DOI 10.1111/j.1365-2133.2007.08037.x

Topical becocalcidiol for the treatment of psoriasis vulgaris: a randomized, placebo-controlled, double-blind, multicentre study

Y.R. Helfrich, S. Kang, T.A. Hamilton and J.J. Voorhees

Department of Dermatology, University of Michigan, Ann Arbor, MI 48109-0314, U.S.A.

Correspondence
Yolanda R. Helfrich.
E-mail: yolanda@med.umich.edu

Accepted for publication
29 March 2007

Key words
becocalcidiol, calcipotriol, psoriasis vulgaris, randomized controlled trial

Conflicts of interest
J.J.V. is a paid consultant for QuatRx Pharmaceuticals.

Summary

Background Becocalcidiol is a vitamin D_3 analogue which has not caused hypercalcaemia or significant irritation in preclinical trials.

Objectives To evaluate the efficacy and safety of two dosing regimens of becocalcidiol ointment (low dose = 75 μg g^{-1} once daily for 8 weeks; high dose = 75 μg g^{-1} twice daily for 8 weeks) in the treatment of plaque-type psoriasis.

Methods One hundred and eighty-five subjects with chronic plaque-type psoriasis affecting 2–10% of their body surface area took part in a multicentre, double-blind, parallel-group, vehicle-controlled, randomized controlled trial comparing topical application of placebo, becocalcidiol 75 μg g^{-1} once daily (low dose) or becocalcidiol twice daily (high dose) for 8 weeks. Main outcomes included Physician's Static Global Assessment of Overall Lesion Severity (PGA) score; Psoriasis Symptom Severity (PSS) score; adverse events; and laboratory assessment.

Results In the intent-to-treat population at week 8, high-dose becocalcidiol was statistically superior to vehicle [P = 0·002; 95% confidence interval (CI) 6·7–32·2], with 16 of 61 (26%) subjects achieving a PGA score of clear or almost clear. Greater improvement in PSS score was seen with high-dose becocalcidiol than with vehicle, but this result did not quite achieve statistical significance (P = 0·052; 95% CI −16·2 to 0·1). In all groups, therapy was safe and well tolerated, with fewer subjects experiencing irritation than is reported in studies using calcipotriol.

Conclusions Treatment with high-dose topical becocalcidiol for 8 weeks led to almost or complete clearing of moderate plaque-type psoriasis in over a quarter of patients. Therapy was safe and well tolerated.

Psoriasis is a chronic, hyperproliferative, inflammatory disease of the skin, characterized by the formation of well-demarcated, erythematous plaques typically surmounted by a silver-white thick scale. Involvement may range from one small lesion on an extremity to generalized involvement of most of the skin surface.

While the exact mechanisms underlying the disease are still not completely clear, it is known that immune mechanisms, mediated by cytokines, eventually lead to hyperproliferation of keratinocytes, which manifests clinically as the scaly plaques characteristic of the disease.

For nearly 20 years, topical vitamin D and its analogues have been known to be effective in treatment of psoriasis. Active vitamin D_3 inhibits keratinocyte proliferation, modulates epidermal differentiation, and has anti-inflammatory effects.[1–3] In the U.S.A., only one analogue is currently approved for clinical use—calcipotriol. It has been demonstrated to be effective in treatment of psoriasis.[4–8] However, there are reports of hypercalcaemia and hypercalciuria when used in high doses.[9–12] This could limit its usefulness in young or small patients and in those with extensive involvement. In addition, calcipotriol causes local skin irritation in approximately 15–25% of patients.[13–16] This lesional or perilesional irritation develops within the first few weeks of therapy and consists of a burning or stinging sensation; in more severe cases, it manifests as erythema or scaling.[13] The ideal topical vitamin D analogue would be highly effective, would not cause hypercalcaemia even when used in large amounts, and would not cause local skin irritation.

