Calcitriol Ointment 3 µg/g Is Safe and Effective Over 52 Weeks for the Treatment of Mild to Moderate Plaque Psoriasis

Mark Lebwohl, MD; Jean-Paul Ortonne, MD; Philippe Andres, MD; Philippe Briantais, MSc

Topical vitamin D_3 agents have emerged as important options for the treatment of psoriasis. Calcitriol, a naturally occurring and biologically active form of vitamin D_3, has been developed in an ointment formulation for topical psoriasis therapy in the United States. The product has been used outside of the United States for years. Several short-term (<6 months) clinical trials have demonstrated that calcitriol ointment 3 µg/g improves symptoms of psoriasis in participants with mild to moderate plaque psoriasis without demonstrating clinical evidence of alterations in calcium homeostasis, but little information has been available about the safety and effectiveness of continuous long-term use of calcitriol ointment. In this open-label, multicenter study, 324 participants with primarily mild to moderate chronic plaque psoriasis were treated with calcitriol ointment 3 µg/g twice daily for up to 52 weeks. A total of 136 participants completed 52 weeks of treatment. Serious adverse events (AEs)(reported by 1 participant each unless otherwise noted) included a pretibial skin ulcer (study drug was used only on the upper body), a joint disorder, metrorrhagia (2 participants), heart failure, hospitalization due to arteriosclerosis, breast carcinoma, and an infection (due to a dog bite). Clinical improvement in psoriasis symptoms was assessed by an investigator-rated global severity score (GSS) and participant-rated global assessment of improvement in psoriasis symptoms from baseline. Improvements in GSS were seen over the course of treatment. Calcitriol ointment 3 µg/g is a safe, effective, and well-tolerated option for the long-term treatment of chronic plaque psoriasis. Clinical improvement was maintained for up to 52 weeks, with no clinical effect on calcium homeostasis or other relevant laboratory test parameters.

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Dr. Lebwohl is from Mount Sinai School of Medicine, New York, New York. Dr. Ortonne is from Hopital l'Archet, Nice, France. Dr. Andres and Mr. Briantais are from Galderma R&D, Sophia Antipolis, France.

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Correspondence: Mark Lebwohl, MD, Mount Sinai School of Medicine, 5 E 98th St, New York, NY 10029 (lebwohl@aol.com).

Psoriasis is a chronic, immune-mediated disease that is characterized by the infiltration of T lymphocytes into the skin, release of inflammatory mediators, keratinocyte hyperplasia, and proliferation of skin epithelial cells.[1] Psoriasis affects approximately 2% of the US adult population and is associated with substantial pain, discomfort, stigmatization, and limitation of daily living activities.[2,3] A large-scale survey

conducted by the European Federation of Psoriasis Patient Associations concluded that patients with psoriasis experience considerable impairment of quality of life associated with daily living activities such as bathing, sports, sleep, work, school, and sexual relationships.[4] The physical impairment associated with psoriasis is similar to other severe chronic illnesses, such as type 2 diabetes mellitus, hypertension, and cardiovascular disease.[5]

According to treatment guidelines from the American Academy of Dermatology, therapy aims to produce durable improvement in psoriasis signs and symptoms while minimizing adverse events (AEs).[6] Most patients with psoriasis have mild to moderate disease that is primarily treated with topical agents.[7] Topical corticosteroids are widely used for the treatment of psoriasis and are available in many different formulations and potencies.[8,9] Although they are effective for many patients, topical corticosteroids are associated with a number of cutaneous and systemic AEs (eg, atrophy, telangiectases, striae, hypothalamic-pituitary-adrenal axis function suppression).[8] Because of the potential for AEs, corticosteroids typically are indicated for limited periods of use (eg, no more than 2–4 weeks for super–high-potency corticosteroids).[9,10] Other topical therapies include retinoids, anthralin, and coal tar. These agents can produce major skin irritation; anthralin and coal tar also are messy to apply and often cause staining of clothing.[8]

