

Efficacy and safety of topical calcitriol 3 [micro]g/g ointment, a new topical therapy for chronic plaque psoriasis

ABSTRACT Topical vitamin D modulators are among the most widely used medications for the treatment of psoriasis. Calcitriol, the naturally occurring active form of vitamin [D.sub.3], has long been used for topical psoriasis therapy in Europe and other parts of the world and was recently approved in the United States. Calcitriol 3 [micro]g/g ointment has been extensively evaluated for the treatment of chronic plaque-type psoriasis and has been shown to be effective, safe and well-tolerated in a number of short-term and long-term clinical trials. Pharmacokinetic studies in patients with psoriasis and healthy control subjects have demonstrated that topical calcitriol ointment produces little systemic absorption of calcitriol and does not alter systemic calcium homeostasis significantly even when applied to approximately one third of the body surface area.

Calcitriol ointment is associated with a low rate of cutaneous irritation and does not increase the sensitivity of treated skin to phototoxicity following treatment with ultraviolet treatment. In two randomized, double-blind clinical trials, twice-daily application of calcitriol ointment for eight weeks resulted in clearing or minimal residual psoriasis in approximately 34% of patients, compared with 12% to 22.5% of patients treated with vehicle ointment ($P = 0.005$ in study 1 and $P < 0.001$ in study 2). Calcitriol ointment also significantly improved ratings of individual psoriasis signs and symptoms of plaque elevation, erythema, scaling and pruritus compared to vehicle. In two long-term studies in which patients were treated with calcitriol ointment for a year or longer, calcitriol ointment produced sustained improvement in physician-rated and patient-rated psoriasis severity. Calcitriol ointment was associated with a low risk of adverse events after one year and did not alter laboratory measures of calcium or phosphorus metabolism in a clinically significant manner. The results of these studies suggest that calcitriol 3 [micro]g/g ointment is an effective, safe and well-tolerated topical psoriasis therapy. Calcitriol ointment offers considerable flexibility for use in a variety of monotherapy and combination therapy regimens for patients with psoriasis.

INTRODUCTION As described in an accompanying article (see The Role of Topical Vitamin [D.sub.3] Receptor Modulators in Psoriasis Therapy by Emil A. Tanghetti, MD, pages 4), topical vitamin [D.sub.3] therapy is among the most widely used approaches to the treatment of psoriasis. A 12-year survey (ending in 2001) of prescribing patterns among office-based physicians (dermatologists and nondermatologists) in the United States (U.S.) found that although corticosteroids are the most commonly used class of medications for psoriasis, the synthetic vitamin [D.sub.3] analog calcipotriene was the single most frequently listed psoriasis medication. (1) Calcipotriene monotherapy has been shown to substantially improve symptoms in approximately 60-70% of patients with chronic plaque psoriasis, reaching its maximum effectiveness after approximately six-to-eight weeks. (2) However, calcipotriene is associated with substantial cutaneous irritation in approximately 20% of patients and is not suitable for application to the face. (3) A second synthetic vitamin [D.sub.3] analog, tacalcitol, is also approved for use in some countries outside the U.S. Tacalcitol is less likely than calcipotriene to produce cutaneous irritation but may also be less effective. (3), (4) There is, therefore, a need for new topical vitamin [D.sub.3] therapies that produce high treatment response rates without causing cutaneous irritation. The vitamin [D.sub.3] modulator calcitriol (1[alpha], 25-dihydroxyvitamin [D.sub.3]), long available in an ointment formulation for the treatment of psoriasis in Europe, is now the only vitamin [D.sub.3] ointment available for use in the U.S. In contrast to synthetic vitamin D products such as calcipotriene, calcitriol is a naturally occurring active form of vitamin D that is an important regulator of normal calcium homeostasis. (5) Although the precise mechanism by which calcitriol improves psoriasis is not completely understood, calcitriol suppresses several physiologic processes that are thought to contribute to the pathogenesis of psoriasis. For example, vitamin [D.sub.3] products have been shown to inhibit keratinocyte proliferation, to promote keratinocyte differentiation, and to decrease the expression of a broad range of proinflammatory cytokines that stimulate T-cell proliferation and cutaneous inflammation. (2), (5) Calcitriol has been extensively evaluated for the treatment of psoriasis in a number of patient populations and treatment regimens. Calcitriol 3 [micro]g/g topical ointment has been shown to improve the symptoms of psoriasis, with a sustained long-term maintenance of benefit and a low incidence of adverse effects, without clinically altering systemic calcium metabolism. This article provides an overview of the clinical research that supports the short-term and long-term efficacy, safety and tolerability of topical calcitriol ointment as monotherapy for the treatment of psoriasis. Calcitriol Ointment Initial Clinical Studies of Calcitriol 3

