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Calcitriol Ointment: A New Option for Topical Psoriasis Therapy

CLINICAL UPDATE

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TOPIC HIGHLIGHTS

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Dr Becker has nothing to disclose.

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Option for Topical Psoriasis Therapy

ABSTRACT

Psoriasis is a common, chronic, inflammatory disorder of the skin that is associated with considerable discomfort, disability, and diminished quality of life. Topical vitamin D derivatives have long been used to treat psoriasis and are effective and safe in a variety of monotherapy and combination-therapy regimens. Calcipotriene (Dovonex®) is a vitamin D product in cream and solution formulations that has been available in the United States since 1994 for the treatment of plaque psoriasis. A new vitamin D agent, calcitriol ointment (Vectical®), has recently been approved in the United States for the treatment of plaque psoriasis as well. Calcitriol, the naturally occurring hormonally active form of vitamin D_3, is an effective topical psoriasis medication with a strong safety profile in long-term treatment. Topical calcitriol 3 µg/g ointment was superior to vehicle ointment alone in two randomized, double-blind clinical trials. In a long-term open-label study, calcitriol produced sustained improvement in psoriatic lesions for up to 1 year, with a low risk of adverse events and without reported clinical effects on systemic calcium homeostasis. In a direct comparison of calcipotriene ointment and calcitriol ointment, the latter produced greater improvement of psoriasis lesions on flexural skin areas with a lower incidence of skin irritation and was preferred by patients. Calcitriol ointment has also been shown to play a role in therapeutic regimens commonly used for psoriasis treatment. Its use significantly increased the treatment response among patients who were treated with ultraviolet B (UVB) phototherapy for psoriasis. Calcitriol ointment proved to be well tolerated and effective when used in rotational and sequential regimens with topical corticosteroids as well. Topical calcitriol 3 µg/g ointment is an important new option for the treatment of plaque psoriasis because of its considerable efficacy, excellent long-term safety profile, and flexibility for use with other topical psoriasis treatments.

Psoriasis is a common, chronic, relapsing inflammatory disorder characterized by the presence of multiple cutaneous, well-demarcated, erythematous, scaly plaques. Approximately 2% of the US population has been diagnosed with psoriasis, affecting an estimated 6 million people in the United States.[1] Typical histopathological characteristics of psoriasis include hyperproliferation and incomplete terminal differentiation of keratinocytes, vascular hyperplasia, decreased extracellular lipid production, and poorly adherent stratum corneum.[2] Models of the pathogenesis of psoriasis emphasize the cutaneous infiltration of self-reactive T lymphocytes and other immune cells, a network of complex interactions between infiltrating leukocytes and resident skin cells, and the release of a large number of inflammatory cytokines, chemokines, and other inflammatory chemical mediators.[2] This dermatologic condition is not merely a cosmetic disorder; rather, it is associated with significant discomfort and diminished quality of life.[3] Psoriasis produces an impairment in quality of life that is similar to the impairment associated with other severe chronic medical conditions such as type 2 diabetes or chronic lung disease.[4] In a survey of 404 individuals conducted by the National Psoriasis Foundation, 37% of individuals with psoriasis and/or psoriatic arthritis described their disease as physically painful, and 26% of patients reported social embarrassment or stigmatization.[3]

According to the American Academy of Dermatology, the goals of psoriasis therapy are to produce durable, substantial, and sustained improvement in psoriasis symptoms while minimizing the risk of adverse effects.[5]

Topical medications such as topical corticosteroids, retinoids, calcineurin inhibitors, and vitamin D derivatives are collectively the most commonly prescribed treatments for psoriasis in the United States.[6] These agents are either used as monotherapy in patients with mild-to-moderate disease, or in therapeutic regimens with mid- to high-potency steroids or systemic agents for patients with more severe psoriasis.[7-9] Topical agents themselves can be used together in a number of combination strategies, including rotational treatment (using one topical therapy for a specified period of time and then switching to a second topical treatment to reduce adverse effects associated with long-term exposure) and sequential treatment (using a stronger but potentially more toxic agent to induce rapid improvement, followed by long-term maintenance with a less toxic agent).[5] High-potency topical corticosteroids, which produce anti-inflammatory, antiproliferative, and immunosuppressive effects,[10] are effective for the short-term treatment of psoriasis and are available in many strengths and formulations.[11] However, many patients experience local cutaneous adverse effects (e.g., atrophy, telangiectases, striae), especially when corticosteroids are applied on a continuous basis for longer periods of time and are used on sensitive areas such as intertriginous regions.[11] In addition, adrenal suppression, which is more common when corticosteroids are applied to a larger body surface area (BSA), occurs in some patients. A number of studies have suggested that prolonged steroid use is associated with the gradual development of tolerance, also known in the literature as tachyphylaxis,[11] which supports the use of corticosteroids, particularly high-potency drugs, for limited periods of time. In fact, most high-potency corticosteroids are approved for only 2 to 4 weeks' continuous use.[12,13]

Calcitriol ointment is a novel vitamin D_3 derivative that has recently been approved in the United States for the topical treatment of mild-to-moderate plaque psoriasis.