This study examines a new vitamin D_3 analogue, 2-methylene-19-nor-20(S)-1α-hydroxy-bishomopregnacalciferol (2MbisP), now known as becocalcidiol (QRX-101; QuatRx,

Ann Arbor, MI, U.S.A.). In preclinical models, becocalcidiol did not appear to cause hypercalcaemia.[17] Prior clinical studies with becocalcidiol ointment at concentrations up to 25 μg g^{-1} once daily have also supported a lack of hypercalcaemia (unpublished data). These studies have demonstrated excellent safety and tolerability, with trends toward improved efficacy at higher concentrations studied (5–25 μg g^{-1}). This study was designed to evaluate the safety and efficacy of becocalcidiol at higher concentrations (75 μg g^{-1}) in the treatment of plaque-type psoriasis.

Subjects and methods

Study design

This was a randomized, double-blind, parallel-group, multicentre, vehicle-controlled study conducted in subjects with chronic plaque-type psoriasis affecting 2–10% of their body surface area (BSA). After a wash-out period of up to 30 days, eligible subjects were randomized to one of the following three treatment groups: (i) becocalcidiol 75 μg g^{-1} twice daily (henceforth referred to as high-dose becocalcidiol); (ii) vehicle applied in the morning and becocalcidiol 75 μg g^{-1} applied at bedtime (henceforth referred to as low-dose becocalcidiol); and (iii) vehicle twice daily.

The protocol and informed consent documents were reviewed and approved by the Institutional Review Board for each investigational centre participating in the study.

Patients

The study was conducted at 12 study sites—both academic and private centres—in the U.S.A. Of 324 male and female subjects screened, 185 subjects were randomized. The study was initiated in September 2004 and completed in March 2005. Subjects were aged 18 years and older and had plaque-type psoriasis affecting 2–10% of their BSA at screening. Psoriasis was of a severity appropriate for topical therapy. Subjects were evaluated by medically trained personnel with experience in treating psoriatic lesions. Subjects refrained from topical psoriasis treatments for 2 weeks and from systemic treatments and ultraviolet radiation therapy for 4 weeks. Use of biologic agents or monoclonal antibodies in the last 6 months was prohibited. Subjects could not have taken a vitamin D supplement exceeding 400 IU per day or a calcium supplement exceeding 1200 mg per day within the last 30 days. Pregnant or nursing women, subjects with significant medical problems, and those with sensitivity to study drug were excluded. Women of childbearing age had to have a negative urine pregnancy test result on day 1 and be willing to use an acceptable method of birth control during the study.

Study medication and blinding

Subjects were randomized 1 : 1 : 1 to vehicle, low-dose becocalcidiol and high-dose becocalcidiol groups. Becocalcidiol and vehicle were supplied by Dow Pharmaceutical Sciences (Petaluma, CA, U.S.A.) in identical containers and were identical in appearance. Subjects were assigned kits containing study medication; subjects were randomized by kit number and were assigned kits in sequential order from the available kits at each site. Subjects, study personnel and investigators were blinded as to the contents of the tubes.

Study medication was applied twice daily (once in the morning and once at bedtime) to all psoriasis plaques (both target plaques and nontarget plaques) for 8 weeks or until clearing [Physician's Static Global Assessment of Overall Lesion Severity (PGA) = 0]. The amount of study medication applied was up to 4 g of ointment per application (maximum 8 g of ointment daily; maximum 56 g of ointment per week). Subjects could take multiple vitamins including up to 400 IU of vitamin D and/or up to 1200 mg of calcium daily during the study. Subjects could use tar shampoo to treat scalp psoriasis but could not use any other antipsoriasis medications during the study. If a subject took any immunosuppressive drugs, other psoriatic therapies, lithium, hydroxychloroquine or biologic agents during the study, the subject was discontinued from the study.

Assessments

Subjects were seen and evaluated at the screening and baseline (day 0) visits, and at weeks 2, 4 and 8. Assessments of efficacy and adverse events (AEs) were made at each visit.