[micro]g/g Ointment for Psoriasis Therapy Calcitriol ointment contains 3 [micro]g/g of calcitriol and the inactive ingredients mineral oil, dl-a-tocopherol and white petrolatum.(6) Calcitriol ointment is non-viscous, with good patient-rated spreadability and cosmetic acceptability. (7) A calcitriol dose of 3 [micro]g/g was selected for clinical development based on the results of a double-blind, parallel-group, vehicle-controlled dose-ranging study that examined four different doses of calcitriol ointment (0.3, 1.0, 3.0 and 9.0 [micro]g/g) in 245 patients with severe psoriasis. (5) At end point (week 8), global improvement of psoriasis symptoms was markedly higher for 71% of patients in the 3.0 [micro]g/g group and 77% in the 9.0 [micro]g/g group compared to 46% in the vehicle group. This study established the dose of 3 [micro]g/g as the minimum concentration of topical calcitriol that was associated with clinically relevant efficacy. Pharmacokinetic studies in patients with psoriasis and healthy control subjects have demonstrated high cutaneous penetration and low plasma absorption of calcitriol 3 [micro]g/g ointment. (5) The pharmacokinetic effects of a maximal topical dose of calcitriol up to 35% BSA were examined in a study of patients with psoriasis affecting [greater than or equal to] 25% of the body surface area (BSA). (6) Calcitriol 3 [micro]g/g ointment was applied twice daily to a total of 35% of the BSA for 21 days. This high-dose calcitriol regimen increased the plasma calcitriol concentration by approximately 36% above the mean baseline value. However, no patients developed clinically significant hypercalcemia, and no correlations were observed between elevated plasma calcitriol concentrations and biochemical parameters of serum albumin-adjusted calcium, serum phosphorus, urinary calcium or urinary phosphorus. The local safety, cutaneous irritation potential, contact sensitization, and potential for photosensitivity of this calcitriol 3 [micro]g/g treatment were extensively evaluated in a series of four clinical studies of patients with psoriasis. (8) In the first study, calcitriol 3 [micro]g/g ointment did not produce cutaneous irritation even when applied five times per week for 21 days under occlusive patches. This repeat insult patch test (RIPT) is a technique that maximizes cutaneous exposure to a potentially irritating test substance. (8) A second study examined skin sensitization induced by calcitriol ointment or white petrolatum in 225 subjects. Calcitriol 3 [micro]g/g ointment, calcitriol vehicle ointment, and white petrolatum were applied under occlusive patches for either 48 or 72 hours over a three-week period, and skin sensitization was examined by skin challenge two weeks after removal of the patches. Application of calcitriol ointment did not induce skin sensitization to subsequent application of calcitriol or vehicle ointment. (8) Only one of the 225 subjects exhibited a mild erythematous reaction upon skin challenge with calcitriol two weeks later, and this reaction did not occur at a second challenge session. A sensitivity reaction to white petrolatum was also noted for one subject. A third study examined photosensitivity to ultraviolet A and ultraviolet B (UVA/UVB) radiation after exposure to calcitriol 3 [micro]g/g ointment, calcitriol vehicle ointment or white petrolatum for 24 hours under occlusive patches. Photosensitivity, as assessed by erythema with UVA/UVB exposure after removal of the occlusive patches, was no greater for calcitriol application sites than for sites that were exposed to calcitriol vehicle or white petrolatum. Finally, a fourth study found that cutaneous photosensitivity was neither increased following repeated applications of calcitriol 3 [micro]g/g ointment under occlusive patches over a period of three weeks nor during a challenge phase two weeks later. Together, these initial studies suggested that calcitriol ointment would be a safe and tolerable treatment in patients with psoriasis.

