ASIAN JOURNAL OF PHARMACEUTICAL AND CLINICAL RESEARCH

INNOVARE ACADEMIC SCIENCES Knowledge to Innovation

Vol 6, Suppl 5, 2013

ISSN - 0974-2441

Research Article

STUDY OF CALCIPOTRIOL BETAMETHASONE OINTMENT IN THE TREATMENT OF PATIENTS WITH REFRACTORY CHRONIC ECZEMA

MEI JU[1], AIE XU[2], YIQUN DUAN[3], HAI WEN[4], TIENAN LI[5], LIMIN XU[6], KUN CHEN*[1], HENG GU *[1]

[1]Institute of Dermatology, Chinese Academy of Medical Sciences, [2]Third People's Hospital of Hangzhou, [3]First People's Hospital of Wuhan, [4]China Society of Integrated Traditional Chinese and WesternMedicine, [5]The Seventh People's Hospital of Shenyang; [6]ChangZheng Hospital of Tianjin. Corresponding anthors: KUN CHEN,Email: Kunchen181@aliyun.com, HENG GU， **Email:** guheng@aliyun.com.

Received: 10 September 2013, Revised and Accepted: 25 September 2013

ABSTRACT

Chronic eczema is an inflammatory-immune disease of the skin, with the characteristics of skin thickening and varying degrees of lichenification, including severe itching, tendency of persistence and recurrence with serious impact on quality of life of patients. Objective: To assess the clinical efficacy and safety of calcipotriol betamethasone ointment in patients with chronic eczema. Methods: In this multi-center, randomized, single-blind, positive drug parallel controlled clinical study, patients were randomly divided into treatment and control groups, to receive calcipotriol betamethasone ointment or halometasone/triclosan cream, respectively, once daily in the evening over a 4-week period. The safety and efficacy of the two regimens were followed up on weeks 1, 2, 4 and at a 4-week treatment-free period. According to the degree of improvement, the total scores (0-4) before and after treatment and the efficacy index were calculated. The overall efficacy was assessed by four levels of evaluation model. Results: After 4 weeks of treatment, the cure rate was high (44.70%) in treatment group compared with control group (15.56%) ($P<0.001$), and the effective rate was 83.33% and 55.56% in the respective groups ($P<0.001$). At 2 and 4 weeks after treatment, there was significant difference ($P<0.05$) between two groups, with a reduction in the intensity of pruritus, inflammation, infiltration/ hypertrophy, lichenification, and area of target lesions. The incidence of adverse events was more (1.52%) in treatment than control group (0.00%) ($P>0.05$). Conclusion: Calcipotriol betamethasone ointment appears to be a safe and effective option for the treatment of chronic eczema.

Keywords: Halometasone/triclosan cream, Hypertrophy, Intensity of symptoms, Quality of life, Skin infiltration, Topical ointments

INTRODUCTION

Eczema is a delayed type of hypersensitivity reaction caused by complex internal and external excitation factors. It runs its course through three distinct phases: acute, sub-acute, and chronic. The prevalence of eczema is been increased two- to threefold in developed and developing countries during the past three decades. Currently in developed countries, an estimated 15% to 30% of children and 2% to 10% of adults are affected[1, 2]. Chronic eczema differs from acute or sub-acute eczema in recurrence. Individuals with lesions developed over three months are referred to as having chronic eczema. Major clinical characteristics of eczema[3] are skin lesions, appearing to be infiltrated and in hypertrophied state with surface having chaff-like scales or moss-like cover; intense itching, often paroxysmal; and quick relapse rate and prolonged healing time. The common sites involved are hands, feet, legs, cubital fossa, cannus, anus etc. The treatment of chronic eczema is difficult and remains a great challenge for the clinician. The first-line therapeutic option includes the use of topical glucocorticoid hormone[4]. Topical tar, salicylic acid, and retinoic acid preparations are also used for treatment. Glucocorticoid hormones in combination with immunomodulators such as tacrolimus[5,6] and pimecrolimus [7] are available for the treatment of refractory chronic eczema. If topical preparations fail, oral methotrexate[8], cyclosporine[9], and other immunosuppressive agents, as well as retinoic acid [10], light therapy[11,12], and X-ray treatment[13] are common alternative treatment options. However, these treatments often have an unsatisfactory result and are prone to induce side effects. The disease being pruritic dermatitis, its psychological effects can have serious repercussions on the quality of lives of patients. Thus, there is an urgent need of new and more effective therapies.