The primary efficacy measurements included the PGA score and the Psoriasis Symptom Severity (PSS) score. The PGA, assessing all of the subject's plaques, was determined at each visit, using a six-point scale (0, clear; 1, almost clear; 2, mild; 3, moderate; 4, severe; 5, very severe). At baseline, PGA had to be at least 3 (moderate). For analysis purposes, this assessment was dichotomized into success vs. failure, with success being defined as a PGA score of 0 or 1. The PGA was a static assessment of the appearance of the psoriasis at the time of the assessment and was not a comparison with any previous assessment. The dichotomized outcome at week 8 was a primary efficacy parameter.

At screening, two to four target plaques were selected for individual study assessments; these could not be on the face or scalp. At each visit, a PSS score was determined for each of the target plaques. The PSS was calculated as a sum of scores for erythema, induration and scaling. A five-point scale (0–4) was used for each variable so that the PSS could range from 0 (plaque completely clear) to 12 (severe erythema, induration and scaling). At baseline, each target plaque had a PSS score of at least 7 and no individual symptom score (erythema, induration or scaling) of < 2. A mean of the PSS values from the two to four target plaques was used for analysis purposes. The percentage change in mean PSS from the baseline visit to week 8 was a primary efficacy parameter. The PSS was selected over the Psoriasis Area and Severity Index (PASI) because of the limited area of disease in this patient group ($< 10\%$ BSA). In patients with limited disease, the PASI is not recommended as

a clinical evaluation tool.[18] Erythema, scaling and induration are severity hallmarks of individual lesions; these are measured in both the PSS and the Total Sign/Severity Score.[19]

The secondary efficacy variables were the dichotomized PGA at weeks 2 and 4; ordinal PGA at weeks 2, 4 and 8; percentage change from baseline mean PSS at weeks 2 and 4; mean ordinal PSS at weeks 2, 4 and 8; individual symptom scores (erythema, induration and scaling) at weeks 2, 4 and 8; and BSA involvement at weeks 2, 4 and 8.

Safety was assessed by monitoring and recording of all AEs throughout the study period. Laboratory evaluations, including serum calcium, serum phosphorus, serum parathyroid hormone and 24-h urine calcium, were performed at the screening visit and at weeks 2, 4 and 8/final treatment (or early termination) visits. All women of childbearing potential took a urine pregnancy test at baseline and week 8/early termination visits.

Subjects were queried about dosing compliance at each visit. Any subject who missed more than three consecutive days (six consecutive doses) of dosing was discontinued from the study due to lack of compliance.

Statistical analysis

Efficacy analyses were performed using three study populations. The intent-to-treat (ITT) population was utilized for all efficacy analyses. Subjects evaluable for the ITT analysis population had to be randomized and to have received at least one dose of study medication. The per protocol (PP) population was a second subset population utilized for all efficacy analyses and included subjects who completed 8 weeks of therapy. Excluded were those subjects who prematurely discontinued treatment for reasons other than worsening of their psoriasis, who did not complete the week 8 efficacy evaluation, or who had noteworthy study protocol violations. The safety population consisted of subjects who were utilized for all safety analyses, were randomized to study medication, and received at least one dose of medication.

Each primary efficacy parameter was compared between each active treatment and its vehicle control using pairwise tests. The dichotomized PGA was analysed using Cochran–Mantel–Haenszel (CMH) analysis stratifying an investigational site and a binomial confidence interval (CI). The percentage change from baseline in PSS score was assessed with analysis of variance (ANOVA). Statistical analysis of discrete secondary parameters employed CMH analysis, stratified for investigational site. Statistical analysis of continuous secondary parameters employed ANOVA.

The assessment of safety was based on the frequency of AEs with other safety data summarized as appropriate. Safety data are summarized using descriptive statistics.

The study was powered based on the analysis of the dichotomized PGA at week 8. Using a two-sided χ^2 approximation to the CMH test, assuming type I error is 5%, the sample sizes of 50 PP subjects per treatment group yielded 80% power to detect a treatment difference in success rates of 30% if the active treatment was assumed to have 60% success.