Topical vitamin D derivatives are an effective, safe, and well-tolerated psoriasis treatment.[11] In addition, topical vitamin D derivatives provide considerable flexibility in psoriasis care. These agents have been shown to produce substantial improvement in psoriasis symptoms when used as monotherapy or in a variety of combination, rotational, and sequential treatment regimens with topical corticosteroids, ultraviolet B (UVB), and psoralen plus ultraviolet A (PUVA) photochemotherapy.[14] The synthetic topical vitamin D product calcipotriene has been available in the United States since 1994 and has been widely prescribed for psoriasis treatment.[6] Calcipotriene treatment significantly improves psoriasis symptoms but does produce cutaneous irritation in a number of patients, especially when applied to sensitive areas such as the face.[15] Calcipotriene is currently available in cream or solution formulations, as well as in combination with the high-potency corticosteroid betamethasone dipropionate. A single-agent calcipotriene ointment was recently discontinued in the United States despite its popularity and perceived superior treatment efficacy.[16]

Calcitriol ointment is a novel vitamin D_3 derivative that has recently been approved in the United States for the topical treatment of mild-to-moderate plaque psoriasis. Calcitriol is the naturally occurring hormonally active metabolite of vitamin D_3.[17] This new chemical formulation offers a unique treatment option for psoriasis because of its efficacy, safety, and tolerability characteristics, which are distinct from those of other vitamin D products. This article reviews the role of topical vitamin D derivatives for treatment of psoriasis and provides an overview of clinical research that has examined the efficacy and safety of topical calcitriol ointment in psoriasis care.

Topical Vitamin D_3: A Mainstay in Psoriasis Care

Vitamin D is a biologically inactive prohormone that is converted within the skin to vitamin D_3, which is subsequently metabolized by the liver and kidneys to yield the biologically active metabolite 1α,25-dihydroxy vitamin D_3 (calcitriol).[18,19] Calcitriol is essential in the regulation of calcium and phosphate absorption from the intestine and also promotes bone formation and mineralization.[18] Calcitriol produces its biological effects by interacting with a specific high-affinity cell-surface vitamin D receptor, which is found in keratinocytes, dermal fibroblasts, and a number of other cell types.[19]

High-dose oral vitamin D was used to treat psoriasis as early as the 1930s, although the mechanism by which vitamin D

improved psoriasis lesions was not well understood at the time.[19] Oral vitamin D formulations were effective for only about 30% of patients with psoriasis and were limited by a substantial risk of hypercalcemia and decreased bone mineral density.[19] Subsequent research has demonstrated that vitamin D not only plays a role in calcium/phosphate homeostasis but is also a powerful modulator of immune function, which inhibits cell growth. Furthermore, calcitriol specifically has been shown to reduce the proliferation of keratinocytes and stimulate the differentiation of these cells, which act in the pathogenesis of psoriasis.[20] Consequently, topical vitamin D derivatives were developed that produced greater clearing of psoriasis and less risk of systemic hypercalcemia as compared with the earlier oral formulations.[19] The topical vitamin D agents approved for treatment of psoriasis within the United States include calcipotriene cream and solution (Dovonex®) and calcitriol ointment (Vectical®) (see **Figure 1** for these structures[21]).

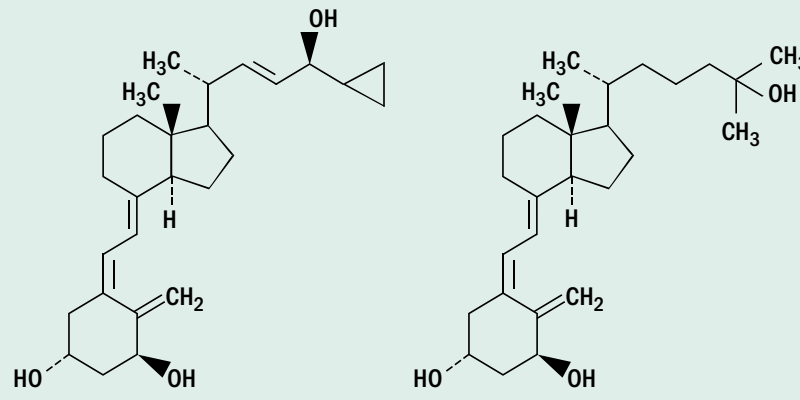
Calcipotriene is a synthetic vitamin D product that was approved for the treatment of plaque psoriasis in the United States in 1994.[6] Calcipotriene is effective for the treatment of mild-to-moderate psoriasis but produces significant skin irritation, redness, and pruritus in approximately 20% of patients.[15] The cutaneous irritation seen with application of calcipotriene limits its use on sensitive skin areas. Although originally available as a steroid-free topical ointment, calcipotriene was recently reformulated to include the steroid betamethasone dipropionate, and single-agent calcipotriene ointment was discontinued.