Calcipotriol, a vitamin D3 analogue, has anti-proliferative and anti-inflammatory effect and can influence keratinocyte differentiation. During the past decade, calcipotriol has been prescribed widely for the treatment of psoriasis and has achieved good effects. Psoriasis, however, shares several pathogenic elements with other skin diseases, viz. impaired differentiation, increased proliferation of keratinocytes, and local activation of T lymphocytes[14]. Calcipotriol affects several of these processes, and may therefore be of potential benefit to the patients with diseases other than psoriasis. Clinical cases reported that calcipotriol has achieved certain beneficial effects in the treatment of inflammatory skin diseases with the characteristics of skin infiltration hypertrophy and varying degrees of lichenification, e.g. verrucous epidermal nevus[15], chronic lichen Keratosis[16], cutaneous amyloidosis[17], and hyperkeratosis type of hand eczema[18].

Calcipotriol betamethasone ointment is a combination product of calcipotriol 50 µg/g and betamethasone dipropionate 0.5 mg/g. The two-compound ointment is a convenient, very effective, safe, and well tolerated therapy for psoriasis. The ointment, when applied for 4 weeks, is more effective and has rapid onset of action than either calcipotriol or betamethasone cream alone[19,20]. This may be related to the synergistic effect of calcipotriol and corticosteroids. The feasibility of using calcipotriol betamethasone ointment for the treatment of chronic eczema and other refractory skin diseases characterized by skin infiltration and hypertrophy hasn't been explored much till date.

In this context, we decided to explore the treatment programs to seek a more effective option. The present study assessed the clinical efficacy and safety of calcipotriol betamethasone ointment with halometasone/triclosan cream as control in patients with chronic eczema.

MATERIALS AND METHODS

The study was conducted between June and November 2011. A multi-center study was conducted in five-different hospitals of china: Institute of Dermatology, Chinese Academy of Medical Sciences; Third People's Hospital of Hangzhou; Changzheng Hospital of Tianjin; First People's Hospital of Wuhan; and Seventh People's Hospital of Shenyang.

Inclusion criteria

- Male or female patients of chronic eczema, between 18 to 65 years of age
- Skin lesions with a total surface area of not more than 10%
- Total score of severity of illness >12 points at first clinic visit
- Subject able and willing to sign the informed consent form

Exclusion criteria

- If they had another dermatological condition that could interfere with clinical evaluation including bacterial, viral or fungal infection
- Skin rash on face and skin folds
- Known allergy to any ingredients or structural analogues of tested products
- Subject with serious heart, liver, kidney dysfunction or immune dysfunction; neuropsychiatric disorders or severe endocrine diseases
- Received any systemic treatment, including corticosteroids or immunomodulators therapy for eczema within 4 weeks prior to screening or antihistamine therapy within 2 weeks, as well as topical glucocorticoid steroids or non-steroidal anti-inflammatory drugs therapy within 2 weeks
- Pregnant or the possibility of pregnancy women and lactating women.

Study Design

This was a multi-center, randomized, single-blind and positive drug parallel controlled clinical study, and was approved by Ethics Committee of Institute of Dermatology, Chinese Academy of Medical Sciences (IRB-02-2011-02 24).

Drugs and usage

Calcipotriol betamethasone ointment (Daivobet) was formulated by the Danish LEO Pharma: calcipotriol 50 μg/g, betamethasone dipropionate 0.5 mg/g. Halometasone/Triclosan cream (Sicorten Plus) was formulated by Novartis Pharmaceuticals: halometasone 0.05%, triclosan 1%. Patients who met the inclusion criteria were treated with calcipotriol betamethasone ointment (treatment group) or halometasone/triclosan cream (control group), respectively in the same way. Both the drugs were evenly applied to the affected area, they was kneaded slightly with the applicator and applied once daily in the evening over a 4-week period.