Topical vitamin D_3 agents have emerged as effective and well-tolerated treatment options for patients with mild to moderate psoriasis. The synthetic vitamin D_3 product calcipotriene was introduced in the United States in 1994 and rapidly became one of the most widely prescribed psoriasis medications.[7] More recently, the discontinuation of calcipotriene ointment has resulted in increased use of the calcipotriene cream formulation. Calcipotriene also is available in a fixed-combination ointment with the mid-potency corticosteroid betamethasone dipropionate. Calcipotriene substantially improves the symptoms of psoriasis, but skin irritation has been noted to occur in approximately 20% of patients, especially when applied to sensitive skin areas.[11,12]

Calcitriol, the naturally occurring and biologically active form of vitamin D_3, has been developed in an ointment formulation for topical psoriasis therapy.[13] Calcitriol produces a number of biologic effects that are thought to be important in the treatment of psoriasis, including inhibition of T-cell proliferation, suppression of inflammatory mediators, and reduction in epidermal keratinocyte proliferation.[13] Calcitrol ointment 3 μg/g is approved by the US Food and Drug Administration for the treatment of mild to moderate plaque psoriasis in patients 18 years and older. In clinical trials conducted for 8 to 12 weeks, calcitriol ointment 3 μg/g applied twice daily substantially improved the signs and symptoms of psoriasis, with a low incidence of AEs and with no clinically significant effects on calcium homeostasis.[14,15]

Lebwohl and colleagues[14] conducted 2 phase 3 clinical studies to confirm the safety and efficacy of calcitriol ointment 3 μg/g versus its vehicle. A total of 839 participants were included in the 2 studies, with 419 treated with calcitriol ointment 3 μg/g and 420 treated with vehicle. The proportion of participants with treatment-related AEs in both studies was comparable between the calcitriol-treated group and the corresponding vehicle group; treatment-related AEs were mild and included overall skin discomfort, pruritus, and erythema.[14]

A randomized, investigator-blinded, left-right comparison study demonstrated that calcitriol ointment caused less irritation of sensitive skin areas than calcipotriene ointment, but it generally was deemed to be equally effective in overall psoriasis treatment.[12] Ortonne et al[12] compared the safety and efficacy of calcitriol ointment 3 μg/g and calcipotriene ointment 50 μg/g in mild to moderate chronic plaque psoriasis affecting sensitive skin areas (ie, retroauricular and flexural areas). A total of 75 participants were enrolled; 10 participants (13%) discontinued treatment. Study results showed that perilesional erythema and edema as well as stinging/burning were significantly less severe with calcitriol versus calcipotriene ($P<.001$, $P<.02$, and $P<.001$, respectively). The difference was especially marked for erythema and stinging/burning. No participant had grade 3 erythema or edema on calcitriol-related lesions. Thirty participants (40%) had a lower mean worst score across target areas for erythema on the calcitriol-treated side compared with 10 (13%) on the calcipotriene-treated side. Calcitriol also was better tolerated in terms of stinging/burning ($P<.01$), with 36 participants (48%) having a lower mean worst score across target areas on the calcitriol-treated side. The investigator global assessment of local safety showed that calcitriol was better tolerated than calcipotriene. Twenty-four of 30 participants (80%) showed excellent tolerability with calcitriol in flexural areas compared with 17 of 30 participants (57%) in the calcipotriene group. Calcitriol was well-tolerated on retroauricular areas by 35 of 56 participants (63%) and calcipotriene by 21 of 56 participants (38%). As for local tolerability evaluated by the participants themselves, 37 (49%) considered calcitriol better or much

better tolerated than calcipotriene, whereas 8 (11%) preferred calcipotriene; the difference was significantly in favor of calcitriol ($P<.0001$) and confirmed the results of the investigator's skin safety evaluation. Two participants (3%) discontinued because of AEs, 6 (8.0%) because lesions cleared, 1 (1.3%) because of a protocol violation, and 1 (1.3%) at his own request.[12]

The primary objective of the current 52-week study was to establish the long-term safety and tolerability of calcitriol ointment 3 μg/g applied twice daily in participants with mild to moderate chronic plaque psoriasis. The secondary objective was to assess the long-term efficacy of calcitriol ointment.