There is concern that the calcipotriene/betamethasone propionate combination ointment may expose patients to the potential for steroid-induced cutaneous adverse effects (e.g., atrophy, telangiectases, striae).[16] Tacalcitol is a second synthetic topical vitamin D product that is approved for the treatment of psoriasis in Europe and Japan but not in the United States. Tacalcitol is less irritating than calcipotriene and may be used to treat facial lesions. However, it has also been described as less effective than calcipotriene.[15] Maxacalcitol is a third synthetic topical vitamin D agent approved for the treatment of psoriasis in Japan but not in the United States. Maxacalcitol has been shown to have similar efficacy compared with calcipotriene.[22] However, its use has been limited by the need for periodic testing of serum calcium levels and renal function secondary to reports of acute renal failure associated with hypercalcemia.[23] There is, therefore, an important need for new vitamin D agents that not only are efficacious in patients with psoriasis but are also associated with a lower risk of adverse events.

Calcitriol 3 µg/g Ointment: A Unique Option for Psoriasis Treatment

Calcitriol 3 µg/g ointment is the only single-agent vitamin D_3 ointment available in the United States for topical psoriasis treatment. Calcitriol is the naturally occurring, hormonally active metabolite of vitamin D. Initial clinical experience with calcitriol ointment demonstrated good patient cosmetic acceptance and favorable tolerability characteristics.[24] As described in detail below, large, prospective clinical trials have demonstrated that calcitriol 3 µg/g ointment possesses a good safety profile with a low incidence of adverse events when administered for up to 52 weeks and with no effects on reports of systemic calcium homeostasis. These studies have also demonstrated that calcitriol ointment produces improvement in psoriasis symptoms within a reasonable time frame, and that the early benefit of calcitriol is sustained or even increased during the course of 1 year. Calcitriol has also been shown to improve psoriasis symptoms when used in established psoriasis treatment regimens (e.g.,

Figure 1. Chemical Structure of the Topical Vitamin D Derivatives Used in the Treatment of Psoriasis[21]



Adapted with permission from Sue Lee C, and Koo JYM. Vitamin D_3 Analogues, In: *Mild to Moderate Psoriasis*. Koo JYM, Lebwohl MG, Sue Lee C, eds. New York: Informa Healthcare, USA Inc.; 2006:60-61.

UVB, betamethasone valerate) and to produce greater improvement than calcipotriene ointment when applied to sensitive skinfold areas, demonstrating a lower incidence of cutaneous adverse events.

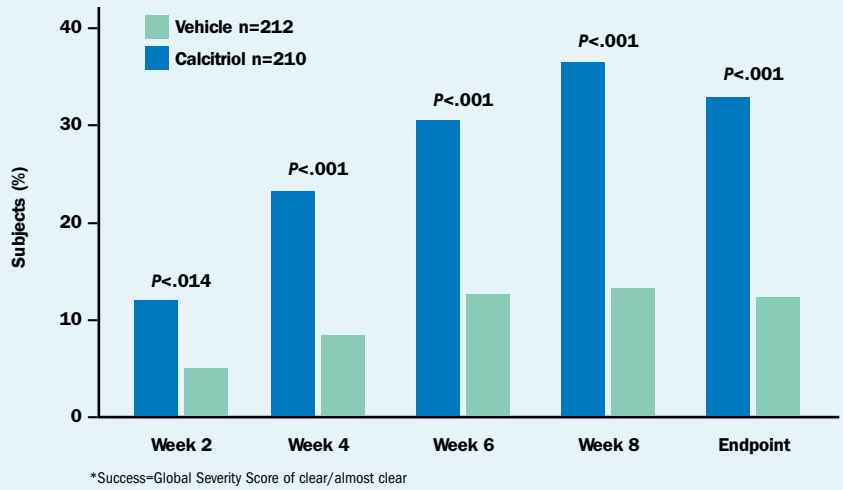
Efficacy and Safety of Topical Calcitriol: Phase III Clinical Trials

The efficacy and safety of topical calcitriol 3 µg/g ointment as monotherapy for psoriasis were evaluated in two randomized, double-blind, vehicle-controlled, parallel-group, phase III clinical trials.[25] A total of 839 patients with chronic mild-to-moderate plaque psoriasis were randomized to treatment with calcitriol ointment or vehicle ointment twice daily for 8 weeks. A psoriasis Global Severity Score (GSS) was rated by the treating physicians on a scale from 0 (clear of psoriasis) to 5 (very severe psoriasis) at baseline and at weeks 2, 4, 6, and 8. The study's primary endpoint was a GSS rating of 0 (clear) or 1 (minimal psoriasis) after treatment. In addition, patients and physicians rated global improvement of psoriasis from baseline on a scale from –1 (worse) to 5 (clear). Adverse events were assessed throughout the study. The baseline clinical and demographic characteristics of the two treatment groups were well matched, and the mean BSA affected by psoriasis at baseline was approximately 10% for both the calcitriol and the placebo (vehicle) groups.