Results

Of the 185 subjects who were randomized, 60 were randomized to vehicle, 61 to high-dose becocalcidiol and 64 to low-dose becocalcidiol. Of these, 158 (85%) completed the study without major protocol violations; the percentage of subjects who completed the study was comparable across groups (86% and 84% for the low- and high-dose becocalcidiol groups, respectively, compared with 87% in the vehicle group). The patients' baseline characteristics were similar across treatment groups (Table 1).

A total of 23 subjects discontinued the study (Table 2). Four subjects completed the study but had major protocol violations. One subject did not have a complete 2-week washout period before enrolment. One subject missed 17 consecutive doses of drug due to shipping delay (subject was allowed to proceed with study). One subject missed 16 consecutive doses of study drug, while the final subject missed 36 consecutive doses of study drug.

Table 3 summarizes the number of randomized subjects excluded from the PP efficacy analysis. Reasons for excluding subjects from the analysis were generally comparable across groups.

Table 1 Baseline characteristics

		Becocalcidiol	
Disposition	Vehicle (n = 60)	High dose (n = 61)	Low dose (n = 64)
Age, mean (range), years	53·1 (23–76)	46·4 (19–78)	47·6 (22–83)
Sex, M/F, n	27/33	35/26	43/21
Weight, mean (range), kg	85·6 (48·0–150·3)	85·6 (46·3–135·5)	86·7 (54·4–148·0)
Psoriasis duration, mean (range), years	17·4 (0·6–57)	18·6 (0·7–65)	16·0 (0·5–51)
Baseline PGA score, mean (range)	3·2 (3–4)	3·1 (3–4)	3·3 (3–4)
Baseline PSS score, mean (range)	8·2 (7·0–10·3)	7·9 (4·7–11·0)	8·1 (6·5–12·0)
Baseline percentage BSA involved, mean (range)	5·43 (2·0–13·0)	4·8 (2·0–10·0)	5·9 (2·0–14·0)

PGA, Physician's Static Global Assessment of Overall Lesion Severity; PSS, Psoriasis Symptom Severity; BSA, body surface area.

Table 2 Disposition of patients

Disposition	Number (%) of subjects		
	Vehicle (n = 60)	Becocalcidiol high dose (n = 61)	Becocalcidiol low dose (n = 64)
Treated	60	61	64
Completed	52	51	55
Completed but with major protocol violation	1	2	1
Discontinued	7	8	8
Reason for discontinuation			
Adverse event	0 (0)	3 (5)	2 (3)
Lost to follow-up	1 (2)	3 (5)	3 (5)
Protocol violation	0 (0)	1 (2)	0 (0)
Subject request	3 (5)	1 (2)	2 (3)
Worsening of condition	2 (3)	0 (0)	1 (2)
Other	1 (2)	0 (0)	0 (0)

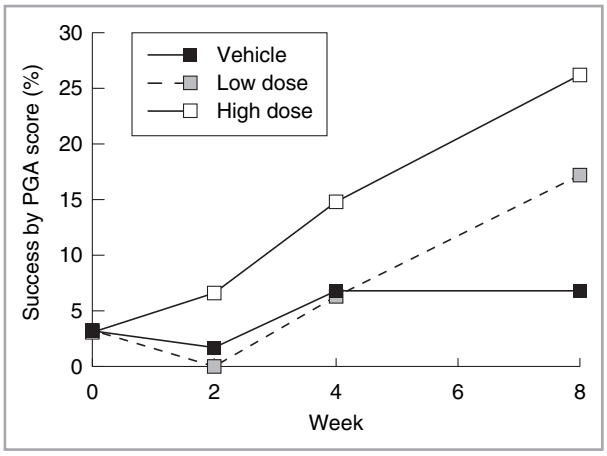

Fig 1. Percentage of subjects achieving success as measured by Physician's Static Global Assessment of Overall Lesion Severity (PGA) = 0 or 1 (intent-to-treat population). For high-dose group and low-dose group vs. vehicle, P = 0·002, 95% confidence interval (CI) 6·7–32·2 and P = 0·078, 95% CI –0·8 to 21·7, respectively.

