethasone foam (n=323) • Placebo aerosol foam vehicle (n=106)	Proportion of patients achieving treatment success at week 4	Week 4 treatment success: • Calcipotriene/betamethasone, 53.3% • placebo, 4.8% • OR 30.3 (95% CI 9.7–94.3; p<0.001)

OR = odds ratio.

reductase. Once absorbed calcipotriene is converted to a 24-ketone and reduced to a 22,23-hydrogenated derivative in the liver. Once the ointment dosage form is applied to the skin, up to 6% of the drug can be absorbed systemically.

Little data exist on the exact amount of systemic absorption after the application of calcipotriene/betamethasone dipropionate aerosol foam. Importantly, the amount of topical calcipotriene 0.005% plus betamethasone dipropionate 0.064% absorbed, like all topical agents, is dependent on the integrity of the skin and the site of application. Factors that could affect skin integrity include patient hygiene, UV exposure, infection and exposure to chemical agents, radiation, heat and electricity. One small study investigated calcipotriene/betamethasone dipropionate pharmacokinetics in patients suffering from plaque psoriasis of the body and/or scalp.[4] Plasma concentrations of calcipotriene and betamethasone dipropionate, as well as their main metabolites were measured after a mean ± SD total weekly dose of 61.8 ± 27.7 grams of the calcipotriene and betamethasone dipropionate aerosol foam. These concentrations were measured after 4 weeks of once daily application of the foam to adult subjects (n=35) with moderate to severe plaque psoriasis with a mean body surface area involvement of 17.5% and a mean scalp involvement of 50.2%. The pharmacokinetic data are summarized in **Table 1**. Following application of calcipotriene/betamethasone dipropionate aerosol foam for 4 weeks, calcipotriene was quantifiable in plasma in 1 out of 35 (2.9%) subjects and its main metabolite MC108, in 3 of 35 (8.6%) subjects. Betamethasone dipropionate was quantifiable in plasma in 5 out of 35 (14.3%) subjects and its main metabolite, betamethasone 17-propionate (B17P), was quantifiable in plasma in 27 out of 35 (77.1%) subjects.

Interactions

Several potential drug-drug interactions exist when using calcipotriene/betamethasone formulations. Studies show that there is limited systemic absorption of the aerosol foam topical formulation.[4] When used topically, calcipotriene and betamethasone can have additive toxicities with certain classes of drugs. Calcipotriene/betamethasone formulations should be avoided with concomitant use of systemic corticosteroids or other topical steroids. Concurrent use of a systemic or topical corticosteroid can increase total glucocorticoid exposure and lead to increased systemic side effects. Calcium containing compounds should also be avoided while taking calcipotriene/betamethasone formulations. Calcium salts and vitamin D formulas can cause hypercalcemia when taken concurrently with calcipotriene and betamethasone. One should avoid the combination of calcipotriene/betamethasone and multivitamins/minerals that contain folate, iron, or vitamins A, D, E and K, as these may increase the adverse/toxic effects of vitamin D analogs.

Clinical Trials

Phase 2 trial

In a phase II, multicenter, single-blinded study, investigators aimed to assess the efficacy of fixed combination calcipotriene/betamethasone aerosol foam compared with an FDA approved calcipotriene/betamethasone ointment, when applied once daily for 4 weeks.[5] A summary of the clinical trials for calcipotriene 0.005%/betamethasone dipropionate 0.064% aerosol foam is outlined in **Table 2**. The study included 427 patients from 35 U.S. dermatology centers. After enrollment, 51 patients were excluded from the study for not meeting inclusion/exclusion criteria. In total, 376 patients (median age 51 years) were randomly allocated to treatment with calcipotriene/betamethasone aerosol foam (n=141), calcipotriene/betamethasone ointment (n=135), a placebo aerosol foam vehicle (n=49), or a placebo ointment vehicle (n=51). Patients were at least 18 years old, with a clinical diagnosis of psoriasis vulgaris of at least 6 months. All patients were required to have psoriasis vulgaris on the body, involving 2% to 30% of body surface area (BSA), of at least mild severity according to the physician's global assessment of disease severity scale (PGA), and a modified psoriasis area and severity index (mPASI; excluding the head, which was not treated) score ≥2. Patients were excluded from the trial if they had received etanercept within 4 weeks, adalimumab or infliximab within 8 weeks, ustekinumab within 16 weeks, other biologics within 4 weeks or 5 half-lives

(whichever was longer), systemic treatments with a possible effect on psoriasis within 4 weeks, psoralen combined with ultraviolet A therapy within 4 weeks, ultraviolet B therapy within 2 weeks or topical antipsoriatic treatment within 2 weeks. Other exclusion criteria were planned excessive exposure of the treated area to sunlight, planned initiation or change to concomitant medication that could affect psoriasis, current diagnosis of guttate, erythrodermic, exfoliative or pustular psoriasis or other inflammatory skin disorders, any skin infections of manifestations, such as herpes or ichthyosis, disorders of calcium metabolism associated with hypercalcemia, severe renal insufficiency or severe hepatic disorders or hypersensitivity to any component of the investigational products.