As shown in **Figure 2**, the proportion of patients with treatment success (i.e., GSS of 0 or 1) was significantly higher for the calcitriol group than the placebo group in both studies.[25] Treatment success was significantly more likely for patients in the calcitriol group as early as the first post-treatment follow-up at week 2 and the success rate remained higher throughout the 8-week study. The proportion of patients who were successfully treated increased over the course of both studies. In Study 1, treatment success was noted for 34.4% of patients in the calcitriol group vs 22.5% of patients in the placebo group after 8 weeks (P=0.009). As shown in **Figure 2**, treatment success in Study 2 was noted for 33.3% vs 12.3% of patients in the calcitriol and placebo groups, respectively (P<0.001).[25] In addition, in these studies, generally 23% of patients in the calcitriol group demonstrated treatment success at 8 weeks and showed a two-grade improvement in disease severity.[26] Global ratings of psoriasis improvement from baseline by patients and clinicians are shown in **Figure 3** (on page 7) for both Study 1 and Study 2. In both studies, clinician and patient ratings of global improvement were significantly better for treatment with calcitriol ointment than treatment with vehicle ointment (P<0.001).[25]

The proportion of patients who experienced adverse events that were considered to be potentially related to study medication was similar for the calcitriol and placebo groups. In Study 1, treatment-related adverse events were noted for 6.7% of patients in the calcitriol group and 9.6% of patients who received placebo. In Study 2, treatment-related adverse events were noted for 10.5% vs 11.8% of patients in the calcitriol and placebo groups, respectively.[25] Treatment-related adverse events generally consisted of mild cutaneous reactions such as skin discomfort, pruritus, and erythema.[25] Examination of systemic calcium homeostasis in a subset of 152 patients from both studies revealed that twice-daily application of calcitriol ointment for up to 8 weeks did not significantly affect systemic calcium homeostasis. Serum calcium values above the upper limit of the normal range were noted for 12 patients in the calcitriol group and 10 patients using vehicle ointment; elevated 24-hour calcium was noted for 15 patients with

Figure 2. Proportion of Patients Who Experience Treatment Success* (Scores of 0 or 1 on the Global Severity Score Rating Scale) in Study 2 of the Phase III Clinical Trials (Calcitriol 3 µg/g Ointment vs Vehicle Ointment).[25]



*Success=Global Severity Score of clear/almost clear

Reprinted with permission from Lebwohl M, Menter A, Weiss J, et al. Calcitriol 3 microg/g ointment in the management of mild to moderate plaque type psoriasis: Results from 2 placebo-controlled, multicenter, randomized double-blind, clinical studies. *J Drugs Dermatol*. 2007;6:428-435.

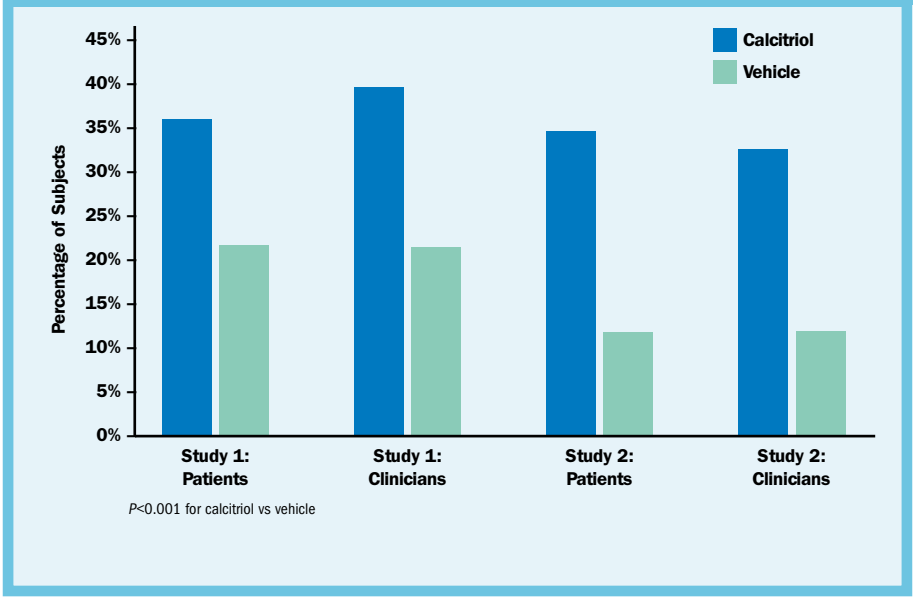
calcitriol vs 26 with vehicle. No patient had an albumin-adjusted calcium result over the alert level of 10% above the upper limit of the normal range.[25] In these studies, calcitriol 3 µg/g ointment produced rapid improvements in psoriasis symptoms that was apparent to both clinicians and patients, with a low rate of treatment-related adverse effects and without affecting systemic calcium homeostasis.[25]