Efficacy

In the PP population, the dichotomized PGA scores at week 8 indicated a successful outcome for three of 52 (6%), 11 of 55 (20%) and 16 of 51 (31%) subjects in the vehicle, low-dose and high-dose becocalcidiol groups, respectively. Both high-dose and low-dose becocalcidiol groups were statistically superior to vehicle [P < 0·001 (95% CI 11·4–39·8) and P = 0·027 (95% CI 1·9–26·6), respectively]. There was no statistically significant difference between the high-dose and low-dose becocalcidiol groups. For the ITT population, the dichotomized PGA scores at week 8 indicated a successful outcome for four of 59 (7%), 11 of 64 (17%) and 16 of 61 (26%) subjects in the vehicle, low-dose and high-dose becocalcidiol groups, respectively. The high-dose becocalcidiol group was statistically superior to vehicle (P = 0·002; 95% CI 6·7–32·2). The low-dose group approached, but did not achieve, significant superiority to vehicle (P = 0·078; 95% CI –0·8 to 21·7) (Fig. 1).

In the PP population, the mean percentage change in PSS score from baseline to week 8 (or end of treatment) was –41·37, –44·35 and –52·40 in the vehicle, low-dose and high-dose becocalcidiol groups, respectively. The high-dose becocalcidiol group was statistically superior to vehicle (P = 0·005; 95% CI –18·3 to –3·2). There was no significant difference between the low-dose and vehicle groups (P = 0·570; 95% CI –9·6 to 5·3). For the ITT population, the mean percentage change in PSS score was –39·99, –40·20 and –48·48 in the vehicle, low-dose and high-dose becocalcidiol groups, respectively. The high-dose becocalcidiol group was marginally superior to vehicle, but this result did not quite achieve statistical significance (P = 0·052; 95% CI –16·2 to 0·1) (Fig. 2).

Secondary efficacy measures supported the findings observed in the primary efficacy measures over time, namely that there was a possible trend towards outcomes of greater success with high-dose becocalcidiol.

Table 3 Subjects excluded from efficacy analysis—per protocol population

Reasons not included in analysis	Number (%) of subjects		
	Vehicle (n = 60)	Becocalcidiol high dose (n = 61)	Becocalcidiol low dose (n = 64)
More than six consecutive missed doses	4 (7)	1 (2)	2 (3)
Completed but major protocol violations	1 (2)	2 (3)	1 (2)
Did not complete, condition not worse, and PGA not zero at week 8/ET	5 (8)	8 (13)	7 (11)
Did not complete, discontinued due to 'worsening of condition', and week 8/ET psoriasis assessments not completed	1 (2)	0 (0)	1 (2)

PGA, Physician's Static Global Assessment of Overall Lesion Severity; ET, early termination.

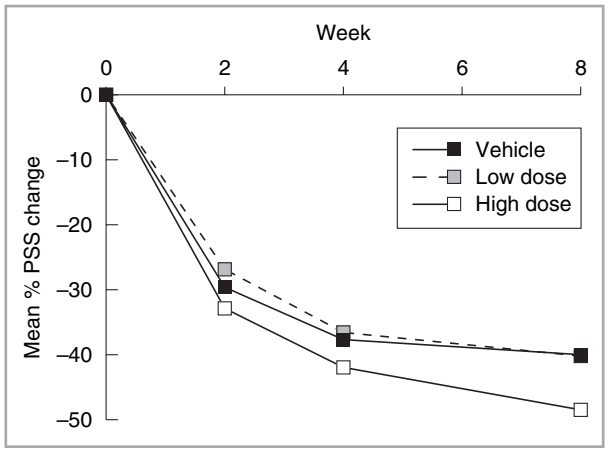

Fig 2. Mean percentage change in Psoriasis Symptom Severity (PSS) score from baseline by visit (intent-to-treat population). For high-dose group vs. vehicle, $P = 0{\cdot}052$, 95% confidence interval −16·2 to 0·1. Difference between low-dose group and vehicle not significant.