Methods

Study Design—This open-label, single-group, multicenter clinical trial examined the local and systemic safety and efficacy of calcitriol ointment 3 μg/g for up to 52 weeks. Male and female participants 12 years or older (except in Germany where the minimum age was 18 years) with stable, chronic, mild to moderate plaque psoriasis (global severity score [GSS], ≥2 [mild] on a 6-point scale) were enrolled at 30 study centers in France, Germany, Hungary, Belgium, and Poland. Participants with psoriasis affecting a body surface area (BSA) of up to 35% were eligible to participate. Participants were excluded if they were pregnant, breastfeeding, or planning to become pregnant; had ongoing physical or psychiatric conditions that, in the opinion of the investigator, put the participants at risk or had the potential to confound the results of the study; presented with forms of psoriasis other than chronic plaque-type psoriasis; had hypercalcemia, renal dysfunction, or calcium-based calculi; had used topical therapies with the potential to affect the study outcome within the preceding 2 weeks (eg, vitamin D_3 derivatives, corticosteroids, retinoids) or systemic therapies within the preceding 4 weeks (eg, corticosteroids, retinoids, immunomodulatory drugs, psoralen plus UVA therapy); recently had started treatment with medications having the potential to aggravate psoriasis; or had medical conditions requiring the use of calcium or vitamin D_3 supplements. Female participants of childbearing potential were required to use an effective method of contraception. The study was performed in accordance with the Declaration of Helsinki, and all participants provided written informed consent before participating. Parental consent was provided for patients younger than 18 years.

The initial study plan called for a 6-month treatment duration. The study protocol subsequently was amended to permit treatment for up to 52 weeks. Termination of the study at either week 26 or week 52 was considered normal completion. One objective of the study was to treat 150 participants for 6 months or more and 100 participants for 1 year. It was estimated that an enrolled study population of 300 participants would be sufficient to meet these 26- and 52-week population goals.

Safety Assessments—The study was divided into 4 periods: period 1 (days 1–90); period 2 (days 91–180); period 3 (days 181–270); period 4 (day 271–study end). The safety population for each study period included all participants who entered the study period. All AEs and abnormal laboratory test findings were classified according to coding symbols for a thesaurus of adverse reaction terms. Spontaneously reported AEs were recorded at baseline and at all follow-up visits. Adverse events were rated as mild (awareness of event but easily tolerated), moderate (discomfort causing interference with usual activity), or severe (incapacitating, leaving participant unable to work or perform usual activity). Psoriasis was reported as an AE when new lesions formed on body areas that were not affected at baseline. Clinically noteworthy worsening of psoriasis also was considered an AE. A serious AE was defined as any medical occurrence that was life threatening or resulted in death, hospitalization or prolongation of existing hospitalization, significant disability, or incapacity.

Laboratory tests conducted to measure calcium homeostasis and systemic safety were assessed throughout the study (at screening and weeks 6, 12, 18, and 26), including calcitriol and parathormone (PTH) plasma levels. All abnormal laboratory test results were classified as AEs. Serum total albumin-adjusted calcium level testing (an assessment of active ionized calcium adjusted for inactive, albumin-bound calcium) was conducted at screening and at weeks 26 and 52. Hypercalcemia, the primary laboratory outcome measure, was defined as a serum total albumin-adjusted calcium level greater than the upper limit of the reference range (2.05–2.55 mmol/L). Other plasma biochemistry tests measured included levels of total calcium, alkaline phosphatase, lactic dehydrogenase, total protein, albumin, urea, creatinine, phosphorus, aspartate aminotransferase, alanine aminotransferase, total and direct bilirubin, cholesterol, triglycerides, glucose, uric acid, sodium, potassium, and chloride. Twenty-four–hour urine calcium and phosphorus concentrations were assessed at baseline and at weeks 26 and 52. Hematology assessments included a complete blood cell count.