Patients who were previously treated with antipsoriatic treatments or other relevant treatments (according to exclusion criteria) underwent a washout period of up to 4 weeks. Patients were instructed on how to apply treatments and the first application was applied under investigator supervision. Treatment was applied to psoriasis plaques on the trunk, arms and legs only; the scalp, face, genitals and skin folds were not treated. Patients classified by the investigator as clear, according to the PGA, at weeks 1 and 2, stopped treatment. If psoriasis reappeared, the patient reinitiated treatment. The primary efficacy endpoint was the proportion of patients at week 4 who achieved treatment success (clear or almost clear with at least a two-step improvement) according to the PGA of disease severity. The PGA, in its typical formulation, is a 7-point scale ranging from clear to sever including factors such as redness, thickness and scale. Secondary objectives of the study were efficacy after 1 week of treatment and safety throughout the study.

By treatment end (week 4), a significantly greater proportion of patients using calcipotriene/betamethasone aerosol foam achieved treatment success (54.6%) compared with those using calcipotriene/betamethasone ointment (43%), for a mean difference of 11.6% (odds ratio [OR] for achieving treatment success, 1.7; 95% CI, 1.1 to 2.8; p=0.025). This success rate was supported by reduced mPASI scores at week 4 for 74.2% of patients using calcipotriene/betamethasone aerosol foam versus 63.2% of patients using calcipotriene/betamethasone ointment (p=0.005) At week 1, the proportion of patients who achieved treatment success was low across all treatment groups with no significant differences between active treatments. As early as week 2, a numerically larger proportion of patients using calcipotriene/betamethasone aerosol foam had achieved treatment success (29.7% vs. 20.9%). The incidence of adverse events (AEs) was low and similar across the active treatments, with most events being mild. All AEs were single events except nasopharyngitis (deemed not treatment-related) and itch (deemed treatment-related), which were each reported by two patients using calcipotriene/betamethasone ointment. Adverse events were reported in one patient using calcipotriene/betamethasone aerosol foam (application-site itch) and four patients using calcipotriene/betamethasone ointment (application-site dryness [n=1], application-site pain and psoriasis [n=1], itch [n=2]). Importantly, no clinically relevant changes were observed in mean albumin-corrected serum calcium or spot urinary calcium:creatinine ratio.

Phase 3 trial

The PSO-FAST trial was a large, phase 3, double-blind, randomized controlled trial comparing the efficacy and safety of the aerosol foam formulation of calcipotriene 0.005% plus betamethasone dipropionate 0.064% with placebo in the form of the aerosol foam vehicle alone in patients with psoriasis.[6] Four hundred twenty-six U.S. patients were randomly assigned (3:1) to calcipotriene/betamethasone foam or an aerosol foam vehicle (placebo) once daily for 4 weeks. Inclusion and exclusion criteria for the PSO-FAST trial were identical to the criteria used in the phase 2 trial discussed previously.

The primary outcome of the study was the proportion of patients who achieved treatment success at week 4, where treatment success was defined as clear or almost clear (for patients with moderate or worse disease at baseline) or clear (for patients with mild disease at baseline), according to the PGA. Secondary outcomes were the mPASI score and patient–perceived itch severity and relief using the visual analog scale. Safety of the aerosol foam was assessed using the number of reported adverse events and calcium homeostasis. The study enrolled 426 patients, including 323 in the calcipotriene/betamethasone arm and 103 in the foam vehicle arm.

The median age of the patients enrolled in this study was 51 years, most patients were white (85.9%) and the mean duration of psoriasis vulgaris prior to enrollment was 15.9 years. The mean body surface area of psoriasis was 7.5%. At baseline, PGA scores indicated mild disease for 15.3% of patients, moderate disease for 74.9% of patients, and severe disease for 9.9% of patients. At week 4, treatment success had occurred in significantly more patients using calcipotriene/betamethasone foam (53.3%) versus the placebo vehicle (4.8%), for an OR of 30.3 (95% CI, 9.7 to 94.3; p<0.001). Mean mPASI score was significantly lower in patients calcipotriene/betamethasone dipropionate aerosol foam versus vehicle (mPASI score, 4.5 vs. 6.2; adjusted mean difference -1.3; 95% CI, -1.8 to -0.8; p<.001). No clinically significant changes in calcium homeostasis were reported. Adverse drug reactions were reported in 10 patients treated with calcipotriene/betamethasone foam versus only 2 patients receiving placebo. The trial concluded that calcipotriene/betamethasone foam was safe and efficacious in the treatment of plaque psoriasis.