Calcitriol Ointment Long-Term Study: Safety and Efficacy for Up to 52 Weeks

The long-term safety, tolerability, and efficacy of calcitriol 3 µg/g were examined in a single-group, multicenter clinical trial of patients with plaque psoriasis who were treated with open-label calcitriol every morning and evening for up to 52 weeks.[27] A total of 324 patients entered the study, and 136 patients completed 52 weeks of treatment. The mean age of the patients at baseline was approximately 46 years, and the mean BSA affected at baseline was approximately 16%. Global severity before treatment was rated as mild for 51 patients (15.7%), moderate for 179 patients (55.2%), severe for 84 patients (25.9%), and very severe for 10 patients (3.1%). Calcitriol treatment was well-tolerated throughout the 52-week study. At least one adverse event was noted for 130 patients (40.1%). In most cases, adverse events consisted of transient laboratory anomalies that were not associated with clinical signs or symptoms and did not require alteration or discontinuation of calcitriol treatment. Only 1.2% of patients discontinued the study prematurely because of adverse events. Adverse events that were considered by the investigators to be possibly related to study medication were noted for 45 patients (13.9%) and consisted primarily of hypercalcinuria, pruritus, irritant dermatitis, or laboratory-value abnormalities. Serious adverse events (e.g., events that were potentially life threatening or that required hospitalization) were noted for 8 patients during 52 weeks of follow-up, but none of these events was considered to be related to treatment. Only 10 patients (3.1%) experienced hypercalcemia (serum calcium level >2.55 mmol/L) at any point during the study. Hypercalcemia was not associated with clinical signs or symptoms, was unrelated to BSA affected by psoriasis, and did not increase during the course of the study. The investigators concluded that twice-daily application of topical calcitriol for up to 1 year did not significantly affect calcium homeostasis.

Although this study was primarily designed to evaluate the long-term safety and tolerability of calcitriol ointment, the investigators also assessed the effectiveness of treatment based on changes from baseline of psoriasis symptoms and BSA involvement. Patients rated their global improvement of psoriasis symptoms from baseline on a 7-point scale from –1 (worse) to 5 (clear). At week 6, 52.6% of patients rated their global improvement as "marked", "almost clear", or "clear"—corresponding to scores of 3, 4, or 5. At week 52, the proportion of patients with marked or better improvement from baseline increased to 63.8%. Efficacy was also evaluated using a physician assessment of global psoriasis severity, which was rated on a scale from 0 (very severe) to 5 (clear). Psoriasis severity was evaluated for patients who remained on calcitriol ointment through four study periods: Period 1 (study days 1–90), Period 2 (study days 91–180), Period 3 (study days 181–270), and Period 4 (study days >271). The proportion of patients who were assigned ratings of "clear" or "mild" (corresponding to scores of 0 or 1) increased over the course of the study from 11.1% of patients during Period 1 to 22.1% during Period 2, 37.3% during

Figure 3. Global Ratings of Psoriasis Treatment from Baseline, by Patients and Clinicians: Proportion of Patients With Improvement Ratings of "Marked," "Almost Clear," or "Clear" From Baseline (Study 1 and Study 2)[25]



Period 3, and 47.1% during Period 4.

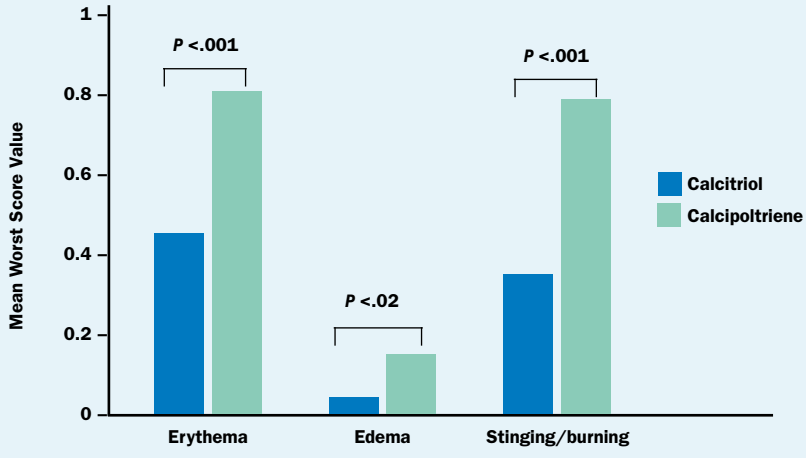
The percentage of BSA affected by psoriasis was evaluated at every visit except screening.[27] Mean percent BSA decreased over time, from 16.07% at baseline to 10.66% at endpoint in the patients who were treated over the full 52-week period. The mean BSA affected by psoriasis also improved over the course of the study.[27] Among patients who used calcitriol through week 26 (n=249), the majority (n=233) improved or maintained the percentage of BSA involved (P<0.001).[27] Furthermore, 127 of the 130 subjects who remained in the study through week 52 exhibited stable or improved BSA involvement (P<0.001).