Efficacy Assessments—A psoriasis GSS for the whole body was assessed by the investigator at

screening, baseline, and all follow-up visits using a 6-point scale (0=clear [no plaque elevation over healthy skin; no scale; erythema defined as ± possible hyperpigmentation, pigmented macules, diffuse faint pink or red coloration]; 1=minimal [possible plaque elevation but difficult to ascertain whether there is slight elevation above healthy skin; scaling may be surface dryness with some white coloration; up to mild erythema with up to light red or pink coloration]; 2=mild [slight but definite plaque elevation, typically edges are indistinct or sloped; fine scale partially or mostly covering lesions; up to moderate erythema with up to definite red coloration]; 3=moderate [moderate plaque elevation with rough or sloped edges; coarse scale covering most or all of the lesions; moderate erythema with definite red coloration]; 4=severe [marked plaque elevation typically with hard or sharp edges; coarse scaling where nontenacious scale predominates, covering most or all of the lesions; severe erythema with very bright red coloration]; 5=very severe [very marked plaque elevation typically with hard sharp edges; very coarse scaling, with thick tenacious scale over most or all lesions, with a rough surface; very severe erythema, with extreme dusky to deep red coloration]). Participant-rated global assessment of improvement from baseline was recorded at weeks 26 and 52 using a 7-point scale (5=clear; 4=almost clear; 3=marked improvement; 2=moderate improvement; 1=minimal improvement; 0=no change; −1=worse). An assessment of percentage BSA affected by psoriasis was conducted at baseline and all follow-up visits.

Study Visits—An initial screening visit was conducted to exclude participants with abnormal pretreatment clinical laboratory test results. Assessments of inclusion and exclusion criteria, demographic characteristics, prior therapy, global severity of psoriasis, and medical history also were conducted at the screening visit, which took place within one week prior to the baseline visit. At the baseline visit, the GSS and BSA affected were assessed, the study drug was dispensed, and participants were instructed to apply calcitriol ointment 3 μg/g twice daily (morning and evening). Concomitant medications required for a participant's welfare could be administered at the discretion of the treating investigator, and the use of all concomitant medications was recorded. Safety and efficacy evaluations were performed every 6 weeks for the first 18 weeks and then every 8 or 9 weeks through week 52. Participants with clearing of psoriasis lesions (GSS, 0) discontinued study medication. Participants with a score of 1 (minimal psoriasis) were allowed to continue or discontinue treatment at their own discretion. Participants who discontinued study medication were contacted at monthly intervals until the end of the 52-week study. Participants who experienced recurrence of their psoriasis after discontinuation were asked to return to the study site and restart drug application until completion of either the 26- or 52-week period.

Statistical Analyses—Safety analyses were performed for all participants enrolled in the study. Laboratory test results were assessed using available data at each time point up to week 52. An end point analysis also was performed using the last available value for each participant. Changes from baseline to end point were tested against zero using the Wilcoxon signed rank test, with *P* values considered as descriptive only. Efficacy parameters were summarized using means and standard deviations. Statistical significance was not calculated for efficacy outcomes.

Results

Study Population—A total of 324 participants were enrolled in the study and received calcitriol ointment 3 μg/g (study period 1), 285 participants entered study period 2, 233 participants completed at least 180 days and entered study period 3, and 140 participants entered study period 4. One hundred sixteen participants completed at least 360 days, and 136 participants completed 52 weeks (the week 52 visit occurred before 360 days in 20 participants).

Approximately 60% (195/324) of the participants were male, 99% (320/324) were white, and the mean age was 45.9 years. The mean BSA involved at baseline was 16.1%, and most participants (55%; 179/324) had moderate psoriasis using the GSS. At screening, the mean time since the onset of psoriasis was 18.0 years, and the mean time since the start of the current relapse was 5.2 months. The mean number of relapses reported per year was 2.4.