Safety

Adverse events

Becocalcidiol therapy was well tolerated. Sixty-eight (37%) of the 185 patients had AEs, which were mostly mild or moderate. Three subjects had a serious AE but none of these events was related to the study medication (abdominal pain, pneumonia, and foot fracture). Five subjects were withdrawn from the study due to treatment-related AEs (application site burning, elevated liver enzymes, allergic dermatitis, contact dermatitis with pruritus, and worsening of psoriasis): three subjects in the high-dose group and two subjects in the low-dose group. The most frequently occurring AE was nasopharyngitis which was reported in seven vehicle subjects, three low-dose subjects and one high-dose subject. Drug-related AEs were reported in two (3%) vehicle-treated subjects, three subjects (5%) in the low-dose and eight subjects (13%) in the high-dose becocalcidiol groups. Nine subjects reported skin-related AEs, of which eight were thought to be possibly or probably related to the study drug. These included pruritus, rashes thought by the investigator to be consistent with allergic dermatitis or contact dermatitis, worsening of psoriasis, rash and urticaria. No allergic or patch testing was performed on any subjects to determine whether becocalcidiol caused an allergic reaction. In the low-dose becocalcidiol group, one subject (2%) developed allergic dermatitis and another (2%) developed rash. In the high-dose group, one subject (2%) developed contact dermatitis, two (3%) developed pruritus, one (2%) developed urticaria, and one (2%) had worsening of psoriasis and localized burning at the application site.