Efficacy and Safety of Calcitriol 3 [micro]g/g Ointment As Monotherapy for Psoriasis

Calcitriol Ointment in Randomized, Double-Blind Clinical Trials

The efficacy and safety of topical calcitriol ointment were examined in two placebo-controlled, randomized, multicenter, parallel-group clinical trials of identical design. (9) In both studies, patients who were [greater than or equal to] 12 years of age with mild-to-moderate chronic plaque psoriasis and with an involved BSA of [less than or equal to] 35% were randomized to receive calcitriol 3 [micro]g/g ointment or vehicle ointment twice daily for eight weeks. (9) A total of 839 patients was randomized (419 received calcitriol ointment and 420 received vehicle ointment), and the study was completed by more than 85% of the patients. (9) The demographic and clinical characteristics of the two groups were well matched at baseline. A baseline global severity rating of "moderate" psoriasis was noted for 74.7% of patients in the calcitriol group and 77.4% of patients in the vehicle group, and the mean BSA affected by psoriasis was 10.3% versus 10.8% for the calcitriol and vehicle groups, respectively. (9) Response to treatment was evaluated using a psoriasis Global Severity Score (GSS), which was rated on a scale of 0 (clear) to 5 (very severe). Success was defined as a GSS after treatment of 0 or 1 (clear or minimal psoriasis). The treatment success rates for calcitriol and vehicle groups of both studies are shown in Figures 1 and 2. (9) In study 1, the success rate at the study end point was 34.4% for patients in the calcitriol group and 22.5% for those in the vehicle group (P = 0.005). In study 2, success at the study end point was noted for 33.3% versus 12.3% for the calcitriol and vehicle groups, respectively (P < 0.001). (9) In both studies, significant differences in success rate between calcitriol and vehicle groups were noted as early as the first postbaseline visit at week 2. In addition, the proportion of patients who attained treatment success increased over time with continued therapy. [FIGURE 1 OMITTED] [FIGURE 2 OMITTED] Treatment response was also evaluated by assessing the individual psoriasis symptoms of plaque elevation, erythema, and scaling, each of which was rated on a scale from 0 (none) to 4 (very severe). For each patient, psoriasis symptoms were assessed at two target lesions, one located at a bony prominence (e.g., the elbow, knee, sacrum) and the other from a nonbony area. Ratings of these individual symptoms were combined into a composite Dermatologic Sum Score (DSS). (9) After eight weeks, the investigators noted that calcitriol ointment resulted in significantly greater improvement from baseline than did vehicle ointment for each of the individual psoriasis symptoms (in study 1, all P values < 0.05 at bony prominences and [less than or equal to] 0.005 at nonbony areas; in study 2, all P values < 0.001) and

also for the composite DSS (P [less than or equal to]0.001 in both studies). (9) Calcitriol also produced significantly greater improvement from baseline in patient ratings of pruritus. In study 1, 51.2% of patients in the calcitriol group and 34.9% of patients in the vehicle group reported no pruritus at week 8; in study 2, 55.2% of the calcitriol group and 34.1% of the vehicle group were free of pruritus at week 8 (P <0.001 for both studies). (9) Global improvement of psoriasis from baseline was rated by both patients and physicians at the study end point on a scale from 5 (clear) to 1 (worse). (9) As shown in Figure 3, both patient and physician rating of global improvement were significantly better with calcitriol ointment than with vehicle ointment. (9) In study 1, improvement from baseline was rated by clinicians as "marked" or better for 39.6% versus 21.2% of patients in the calcitriol and the vehicle groups, respectively. In study 2, marked or better global improvement was noted for 32.7% of patients treated with calcitriol and 12% of those treated with vehicle (P <0.001 in both studies). Similar findings were reported by the patients. Marked or better improvement was noted by 35.7% versus 21.6% of calcitriol-treated and vehicle-treated patients, respectively, in study 1 and 34.7% versus 12%, respectively, in study 2 (P <0.001 in both studies). (9) FIGURE 3. Global improvement of at least "marked" or better: Patient And investigator ratings at end point, Studies 1 and 2. (9) Calcitriol Vehicle Study 1: Patients 35.7% 21.6% Study 1: Investigators 39.6% 21.2% Study 1: Patients 34.7% 12.0% Study 2: Investigators 32.7% 12.0% P <0.001 for calcitriol ointment vs vehicle (assessed by investigators) Note: Table made from bar graph. The incidence of adverse events was similar for the calcitriol and the vehicle groups. In study 1, treatment-related adverse events were noted for 6.7% of patients in the calcitriol group and 9.6% of those in the vehicle group; in study 2, these events were noted for 10.5% in the calcitriol group and 11.8% in the vehicle group. (9) Treatment-related adverse events included skin discomfort, pruritus, and erythema, which were generally mild. (9) In addition to its antiproliferative and anti-inflammatory effects, calcitriol is an important modulator of systemic calcium absorption. Calcitriol stimulates both the absorption of calcium from the gastrointestinal tract and the mobilization of calcium from bone and, when used orally, has been shown to elevate serum calcium levels. (2) Topical vitamin [D.sub.3] modulators therefore possess the theoretical risk that they might alter systemic calcium metabolism substantially. Clinical experience with calcipotriene in the U.S. has suggested that this agent is associated with a generally low incidence of significant calcium abnormalities, although some small studies and case reports have described substantial elevations of serum calcium concentrations in patients using topical calcipotriene for psoriasis. (10) A subset of 152 patients from both phase 3 calcitriol ointment studies underwent extensive laboratory testing for a number of measures of calcium homeostasis, including serum total calcium and albumin-adjusted calcium concentrations, as well as levels of 24-hour urinary calcium, phosphorus, and creatinine, creatinine clearance, and the urinary calcium to creatinine ratio. (9) Calcitriol ointment did not significantly alter the mean values of any routine laboratory assessment or measure of calcium homeostasis. Albumin-adjusted serum calcium values exceeding the upper limit of normal were noted for a total of 12 patients in the calcitriol group and 10 patients in the vehicle group. (9) None of the elevated serum calcium values exceeded the alert level of 10% or more above the upper limit of normal. At least one 24-hour urine calcium value above the normal range was noted for 15 patients in the calcitriol group and 26 patients in the vehicle group. (9) Together, the results of these two randomized, placebo-controlled, double-blind clinical trials demonstrated that twice-daily application of calcitriol 3 [micro]g/g ointment significantly improved the signs and symptoms of psoriasis. Calcitriol ointment was safe and well tolerated, and did not significantly affect calcium homeostasis or other routine laboratory parameters. Supporting Open-Label or Single-Group Studies of Calcitriol Ointment The efficacy and safety of calcitriol ointment were also evaluated in several open-label, single-group studies. Two small, single-group studies examined the efficacy and safety of calcitriol ointment for treatment of moderate to severe psoriasis of the face, hairline, or retroauricular folds. (11) In the first study, which enrolled 31 patients, twice-daily application of calcitriol 3 [micro]g/g ointment resulted in physician-rated global improvement of "definite" or better in 74% of patients after eight weeks. In the second study, clearance of psoriasis was rated as definite, considerable, or complete in 19 of 20 patients. (11) A prospective observational study by Carboni et al. enrolled 60 patients with mild-to-moderate psoriasis affecting <35% BSA. (12) This study included 20 patients with psoriasis involving sensitive skin areas such as the face, the flexural areas, or both. The mean PASI score at baseline was 8.3, which decreased to 2.4 after 12 weeks of twice-daily application of calcitriol ointment. (12) Clinical remission, which was defined as a reduction of PASI score of >75% from baseline, was noted for 11.6% of patients at week 4, 28.3% of patients at week 8, and 63.3% of patients at week 12. (12) Of the 20 patients with psoriasis affecting sensitive areas, 17 were completely clear of psoriasis and three were partially clear after 12 weeks. (12) Mild skin irritation and pruritus were noted for 12 of the 60 patients. No patients developed hypercalcemia, nor were any significant changes in laboratory measures of calcium or phosphorus homeostasis observed during the 12-week study. Six patients discontinued the study between week 4 and week 12 because of increasing pruritus, which the investigators attributed to excessive use of the calcitriol ointment. (12) These observations suggest that calcitriol ointment is effective and well tolerated even for patients with psoriasis affecting sensitive skin areas. Effect of Calcitriol on Calcium Homeostasis As described above, the clinical studies of calcitriol ointment suggested that the risk of hypercalcemia is low. However, some investigators hypothesized that patients with psoriasis affecting relatively large body surface area might be at greater risk of hypercalcemia or other metabolic effects of calcitriol because of the larger area of medication application. (13) Barker and colleagues therefore conducted a prospective, open-label clinical trial that examined the effects of topical calcitriol administration on calcium homeostasis for patients with varying degrees of BSA affected by psoriasis at baseline. (13) Patients with at least