Calcitriol 3 µg/g Ointment vs Calcipotriene Ointment

Zhu and colleagues compared the efficacy and safety of calcitriol 3 µg/g ointment and calcipotriene 50 µg/g ointment in a multicenter, randomized, investigator-blinded, 12-week clinical trial of 250 patients with mild-to-moderate chronic plaque psoriasis.[28] The mean BSA affected by psoriasis before treatment was approximately 18% for patients in both treatment groups.[28] Global improvement in psoriasis severity from baseline was assessed by the investigators on a scale from 0 (no change) to 3 (clear or nearly clear of psoriasis). After 12 weeks, the mean global improvement score was similar for the two treatments (2.22 for the calcipotriene group and 2.27 for the calcitriol group), and calcitriol was considered statistically noninferior to calcipotriene. The effect of treatment on individual psoriasis plaques was evaluated by examining plaque elevation, erythema, and scaling, each of which was rated on a scale of 0 to 4 (with lower scores indicating less severe symptoms). These individual symptom ratings were combined into a composite Dermatologic Sum Score (DSS). Baseline values for the DSS varied between 3 and 12 points, with a mean of approximately 8.1 in both groups.[28] After treatment, there was a small but statistically significant difference between the two groups in the final DSS scores in favor of calcitriol (1.87 vs 2.54 points with calcitriol and calcipotriene, respectively; P<0.01). Both treatments were well-tolerated by the patients, and discontinuations due to adverse events were rare in both groups (2 of 125 patients in the calcitriol group, 6 of 125 patients in the calcipotriene group). Moderate-to-severe cutaneous reactions were noted for 11 patients (8.9%) in the calcipotriene group, but for only one patient (0.8%) in the calcitriol group (P=0.0053).[28] Moderate-to-severe cutaneous discomfort was also less common for patients in the calcitriol group (3.2% vs 7.3% for the calcitriol and calcipotriene groups, respectively; P=0.0246). These findings demonstrated that calcitriol and calcipotriene produce generally similar improvement in the global severity of plaque psoriasis after 12 weeks. Both treatments were well tolerated by patients, although the incidence of cutaneous adverse events was lower with calcitriol in this study.

Ortonne and colleagues conducted a multicenter, investigator-blinded clinical trial to compare the safety, tolerability, efficacy, and patient acceptance of calcitriol 3 µg/g ointment and calcipotriene 50 µg/g ointment in 75 patients with mild-to-moderate psoriasis affecting the face, hairline, flexures, and retroauricular areas.[29] The investigators used a randomized, intraindividual design in which 1 to 4 pairs of bilateral and symmetrical lesions were selected for treatment for each patient, and patients applied calcitriol ointment to lesions on one side of the body and calcipotriene to lesions on the opposite side. Study medication was applied twice daily for 6 weeks.[29] For each

Figure 4. Mean Worst Scores* in a Multicenter, Investigator-Blinded Clinical Trial Comparing the Safety, Tolerability, Efficacy and Patient Acceptance of Calcitriol 3 µg/g Ointment and Calcipotriene 50 µg/g ointment in 75 Patients With Psoriasis Affecting the Face, Hairline, Flexures, and Retroauricular Areas.[29]



*Mean Worst Score=(sum of the worst score for each target lesion ÷ total # of target lesions per area)

Adapted with permission from Ortonne JP, Humbert P, Nicolas JF, et al. Intra-individual comparison of the cutaneous safety and efficacy of calcitriol 3 microg g(-1) ointment and calcipotriol 50 microg g(-1) ointment on chronic plaque psoriasis localized in facial, hairline, retroauricular or flexural areas. *Br J Dermatol*. 2003;148:326-333.

treated lesion, the investigators rated erythema, edema, and stinging/burning, on a scale from 0 (none) to 3 (severe). Clinical evaluations were performed at baseline and at weeks 1, 2, 3, 4, and 6. A mean worst score was calculated by summing the worst score observed for each target lesion at any evaluation during the 6-week study, divided by the total number of lesions on that side.[29] The mean worst erythema, edema, and stinging/burning scores for calcitriol ointment and calcipotriene ointment are shown in **Figure 4**.[29] As illustrated in the figure, calcitriol ointment was significantly better tolerated than calcipotriene ointment for all three cutaneous tolerability measures: erythema, edema, and stinging/burning.[29]

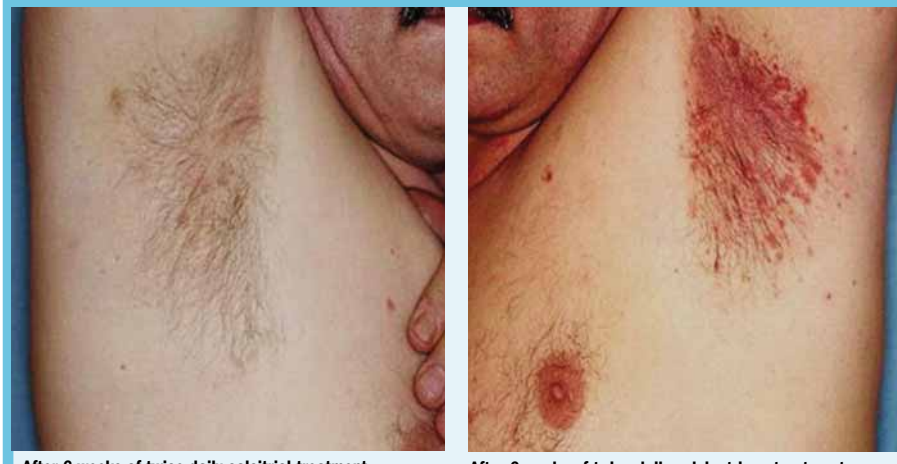
The efficacy of the two treatments was evaluated using an investigator rating of global improvement for each treated lesion from baseline to the end of the 6-week study. The overall mean improvement for all treated lesions was significantly greater for lesions treated with calcitriol than for those treated with calcipotriene ($P<0.02$), which was primarily attributed to a significantly higher re-sponse rate for psoriasis lesions of the flexural areas. Approxi-mately 67% of subjects treated with calcitriol ointment were rated by clinicians as "clear" or "almost clear" of psoriasis, compared with 33% of subjects treated with calcipotriene ointment.[29] Calcitriol and calcipotriene produced similar improvement when applied to lesions of the face, retroauricular areas, and hairline. **Figure 5** illustrates the difference in response to twice-daily application of calcitriol ointment vs calcipotriene ointment applied to matched lesions of the axillae on opposite sides of the body.[29]