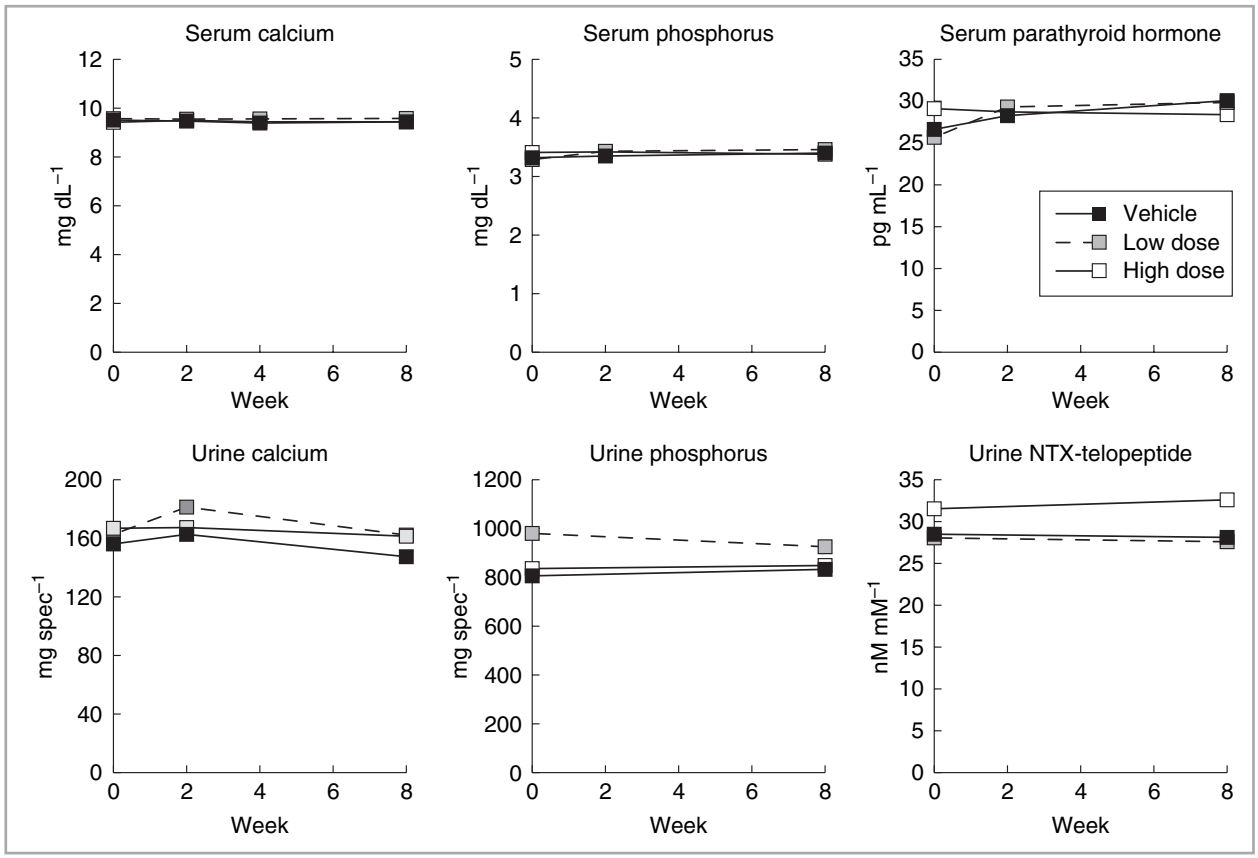

Fig 3. Mean laboratory values over the course of the study.

Laboratory findings

Mean and median clinical laboratory values were generally comparable across groups at all laboratory measurement intervals. There were no clinically significant findings in serum or urinary calcium, serum or urinary phosphorus, serum parathyroid hormone level or urinary NTX-telopeptide (Fig. 3). Elevated glucose levels were frequently observed in all groups throughout the study. Fourteen subjects with a history of diabetes (type 1 and type 2) were enrolled in the study. None of the subjects developed hypercalcaemia.

Discussion

This phase IIb study demonstrates the effectiveness of becocalcidiol in treatment of mild to moderate plaque-type psoriasis. Over 25% of patients applying becocalcidiol twice daily experienced almost or complete clearing of their psoriasis (PGA = 0 or 1). Twice daily application of becocalcidiol also induced greater improvement in the individual plaque severity scoring, as assessed by the PSS, compared with vehicle.

Localized burning and pruritus are the major complaints associated with calcipotriol, and in studies of calcipotriol, up to 25% of patients complain of irritation.[16] In our study, localized burning was seen in only one subject applying becocalcidiol twice daily. Two subjects (3%) in the high-dose group complained of pruritus. Other skin-related side-effects were also rare. In general, the drug was very well tolerated. No subjects developed hypercalcaemia or hypercalciuria. No significant increase in either blood or urine biochemical parameters related to calcium metabolism was observed with application of up to a maximum of 56 g of ointment per week. Doses greater than 100 g per week were not used in this study, so we are unable to say whether this drug is more or less likely than calcipotriol to produce hypercalcaemia at high doses. Our results demonstrate that topical becocalcidiol (75 $\mu g\ g^{-1}$) applied twice daily is an effective, safe and well-tolerated therapy for treatment of plaque-type psoriasis, with at least a 66% reduction in the frequency of cutaneous side-effects as compared with calcipotriol. However, no studies have been performed which directly compare becocalcidiol with calcipotriol. Further studies are necessary to determine the role of this agent in the management of psoriasis. It would also be interesting to test whether increased concentrations of becocalcidiol lead to improved therapeutic efficacy while maintaining the drug's favourable side-effect profile.

Acknowledgments

The following investigators also participated in the study: P. Westmoreland, Simpsonville, SC; S. Feldman, Winston-Salem, NC; M. Pierson, Kansas City, KS; F. deCastro, Lexington, KY; T. Knoepp, Anderson, SC; M. Lee, San Antonio, TX; J. Buzas, Reading, PA; D. Stough, Hot Springs, AR; L. Kircik, Louisville, KY; B. Deaton, Minneapolis, MN; K. Stein, Santa Rosa, CA. The study was sponsored by QuatRx Pharmaceuticals. This study has been registered with ClinicalTrials.gov, NCT 00373516.