Adverse Events and Precautions

One of the main concerns with patients taking topical therapies to treat plaque psoriasis is the potential for topical adverse effects. Significant adverse events reported in <1% of subjects treated with calcipotriene/betamethasone aerosol foam include application site irritation, application site pruritus, folliculitis, skin hypopigmentation, hypercalcemia, urticaria and exacerbation of psoriasis.[4] Rare adverse reactions include ecchymosis, infection and telangiectasia. Patients with diabetes mellitus should routinely monitor their blood glucose when using calcipotriene/betamethasone as hyperglycemia may result from systemic absorption of topical corticosteroids.[7] Patients should be counseled on the avoidance of tanning booths or tanning under the natural sun as excessive exposure of treated skin can cause irritation. Skin infections should be monitored for and calcipotriene/betamethasone should be discontinued until any infection is resolved. Patients should avoid smoking, fire or flame during and shortly after calcipotriene/betamethasone aerosol foam administration, as the propellants in the aerosol foam are flammable.[4] No contraindications are listed by the manufacturer for the use of calcipotriene/betamethasone.

Also concerning, however, is the potential for systemic adverse events such as adrenal suppression with topical steroids and calcium homeostasis with the use of vitamin D3 analogs. In a multicenter, single-arm, open-label, 4-week study, Taraska and

colleagues assessed the effects of calcipotriene 0.005% and betamethasone dipropionate 0.064% on the hypothalamic-pituitary adrenal (HPA) axis and calcium homeostasis in patients with psoriasis vulgaris.[8] Primary endpoints included an abnormal adrenocorticotropic hormone (ACTH) challenge test and changes in albumin corrected serum calcium (sCa), 24-hour urinary calcium excretion (24hCa), and urinary calcium creatinine ratio (Ca:Cr) from baseline at week 4. The study enrolled 37 patients with mean body surface involvement of 21%. At 4 weeks, 6 patients (11%) reported adverse events of mild or moderate intensity, with only 1 event (severe erythema) considered treatment-related. In regards to the effect on the HPA axis, at 4 weeks all patients had normal ACTH tests with 100% achieving serum cortisol levels >18 mcg/dL after the ACTH challenge test. In regards to calcium homeostasis, no clinically significant changes were observed in all median and individual sCa and 24hCa values over the 4-week treatment period as well as no elevations in the urinary Ca:Cr ratio.

Dosing and Administration

Calcipotriene/betamethasone dipropionate aerosol foam is indicated for the treatment of plaque psoriasis in patients aged 18 years and older. Calcipotriene/betamethasone aerosol foam can be applied to the affected area of the skin once daily for up to 4 weeks. Patients should discontinue the medication when control is achieved. Doses should not exceed 60 g of foam every 4 days. Each gram of calcipotriene/betamethasone aerosol foam contains 52.2 mcg of calcipotriene and 0.5 mg of betamethasone. Patients should be instructed to wash hands before and after use, shake the can before each application and spray the foam approximately 1.5 inches away from the skin. After spraying, the patient should gently rub the foam into the affected body area. The medication should not be applied to face, axillae, groin or an area of preexisting skin atrophy at the treatment site. Patients should be advised to not use calcipotriene/betamethasone aerosol foam on more than 30% of their body surface area.

Cost

The new aerosol foam formulation of calcipotriene and betamethasone is priced comparatively similar to the other dosage forms of topical calcipotriene/betamethasone, as summarized in **Table 3**.[7] Prices are listed for a 60 gram quantity of each dosage form. A month supply of any of the dosage forms could range between 60 grams to 240 grams.

Conclusion

Enstilar® shows promise in the treatment of psoriasis. The potential added benefit of Enstilar® over the ointment formulation is primarily the ease of administration through the new aerosol dosage form. This formulation could potentially improve patient's compliance, and therefore improve patient outcomes, such as redness, itchiness and scale severity. In addition to ease of administration, several studies have shown that this new dosage formulation is also efficacious in alleviating the symptoms of psoriasis. Little risk has been associated with the use of Enstilar® as seen in the clinical trials, however, the additional benefit over previous therapy options remains to be elucidated.

Table 3 | Cost comparison of various dosage forms of calcipotriene 0.005%/betamethasone dipropionate 0.064%.

Brand name	Formulation	Cash price per 60-g
Enstilar®	Foam	$997.16
Taclonex®	Ointment	$1,074.97
Calcipotriene/betamethasone[a]	Ointment	$788.94
Taclonex®	Suspension	$997.16

[a]Generic product for Taclonex® ointment.

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