mild-to-moderate plaque psoriasis affecting 5% to 35% of the BSA were stratified into 3 groups based on BSA affected at base line: 5% to <15% of BSA, 15% to <25% of BSA, and 25% to 35% of BSA. Calcitriol was applied twice daily for 12 weeks, and, where possible, additional posttreatment evaluations were performed two weeks and eight weeks after calcitriol was discontinued. (13) The primary safety measure was the albumin-adjusted serum calcium concentration, which is a measure of biologically active ionized calcium after subtraction of inactive, protein-bound calcium. A total of 59 patients began treatment with calcitriol, and 45 patients completed 12 weeks of treatment. (13) Six patients discontinued the study because of adverse events; five patients were lost to follow-up, two patients discontinued at their own request, and one patient discontinued for other reasons. As shown in Figure 4, the mean albumin-adjusted serum calcium values for each of the three BSA groups remained within the normal range throughout the 12-week calcitriol application phase and at post-treatment evaluations up to eight weeks after calcitriol was discontinued. (13) At a single time point (week 12), there was a small but statistically significant difference between the BSA groups for the change from baseline in albumin-adjusted calcium concentration ($P=0.003$), although calcium values for all of the patients remained within the normal range at every evaluation. None of the patients exhibited clinical signs or symptoms of hypercalcemia. A similar pattern was observed for serum total calcium concentrations, with a small but statistically significant difference between groups at week 12 ($P=0.017$) but not at any other evaluation. (13) Mean values for all other laboratory parameters (i.e., albumin, creatinine, alkaline phosphatase, phosphorus, and urea) also remained within normal limits throughout the study. Transient hypercalciuria was noted for five patients, none of whom required treatment discontinuation. (13) [FIGURE 4 OMITTED] These observations suggested that calcitriol ointment does not produce hypercalcemia or otherwise significantly affect calcium metabolism even when applied to psoriasis lesions covering approximately one third of the body surface over 12 weeks.

Long-Term Safety and Efficacy of Calcitriol Monotherapy Psoriasis is a chronic condition that often requires continuous treatment for many months. It is therefore essential to understand the long-term efficacy, safety, and tolerability of psoriasis treatments. For example, although corticosteroids are a mainstay of psoriasis therapy, the use of topical high-potency corticosteroids is generally limited to a period of a few weeks because of the risk of cutaneous adverse events and the potential for suppression of the hypothalamic-pituitary axis. Two long-term prospective clinical trials have examined the safety and efficacy of twice-daily application of calcitriol 3 [micro]g/g ointment for one year or longer. The first study was an open-label, multicenter, prospective clinical trial in which 257 patients with chronic plaque psoriasis applied calcitriol 3 [micro]g/g ointment twice daily to all psoriasis lesions except lesions of the head. (14) This study used a fixed cutoff date in which follow-up evaluation continued for 18 months after the enrollment of the first patient. Thus, patients were treated for varying periods of time up to a maximum of 18 months. (14) A total of 219 patients was treated continuously for [greater than or equal to] 3 months, 149 patients were treated for [greater than or equal to] 6 months, 75 patients were treated for [greater than or equal to] 12 months, and 16 patients were treated for 18 months. (14) Calcitriol ointment was well tolerated. A total of eight patients withdrew because of adverse events: seven patients withdrew because of local skin irritation reactions, and one patient developed transient, asymptomatic hypercalcemia. (14) No statistically or clinically