Adverse Events—A total of 103 participants (31.8%) discontinued the study at week 26 (47 participants [14.5%] at their request; 15 participants [4.6%] were lost to follow-up; 13 participants [4.0%] discontinued because of a lack of efficacy; 8 participants [2.5%] discontinued because of AEs; 1 [0.3%] discontinued because of a protocol violation; and 1 [0.3%] discontinued because of pregnancy). A total of 130 participants (40.1%) experienced 264 AEs (including abnormal laboratory test results) at some point during the 52-week study. Hypercalcemia was the primary laboratory outcome measure evaluated in this study. A total of 10 participants (3.1%) experienced at least 1 episode of hypercalcemia, which was defined as a serum total albumin-adjusted calcium level greater than

2.55 mmol/L. One of these participants experienced 2 episodes of hypercalcemia. None of the cases of hypercalcemia was considered clinically significant by the treating investigator or led to discontinuation of study medication. Hypercalcemia occurred with similar frequency throughout the course of the study and was not associated with the duration of treatment or BSA at baseline. Two of the participants with hypercalcemia experienced AEs. One participant had influenza and renal calculus, which were considered unlikely to be related to the study drug. The second participant had pruritus, abnormal urinalysis results, abnormal laboratory test results, psoriasis, and skin infection, of which the pruritus, abnormal laboratory test results, and skin infection were determined to be possibly related to the study drug; the abnormal urinalysis results probably related; and the psoriasis unrelated.

Adverse events were reported for 40% of participants. The most common AEs were abnormal laboratory test results, which included elevated blood calcitriol levels (23 participants [7%]), pathological blood PTH and calcitriol levels (1 participant [0.3%]), and elevated blood PTH levels (1 participant [0.3%]). Urinalysis abnormalities (the second most common AE) were noted for 14 participants (4.3%), including elevated phosphorous levels (10 participants [3.0%]), low calcium levels (2 participants [0.6%]), elevated calcium levels (1 participant [0.3%]), elevated phosphorous and calcium levels (1 participant [0.3%]), and elevated phosphorous and creatinine levels (1 participant [0.3%]).

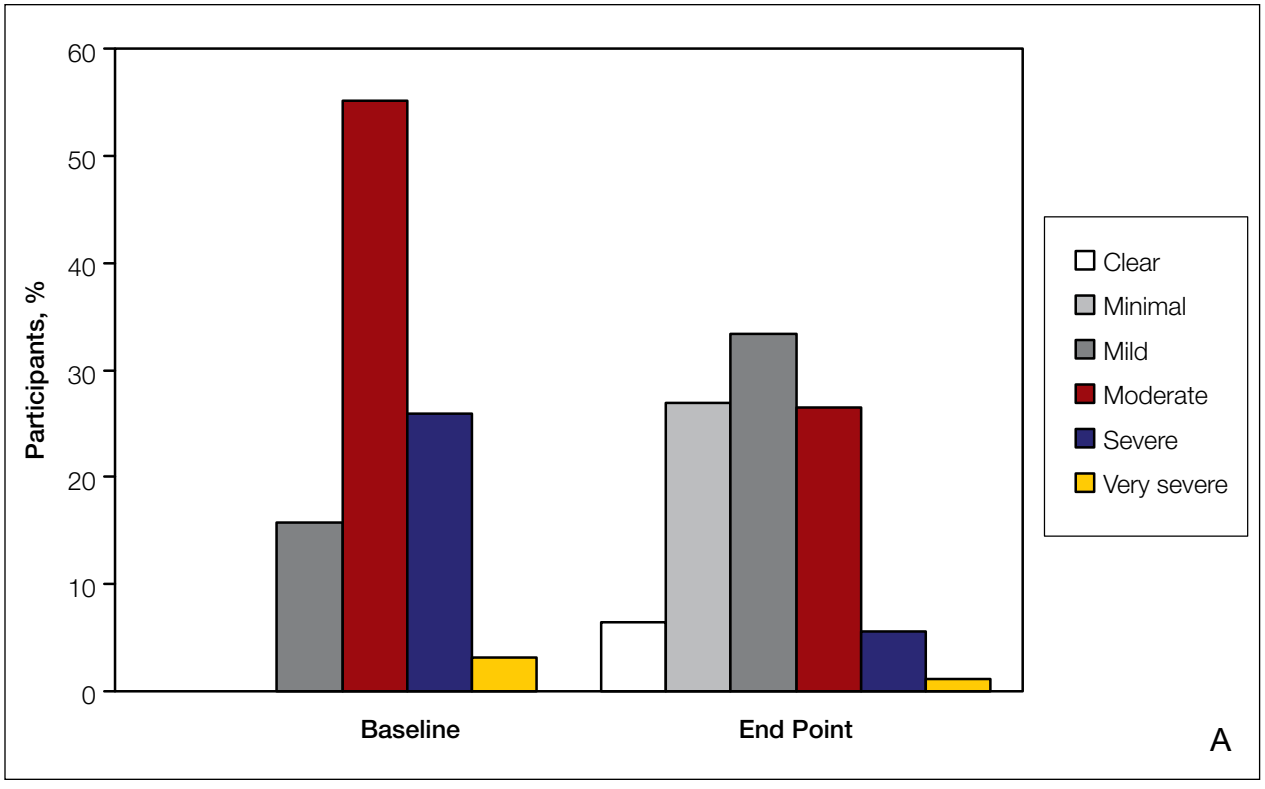
In addition to regularly scheduled urinalysis, hypercalciuria also was reported separately as an AE by 11 participants (3.4%); hyperlipidemia was reported by 4 participants (1.2%); and hyperuricemia, hypercholesterolemia, hyperglycemia, elevated white blood cell count, and anemia were each reported by 1 participant (0.3%). No clinically significant changes in mean values were noted for any of the standard laboratory test parameters over the course of the study. Two cases of painful urinary stones and 1 case of clinically silent nephrolithiasis were reported, all in participants with chronic hypercalciuria. These events were considered unrelated to study medication and contributed to early discontinuation of treatment in 1 of 3 participants.