Follow-up

Patients were followed up on weeks 1, 2, and 4. Cured patients were followed up again at 4 weeks after discontinuation of treatment.

Criteria for efficacy endpoints of symptoms and signs

Intensity of pruritus, inflammation, infiltration/hypertrophy, lichenification, and area of target lesions was evaluated using score values from 0 to 4. The area of target lesions was set at a score of 4 before the treatment (Table 1).

Table 1: Scoring method for symptoms/signs of chronic eczema

	0	1	2	3	4
Pruritus intensity	Asymptomatic	Extremely mild; Lightly sensible, easily endurable, no scratching required	Mild Sensible, influential, but undurable, scratching required sometime	Moderate obviously sensible, can influence patients' daily life and sleep, but the patient can have optimum sleep, required to scratch frequently	Severe obviously sensible, can influence patients' daily life and sleep, leading to loss of sleep time, waking up 1-2 times every night
Degree of Inflammation	None	Reddish	Red	Less than erubescent	Erubescent
Degree of Infiltration/ hypertrophy	None	Light	More Obvious	Obvious	Severe
Degree of Lichenification	None	Light	More Obvious	Obvious	Severe
Area of Target lesions	Completely dissipated	Reduction in area of target lesions il75%	Reduction in area of target lesions ≥50% but < 75%	Reduction in area of target lesions ≥ 25% but < 50%	Reduction in area of target lesions 25% or without reduction

Comprehensive evaluation

Therapeutic index was calculated according to the degree of clinical improvement before and after treatment, and the overall effect evaluation was made after treatment according to four levels: cured, effective, progressive, and invalid.

Therapeutic index % = (score of before treatment – score of after treatment)/ score of before treatment×100%.

Cured: the degree of clinical improvement ≥ 90%; effective: 60% ≤ the degree of clinical improvement < 90%; progressive: 20% ≤ the degree of clinical improvement <60%; invalid: the degree of clinical improvement <20%.

The efficiency was calculated on valid cases (cured cases coupled with effective cases). Re-visit was carried out at 4 weeks after withdrawal in cured patients to calculate the relapse rate.

Safety evaluation

After treatment, the adverse events (AEs) in patients at each visit were inquired and recorded.

Statistical Analysis

Statistical analysis included t test and for count data chi-square test with SPSS 17.0 statistical software.

RESULTS

Two hundred fifty patients were enrolled into the study after considering the inclusion and exclusion criteria. Out of which two hundred twenty two patients completed the study (i.e., 3 follow-ups), 132 patients in treatment group and 90 patients in control group. A total of 28 patients did not complete the study, out of which 5 patients were lost to follow-up (treatment group 2.67% and control group 1%) and 23 patients were excluded from the study (treatment group 9.33% and control group 9.00%). Also, there was no significant difference between two groups with respect to gender, age, course of treatment, prior treatment, and accompanying diseases; however, they were comparable. Also, there was no

significant difference between two groups before treatment with respect to area of target lesions, intensity of infiltration and hypertrophy, lichenification, inflammation, and pruritus as well as total score of signs and symptoms; however, they were comparable (Table 2-4).

Table 2: Baseline demographic details of the patients:

		Treatment group (n=132)	Control group (n=90)	t	*P* value
Gender	Male	69 (52.27%)	51 (56.67%)	0.42	0.519
	Female	63 (47.73%)	39 (43.33%)		
Age (years)	Mean±SD	45.75±12.84	44.58±13.07	0.663	0.508
Course of disease (months)	M±Q	59.37±86.26	64.54±94.98	-0.421	0.674
Treatment history	No	57 (43.18%)	39 (43.33%)	0.00	0.982
	Yes	75 (56.82%)	51 (56.67%)		
Other diseases	No	124 (93.94%)	85 (94.44%)	0.02	0.875
	Yes	8 (6.06%)	5 (5.56%)		