significant changes were observed between baseline and posttreatment follow-up for any laboratory parameter, including several measures of calcium and phosphorus metabolism. Definite or considerable improvement in psoriasis between each patient's baseline and final assessment was noted for 96 patients (40.1%), and clearing of psoriasis was noted for 39 patients (16.3%). The percentage of patients with severe or very severe psoriasis decreased from 47.4% at baseline to 21.4% at end point, and the percentage of patients with no or only slight psoriasis increased from 7.5% to 38.8%. (14) The mean PASI score (modified to exclude the head) decreased from 9.71 points at baseline to 4.24 points after three months of treatment with twice-daily calcitriol ointment, a reduction of 53%. The PASI score remained approximately 50% to 60% below baseline values throughout the 18-month study. (14) Although these results suggested that calcitriol ointment is safe and effective for the long-term treatment of psoriasis, only 75 patients were evaluated for [greater than or equal to] one year, and only 16 patients were evaluated for a full 18 months. A second prospective clinical trial was conducted to further characterize the long-term safety and efficacy of calcitriol ointment in a larger patient population. (15) This open-label, single-group study was designed to enroll enough patients to ensure that at least 100 patients received one year of treatment. A total of 324 patients with mild to moderate chronic plaque psoriasis was enrolled at 30 centers in Europe. Patients older than 12 years of age (older than 18 years in Germany) with psoriasis affecting a BSA of [less than or equal to] 35% applied calcitriol 3 [micro]g/g ointment twice daily. Treatment was continued for [greater than or equal to] 180 days by 233 patients, 116 patients continued treatment for [greater than or equal to] 360 days, and 136 patients completed 52 weeks (the 52-week visit occurred before the 360-day visit for 20 patients). Approximately 60% of the patients were male, their mean age was 45 years, and 99% were white. (9) At baseline, the mean BSA affected by psoriasis was 16.1%, and the baseline severity of psoriasis was rated as "moderate" for most patients (55%). As in the studies described previously, twice-daily application of calcitriol ointment was well tolerated. Most adverse events consisted of abnormal laboratory values that were not considered related to study medication and that were not associated with symptoms or premature study discontinuation. Hypercalcemia (an elevated albumin-adjusted calcium concentration above the normal limit of 2.55 mmol/L ([10.2 mg/dL]) was noted for 10 patients at some point during the study, with one patient experiencing two episodes of hypercalcemia. No episode of hypercalcemia was considered by the treating physician to have been clinically significant or led to the premature

discontinuation of therapy. Adverse events that were considered to be related to study medication were reported for 45 patients (13.9%) and usually consisted of laboratory abnormalities without clinical signs or symptoms. Eight patients discontinued the study because of adverse events (2.5%), and only four of these events were considered by the investigators to be potentially related to study medication (one case each of irritant dermatitis, pruritus, kidney pain, and urine abnormality). Efficacy was evaluated by a 6-point GSS scale from 0 (clear) to 5 (very severe). Of the 324 patients who entered the study, 138 (42.6%) attained a GSS rating of 0 or 1 (clear or minimal psoriasis) on at least one post-baseline assessment. The change in GSS ratings of severity over time is shown in Figure 5. (15) In order to assess the effect of calcitriol therapy over time, GSS scores were evaluated during four 90-day periods: Period 1 (days 1-90), Period 2 (days 91-180), Period 3 (days 181-270), and Period 4 (days 271 through the end of the study). The proportion of patients with GSS ratings of clear or minimal psoriasis increased over time, from 11.1% during Period 1, to 22.1% during Period 2, to 37.3% during Period 3, and, finally, to 47.1% during Period 4 (Figure 6). Patient self-reported improvement from baseline was rated on a seven-point scale of -1 (worse) to 5 (clear). Marked or better improvement in psoriasis from baseline (corresponding to a numerical score of 3 to 5) was reported by 131 of 249 patients (52.6%) after 26 weeks and by 83 of 130 patients (63.8%) after 52 weeks. The mean percent BSA affected by psoriasis decreased from 16.1% at baseline to 10.7% at the final evaluation. The results of this long-term clinical