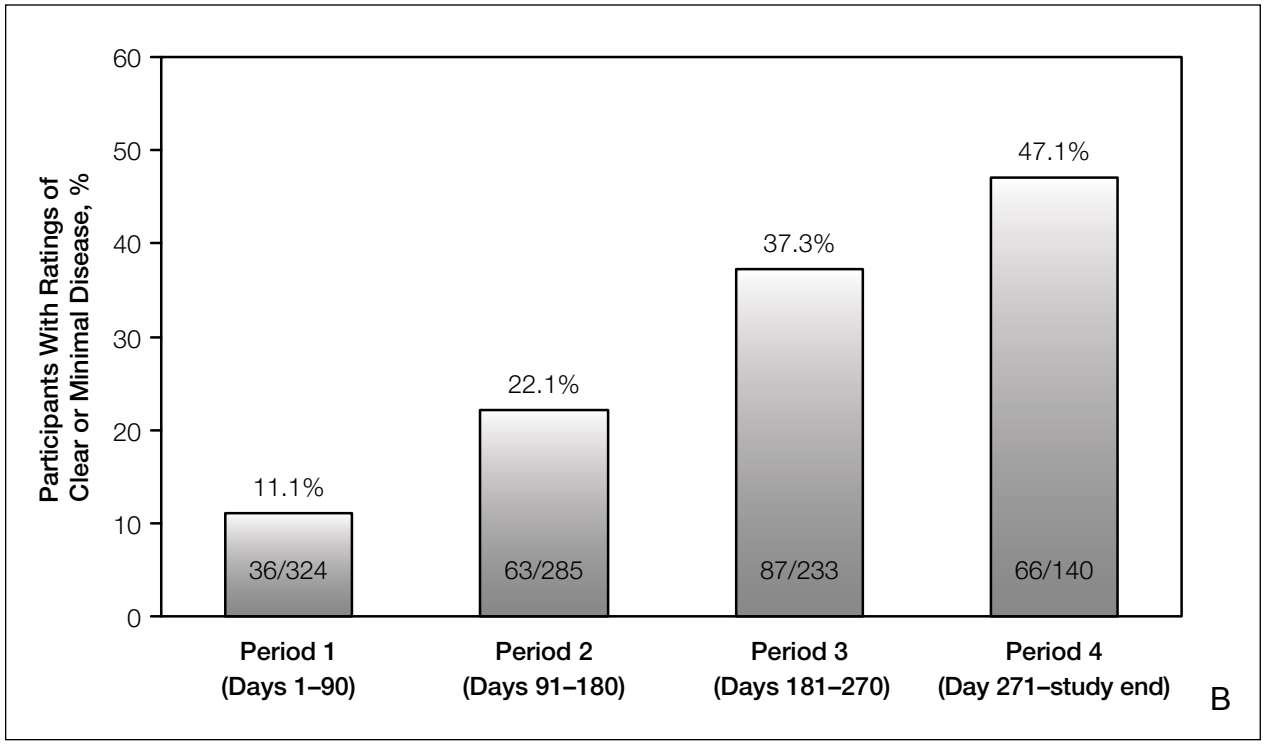
Adverse events thought to be related to study treatment were noted for 45 participants (13.9%). Serious AEs were reported for 8 participants (2.5%); none were deemed to be related to study treatment. Serious AEs (reported by 1 participant each unless otherwise noted) included a pretibial skin ulcer (study drug was used only on the upper body), a joint disorder, metrorrhagia (2 participants), heart failure, hospitalization due to arteriosclerosis, breast carcinoma, and an infection (due to a dog bite). Eight participants (2.5%) had AEs leading to study discontinuation, and AEs for 4 of these participants (1.2%) were considered related to treatment. These events included irritant dermatitis, pruritus, kidney pain, and urine abnormality (1 participant each). Six participants experienced severe AEs; none were related to calcitriol treatment.