References

1 Bikle DD, Ng D, Tu CL *et al.* Calcium- and vitamin D-regulated keratinocyte differentiation. *Mol Cell Endocrinol* 2001; **177**:161–71.
2 van de Kerkhof PCM. An update on vitamin D_3 analogues in the treatment of psoriasis. *Skin Pharmacol Appl Skin Physiol* 1998; **11**:2–10.
3 Kang S, Yi S, Griffiths CEM *et al.* Calcipotriene-induced improvement in psoriasis is associated with reduced interleukin-8 and increased interleukin-10 levels within lesions. *Br J Dermatol* 1998; **138**:77–83.
4 Kragballe K, Beck HI, Sogaard H. Improvement of psoriasis by a topical vitamin D_3 analogue (MC 903) in a double-blind study. *Br J Dermatol* 1988; **119**:223–30.
5 Dubertret L, Wallach D, Souteyrand P *et al.* Efficacy and safety of calcipotriol (MC 903) ointment in psoriasis vulgaris. A randomized, double-blind, right/left comparative, vehicle-controlled study. *J Am Acad Dermatol* 1992; **27**:983–8.
6 Highton A, Quell J. Calcipotriene ointment 0·005% for psoriasis: a safety and efficacy study. Calcipotriene Study Group. *J Am Acad Dermatol* 1995; **32**:67–72.
7 Harrington CI, Goldin D, Lovell CR *et al.* Comparative effects of two different calcipotriol (MC903) formulations vs. placebo in psoriasis vulgaris: a randomized, double-blind, placebo-controlled, parallel group multicentre study. *J Eur Acad Dermatol Venereol* 1996; **6**:152–8.
8 Kragballe K, Gjertsen BT, de Hoop D *et al.* Double-blind, right/left comparison of calcipotriol and betamethasone valerate in treatment of psoriasis vulgaris. *Lancet* 1991; **337**:193–6.
9 Bourke JF, Berth-Jones J, Iqbal SJ, Hutchinson PE. High-dose topical calcipotriol in the treatment of extensive psoriasis vulgaris. *Br J Dermatol* 1993; **129**:74–6.
10 Hoeck HC, Laurberg G, Laurberg P. Hypercalcaemic crisis after excessive topical use of a vitamin D derivative. *J Intern Med* 1994; **235**:281–2.
11 Bourke JF, Mumford R, Whittaker P *et al.* The effects of topical calcipotriol on systemic calcium homeostasis in patients with chronic plaque psoriasis. *J Am Acad Dermatol* 1997; **37**:929–34.
12 Bleiker TO, Bourke JF, Mumford R *et al.* Long-term outcome of severe chronic plaque psoriasis following treatment with high-dose topical calcipotriol. *Br J Dermatol* 1998; **139**:285–6.
13 Fogh K, Kragballe K. Recent developments in vitamin D analogs. *Curr Pharm Des* 2000; **6**:961–72.
14 Ashcroft DM, Li Wan Po A, Williams HC, Griffiths CEM. Systematic review of comparative efficacy and tolerability of calcipotriol in treating chronic plaque psoriasis. *BMJ* 2000; **320**:963–7.
15 Witman P. Topical therapies for localized psoriasis. *Mayo Clin Proc* 2001; **76**:943–9.
16 PDR Drug information for Dovonex ointment 0·005%. Physicians' Desk Reference. Available at: http://www.drugs.com/pro/dovonex-ointment.html (accessed 2 June 2007).
17 Plum LA, Prahl JM, Ma X *et al.* Biologically active noncalcemic analogs of 1α,25-dihydroxyvitamin D with an abbreviated side chain containing no hydroxyl. *Proc Natl Acad Sci USA* 2004; **101**:6900–4.
18 van de Kerkhof PCM, Kragballe K. Recommendations for the topical treatment of psoriasis. *J Eur Acad Dermatol Venereol* 2005; **19**:495–9.
19 Goodfield M, Kownacki S, Berth-Jones J. Double-blind, randomised, multicentre, parallel group study comparing a 1% coal tar preparation (Exorex) with a 5% coal tar preparation (Alphosyl) in chronic plaque psoriasis. *J Dermatolog Treat* 2004; **15**:14–22.