trial confirmed the favorable safety profile and efficacy of topical calcitriol 3 [micro]g/g ointment for the treatment of chronic mild-to-moderate psoriasis. [FIGURE 5 OMITTED] Percentage of Patients With Ratings of Clear or Minimal, % Period 1 (days 1 to 90) 36/324 11.1% Period 2 (days 90 to 180) 63/285 22.1% Period 3 (days 181 to 270) 87/233 37.3% Period 4 (days 271 to end of study) 66/140 47.1% Note: Table made from bar graph. A post hoc analysis was conducted on those patients who stayed in the study through week 26 (n=249). In this analysis, patients were grouped according to their baseline BSA and the distribution of week 26 BSA was determined for each group (Figure 7). In this analysis, 93.2% (232/249) of patients maintained or improved with respect to BSA by week 26. A similar analysis was repeated for patients who stayed in the study through week 52 (n=130; Figure 8). Among these patients, 97.7% (127/130) of patients maintained or improved with respect to BSA by week 52. (15), (16) These findings suggest that calcitriol ointment is a valuable new option in the management of psoriasis. [FIGURE 7 OMITTED] [FIGURE 8 OMITTED] CONCLUSION The synthetic topical vitamin D analog calcipotriene has been approved for use in the U.S. for more than 15 years and is widely used for the treatment of psoriasis. However, the ointment formulation, more popular with prescribers, is no longer available. Although it is clearly effective for psoriasis therapy, many patients experience significant cutaneous irritation with calcipotriene. Calcitriol ointment has long been used for the treatment of psoriasis in Europe and is now the only vitamin [D.sub.3] ointment available for use in the U.S. Calcitriol is not a synthetic vitamin D analog, but is the naturally occurring active form of vitamin [D.sub.3]. A number of clinical studies have demonstrated that calcitriol is effective, safe, and well tolerated for the treatment of psoriasis. Studies of cutaneous irritation with calcitriol have demonstrated that calcitriol is well tolerated and does not induce sensitization, phototoxicity, or photosensitization. Several short-term and long-term studies demonstrated that calcitriol ointment does not significantly alter calcium metabolism even when applied twice daily for up to 12 months on up to 35% of the BSA. In two randomized, double-blind clinical trials, calcitriol ointment was superior to placebo ointment on global ratings of psoriasis severity, as well as ratings of individual signs and symptoms of psoriasis. In long-term studies of 52 weeks, calcitriol ointment has been well tolerated, with no clinically significant effects on calcium homeostasis or other clinical laboratory parameters. The efficacy of calcitriol ointment for the treatment of psoriasis, in combination with its favorable safety profile, suggest that the vitamin [D.sub.3] ointment is appropriate for use in a variety of monotherapy and combination therapy regimens for patients with psoriasis. ACKNOWLEDGEMENTS Writing and Editorial assistance was provided by Mark P. Bowes, PhD and Medisys Health Communications. Funding was provided by Galderma Laboratories, L.P. DISCLOSURES Dr. Kircik is a consultant and investigator, and is on the Advisory Board, for Valeant Pharmaceuticals, Intl., Warner-Chilcott, Intendis, Amgen, Inc., and Galderma Laboratories, LP. He is an investigator, speaker, and is on the Advisory Board for Allergan, Inc. He is a speaker, investigator, consultant, and is on the Advisory Board for OrthoNeutrogena, SkinMedica, Inc., Stiefel Laboratories, Inc., and Connetics Corporation. He is an investigator, consultant and speaker for CollaGenex. He is a consultant and is on the Advisory Board for Colbar. He is a consultant for and stockholder in Johnson & Johnson. He is an investigator and speaker for Leo, PharmaDerm, UCB, and Asteilas Pharma US, Inc. He is an investigator and is on the Advisory Board for Nano Bio and Ferndale Laboratories, Inc. He is a speaker and is on the Advisory Board for Genentech, Inc. He is an investigator for GlaxoSmithKline, PLC, Health Point, LTD, Medicis Pharmaceutical Corp., Navartis AG, Nucrust Pharmaceuticals Corp., Obagi, QLT, Inc., Pfizer, Quatrix, TolerRx, Acambis, Asubio, Berlex Laboratories (Bayer HealthCare Pharmaceuticals), Biolife, Breckinridge Pharma, Centocor, Inc., Combinatrix, Coria, Dow Sciences and Dusa. He is a speaker for Innovail, 3M, Serono (Merck Serono International SA), Triax, Abbott Laboratories, and Dermik Laboratories. He is on the Advisory Board for Biogen-Idec. REFERENCES (1.) Pearce DJ, Stealey KH, Balkrishnan R, et al. 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