Most dermatologic AEs consisted of individual symptoms (eg, pruritus) without clinical signs. Pruritus and folliculitis were the most common dermatologic AEs, each reported by 10 participants (3.1%). Clinical signs of intolerance to calcitriol generally occurred during the first 3 months of treatment and included skin infection (folliculitis) in 10 participants (3.1%), irritant dermatitis in 5 participants (1.5%), allergic reactions in 4 participants (1.2%), and eczema in 4 participants (1.2%). Over the course of the study, new psoriasis lesions were reported by 13 participants (4.0%).

Efficacy—The GSS was assessed at every study visit on a 6-point scale (0=clear; 5=very severe). A rating of 0 or 1 (clear or minimal psoriasis) was reported in 138 participants (42.6%) at any given point during the study and for 66 participants (47.1%) during the last treatment period (Figure, A). The GSS was evaluated during four 90-day periods: period 1 (days 1–90), period 2 (days 91–180), period 3 (days 181–270), and period 4 (day 271–study end). The proportion of participants with clear or minimal psoriasis increased over time (11.1% during period 1; 22.1% during period 2; 37.3% during period 3; 47.1% during period 4) (Figure, B).

Global assessment of improvement from baseline was rated by the participants at weeks 26 and 52 using a 7-point scale (5=clear; −1=worse). At least marked improvement was reported by 131 of 249 participants (52.6%) at week 26 and 83 of 130 participants (63.8%) at week 52. Approximately 21% (52/249) of participants rated themselves as clear or almost clear at week 26 and 30% (39/130) at week 52. Percentage BSA affected by psoriasis was evaluated at every study visit, except screening. Mean percentage BSA decreased over time from 16.1% at baseline to 10.7% at end point. A post hoc analysis revealed that the mean BSA affected by psoriasis also improved over the course of the study. Among participants who used calcitriol ointment 3 μg/g through week 26, most maintained or improved the percentage BSA involved (233/249). Furthermore, 127 of 130 participants who remained





Psoriasis global severity scores at baseline and end point following treatment with calcitriol ointment 3 µg/g (N=324)(A). A 6-point scale was used to determine the global severity score (0=clear; 1=minimal; 2=mild; 3=moderate; 4=severe; 5=very severe). At baseline, none of the participants were rated as having clear or minimal disease, and approximately 29% were rated as having severe or very severe disease. At end point, approximately 33% of participants were rated as having clear or minimal disease, and approximately 7% were rated as having severe or very severe disease. Global severity also was evaluated during four 90-day periods: period 1 (days 1–90), period 2 (days 91–180), period 3 (days 181–270), and period 4 (day 271–study end)(B). The proportion of participants with ratings of clear or minimal disease increased over time.

in the study through week 52 exhibited stable or improved BSA involvement.