The patients in this study were also asked to rate their preferences regarding the tolerance, efficacy, and overall global outcome for the two study medications after 6 weeks of treatment. Calcitriol ointment was rated as better or much better tolerated than calcipotriene ointment by 37 of the 75 patients (49.3%), calcipotriene was preferred by 8 patients (10.7%), and the remaining 30 patients (40%) did not express a preference for either treatment ($P<0.0001$ for the difference between calcitriol and calcipotriene ointments). When asked about treatment efficacy, more patients tended to prefer calcitriol than calcipotriene (44.0% vs 29.3%), although the difference between the two treatments was not statistically significant. When asked to describe their overall global preference for treatment, 43 patients (57%) preferred calcitriol ointment, 23 patients (31%) preferred the calcipotriene side, and 9 patients (12%) described the two treatments as equal ($P<0.02$ for the difference between the calci-triol and calcipotriene ointments).[29]

Calcitriol Ointment: Use in Psoriasis Treatment Regimens

Several studies have examined the role of topical calcitriol 3 µg/g ointment in combination with other psoriasis therapies. A phase III, prospective, randomized, double-blind clinical trial compared the efficacy and safety of UVB phototherapy in combination with either calcitriol ointment or vehicle ointment for 8 weeks. Ointments were applied immediately after or at least 6 hours before therapy.[30] A total of 104 patients entered the study, and clinical evaluations were performed at weeks 1, 2, 4, 6, and 8 and at a final assessment up to 10 weeks after enrollment.[30] Change in psoriasis severity between baseline and each clinical evaluation was rated on a scale from –1 (worse) to 4 (clear). As early as the first post-treatment evaluation at week 1, mean improvement from baseline was significantly greater for patients who received UVB plus calcitriol than for patients who received UVB and vehicle ointment (see **Figure 6**).[30] By the end of the

Figure 5. Difference in Response to Twice-Daily Application of Calcitriol Ointment vs Calcipotriene Ointment Applied to Matched Lesions of the Axillae on Opposite Sides of the Body[29]



After 6 weeks of twice-daily calcitriol treatment

After 6 weeks of twice-daily calcipotriene treatment

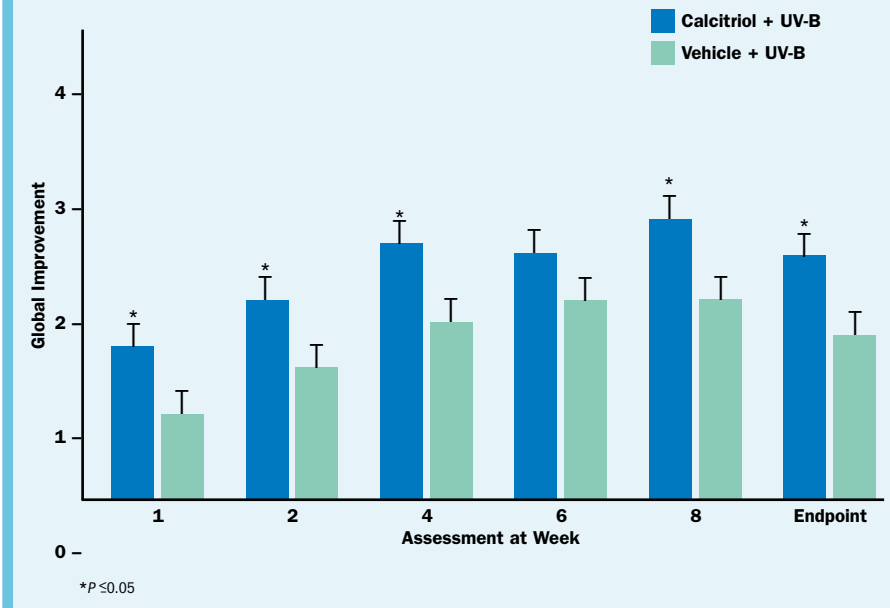
Reprinted with permission from Ortonne JP, Humbert P, Nicolas JF, et al. Intra-individual comparison of the cutaneous safety and efficacy of calcitriol 3 microg g(-1) ointment and calcipotriol 50 microg g(-1) ointment on chronic plaque psoriasis localized in facial, hairline, retroauricular or flexural areas. *Br J Dermatol*. 2003;148:326-333.

study, considerable improvement or clearing of psoriasis was noted for 45% of patients in the calcitriol group vs 20% for the vehicle group ($P<0.05$).[30] Patients in the calcitriol group also exhibited significantly better global ratings of psoriasis severity, as well as significantly lower scores on the Psoriasis Area Severity Index (PASI) rating scale.