Table 3: Comparison of score of signs and symptoms between two groups before and after treatment

	Each Week Mean Score											
	Before treatment			**After treatment**								
	1st Week						**2nd Week**			**4 th Week**		
	(Mean ± SD)	**t**	**p**	**(Mean ± SD)**	**t**	**p**	**(Mean ± SD)**	**t**	**p**	**(Mean ± SD)**	**t**	**p**
Treatment (n=132)	2.92±0.76			1.55±1.01			0.95±0.89			0.43±0.72		
Control (n=90)	2.89±0.71	0.35	0.727	2.01±0.88	-3.649	0	1.42±0.97	-3.775	0	0.99±1.03	-4.43	0
Treatment (n=132)	2.45±0.91			1.51±0.90			0.90±0.80			0.46±0.76		
Control (n=90)	2.31±0.92	1.087	0.278	1.60±0.78	-0.796	0.427	1.20±0.75	-2.797	0.006	0.81±0.79	-3.313	0.001
Treatment (n=132)	2.95±0.64			1.83±0.81			1.14±0.83			0.58±0.74		
Control (n=90)	2.88±0.82	0.747	0.456	2.21±0.92	-3.227	0.001	1.50±0.92	-3.022	0.003	1.07±0.91	-4.411	0
Treatment (n=132)	2.68±0.79			1.67±0.84			0.99±0.80			0.53±0.74		
Control (n=90)	2.88±0.81	-1.808	0.072	2.19±0.97	-4.282	0	1.54±0.93	-4.612	0	1.01±0.95	-4.233	0
Treatment (n=132)	4.00±0.00			3.18±1.01			2.26±1.25			0.95±1.17		
Control (n=90)	4.00±0.00		1	3.10±0.65	-3.752	0	2.84±1.13	-3.565	0	1.92±1.46	-5.244	0

Table 4: Comparison of total score of signs and symptoms between two groups of patients before treatment

Group	n	Mean±SD	*t*	*P*
Treatment	132	15.01±1.86	0.195	0.846
Control	90	14.96±2.08		

Cure rate and effective rate

After 4 weeks of treatment, the cure rate was more in the treatment group (44.70%) compared with the control group (15.56%) (P<0.001). The efficacy rates were significantly higher in treatment group (83.33%) than the control group (55.56%) (P<0.001) (Table 5).

Table 5 Clinical analysis of overall efficacy between two groups after treatment

Group	Efficacy evaluation				Cure rate (%)	X^2	*P*	Effective rate (%)	X^2	*P*
	Cured	Markedly effective	Progressive	Invalid						
Treatment (n=132)	59	51	19	3	44.70	20.59	<0.001	83.33	20.51	<0.001
Control (n=90)	14	36	36	4	15.56			55.56		

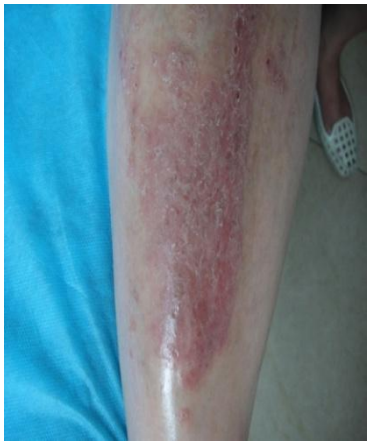
Comparison of the total score and score changes of symptoms/signs between the two groups

At weeks 1, 2, and 4, the total score in the treatment group was significantly lower than the control group (P<0.001). On week 1, except for inflammation intensity the other symptoms and signs

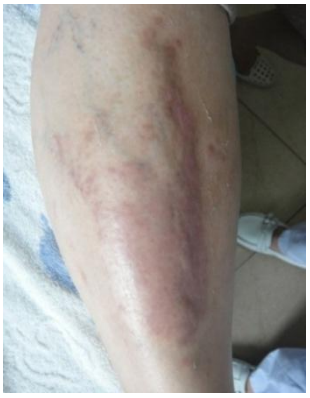
score (pruritus intensity, lichenification, infiltration/hypertrophy intensity, and target lesion area) for the treatment group were significantly lower than the control group (P<0.001). On weeks 2 and 4, all the symptoms and signs score of the treatment group were significantly lower than the control group (P<0.001) (Table 3, 6 Figures 1-2).