Comment

This study confirmed the favorable long-term safety, tolerability, and efficacy profile of calcitriol ointment 3 μg/g for the treatment of mild to moderate chronic plaque psoriasis. The most common AEs were abnormal laboratory test results, which were not associated with clinical signs or symptoms of psoriasis. Administration of calcitriol ointment 3 μg/g twice daily for up to 52 weeks did not clinically affect calcium homeostasis, and no serious or severe AEs related to treatment were noted. The incidence of hypercalcemia was low (11 instances in 10 of 324 participants after treatment for up to 52 weeks), was not related to the duration of treatment, was not associated with clinical signs or symptoms of psoriasis, and did not lead to discontinuation of study medication. There were no clinically significant changes from baseline in serum calcitriol levels. Calcitriol was well-tolerated throughout the study, with 8 participants discontinuing the study because of AEs; only 4 of these participants had AEs related to treatment (ie, irritant dermatitis, pruritus, kidney pain, and urine abnormality). Other AEs included psoriasis symptoms in 13 participants (4.0%), skin infection (folliculitis) in 10 participants (3.1%), and pruritus in 10 participants (3.1%). A total of 10 participants (3.1%) experienced at least 1 episode of hypercalcemia, which was defined as a serum total albumin-adjusted calcium level greater than 2.55 mmol/L. In all participants but one, the maximum calcium concentration was within 5% of the upper limit of the reference range. Hypercalcemia occurred with similar frequency throughout the course of the study and was not associated with the duration of treatment or BSA at baseline. Eighteen instances of hypercalciuria were reported by 11 participants (3.4%) during the study.

At least marked improvement in psoriasis symptoms from baseline was reported by 131 of 249 participants (52.6%) at week 26 and 83 of 130 participants (63.8%) at week 52. Investigator-rated GSS indicated that 138 participants (42.6%) had a rating of clear or minimal psoriasis at any given point during the study. Improvement in GSS was greater for participants who remained in the study for up to 52 weeks. Compared with baseline, BSA affected by psoriasis remained stable or improved in 233 of 249 participants (93.6%) who remained in the study for 26 weeks, and in 127 of 130 participants (97.7%) who remained in the study for 52 weeks.

These results are consistent with several other studies that have demonstrated the favorable safety and tolerability of calcitriol ointment 3 μg/g for the treatment of psoriasis. A prior long-term study examined the safety and tolerability of calcitriol ointment, with 75 participants receiving treatment for 52 weeks or longer. No significant or clinically relevant changes were noted in calcium or phosphorous homeostasis, including participants who treated 25% to 35% BSA with calcitriol ointment over a period of several months.[16]

Another randomized, investigator-blinded clinical trial examined the cutaneous tolerability of 3 different vitamin D_3 agents after repeated administration.[17] A cumulative irritancy index was calculated using a 5-point scale. Evaluations were performed 24 hours after application of the medication. Calcitriol ointment 3 μg/g was classified as nonirritating, white petrolatum and the synthetic vitamin D_3 product tacalcitol (not available in the United States) were classified as slightly irritating, and calcipotriene was classified as moderately irritating when applied in this manner.[17]

Conclusion

Calcitriol ointment 3 μg/g is a safe, effective, and well-tolerated option for the long-term treatment of chronic plaque psoriasis. Improvement in psoriasis symptoms was seen over the course of the study in a substantial number of study participants, with no clinical effect on calcium homeostasis or other laboratory test parameters. The results of this 52-week study suggest that calcitriol ointment offers continued control in a long-term psoriasis treatment plan.

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