A small, randomized, double-blind clinical study evaluated the addition of calcitriol ointment to betamethasone valerate 0.1% in patients with psoriasis.[31] Patients were randomly assigned to treatment with betamethasone valerate twice daily (morning and evening; n=10) or betamethasone valerate every morning and calcitriol every evening (n=9) for 6 weeks.[31] Patients in the calcitriol plus betamethasone group exhibited better mean scores on each of three study efficacy endpoints, including a global improvement rating of "considerable" or better from baseline (60% vs 78% for the betamethasone and betamethasone plus calcitriol groups, respectively); a final global psoriasis severity rating of "slight" or better (50% vs 78%); and decrease from baseline on the PASI rating scale (75% vs 81%).[31] Although differences between the two treatment groups were not analyzed statistically because of the small number of patients enrolled, these observations suggest that once-daily betamethasone plus calcitriol ointment is at least as effective as twice-daily betamethasone valerate.

Calcitriol ointment and other vitamin D receptor modulators have also been examined for use in sequential therapy regimens, in which treatment is initiated with the combination of a corticosteroid and a vitamin D derivative (ie, am/pm; weekend, weekday), and the corticosteroid is gradually tapered and discontinued.[8] A randomized, double-blind clinical trial compared calcitriol ointment and calcipotriene ointment in a sequential therapy regimen with the ultrapotent corticosteroid clobetasol propionate cream.[32] Patients received combination therapy consisting of clobetasol propionate in the am with either calcitriol or calcipotriene ointment in the pm for the first 2 to 4 weeks. Clobetasol was then discontinued, and the patients remained on topical vitamin D maintenance therapy for a total of 12 weeks.[32] Both regimens produced rapid improvement in psoriasis symptoms, as measured by clinician global ratings of improvement and improvement in PASI scores from baseline.[32] The efficacy and safety of the calcitriol and calcipotriene regimens were similar at all follow-up evaluations. At week 12, treatment success (defined as a clinician global rating of "markedly improved", "almost clear", or "clear") was noted for 79% of patients in the calcitriol ointment group and 88% of patients in the calcipotriene ointment group (not statistically significant).[32] These data suggest that calcitriol ointment is a safe and effective alternative to calcipotriene ointment for sequential therapy with high-potency corticosteroids.[32]

Figure 6. Improved Outcomes of Calcitriol in Combination With UVB Phototherapy: Ratings of global improvement from baseline were significantly better with the combination of calcitriol and UVB phototherapy than with UVB phototherapy alone. The benefit of calcitriol ointment on psoriasis improvement was evident at the first evaluation 1 week after the initiation of treatment. Values are mean +/- standard error of measure.[30]



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Summary and Conclusions

Calcitriol, the naturally occurring, hormonally active form of vitamin D_3, is a new chemical entity in the United States and is the only single-agent topical vitamin D ointment. It represents a significant advance in topical vitamin D therapy for psoriasis. The vitamin D cream,

calcipotriene, is widely used for the treatment of psoriasis but is associated with cutaneous adverse events in many patients, especially when applied to sensitive skin areas. In two phase III, vehicle-controlled clinical trials, calcitriol 3 µg/g ointment improved psoriasis symptoms, with significant improvement at the first post-treatment evaluation after 2 weeks. Calcitriol ointment was safe and well-tolerated when applied twice daily for up to 52 weeks, with a low incidence of adverse events and with no reported clinically significant effect on calcium homeostasis. Compared with baseline, BSA affected by psoriasis remained stable or improved in 233 of 249 patients (94%) who remained in the study for 26 weeks, and in 127 of 130 patients (98%) who remained in the study for 52 weeks. In a study that directly compared calcitriol and calcipotriene ointments for patients with mild-to-moderate psoriasis in sensitive skin areas, calcitriol was associated with significantly lower ratings of erythema, edema, and stinging/burning of target lesions and significantly greater improvement of psoriasis lesions in sensitive skin-fold areas from baseline. Calcitriol also was preferred by patients for its greater tolerability and overall effectiveness. Clinical studies of combination regimens for psoriasis have demonstrated the efficacy and safety of calcitriol ointment when used with other conventional psoriasis therapies, including UVB, betamethasone valerate, and in sequential therapy with clobetasol propionate. Calcitriol 3 µg/g ointment is an important new option that offers patients and physicians flexible, long-term topical psoriasis treatment.

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