Table 6: Total score of signs and symptoms between two groups of patients before and after administration

Time		Group	n	X ±s	*t*	*P*
Before treatment		Treatment	132	15.01±1.86		
		Control	90	14.96±2.08	0.195	0.846
After treatment	Week 1	Treatment	132	9.73±3.16		
		Control	90	11.61±2.86	-4.513	<0.001
	Week 2	Treatment	132	6.22±3.40		
		Control	90	8.53±3.42	-4.966	<0.001
	Week 4	Treatment	132	2.95±3.48		
		Control	90	5.80±4.15	-5.541	<0.001

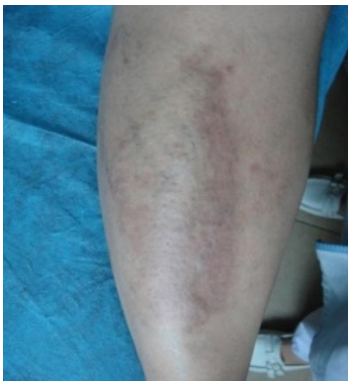


a) Before Treatment

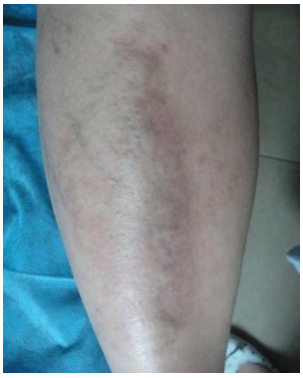


b) After 1st Week treatment

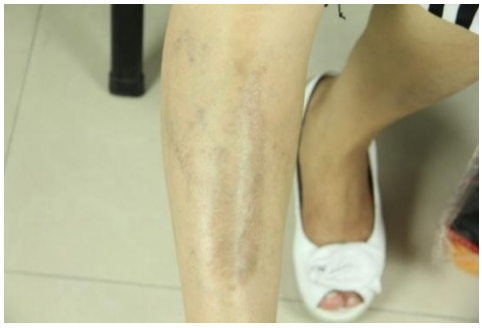
Figure 1: a) The calf pretibial hypertrophic erythema with external application of white scale before treatment; b) 1 week treatment of calcipotriol betamethasone ointment show a regression of scale and a part remission of hypertrophic erythema.



a) After 2nd Week Treatment



b) After 3rd Week



c) After 6 th Week

Figure 2: a) 2 weeks treatment of calcipotriol betamethasone ointment show a most regression of hypertrophic erythema; b) Drug withdrawal when 3 weeks treatment of calcipotriol betamethasone ointment shows a complete regression of hypertrophic erythema; c)

Original lesion area had no relapse after drug withdrawal for 6 weeks.

Comparison of the difference in symptoms and signs score between the two groups before and after treatment

At weeks 1, 2, and 4 after treatment, the decrease in the total score in the treatment group was significantly higher than the control group (P<0.001). Comparing the decrease in score value of each symptom and sign, it was significantly higher in the treatment group than the control group (P<0.001) (Table 7, 8).

Table 7: Comparison of the difference in symptoms and signs score between the two groups before and after treatment

Time	Group	n	X±s	*t*	*P*
Week 1	Treatment	132	5.27±3.08		
	Control	90	3.34±2.40	5.223	0
Week 2	Treatment	132	8.79±3.42		
	Control	90	6.42±3.13	5.235	0
Week 4	Treatment	132	12.06±3.62		
	Control	90	9.18±3.84	5.684	0

Table 8: Week wise comparison of the difference observed in symptoms and signs scores

		Comparison of each week mean score								
		1st Week (Mean ± SD)	t	p	2nd Week (Mean ± SD)	t	p	4th Week (Mean ± SD)	t	p
Pruritus intensity	Treatment (n=132)	1.38±1.03			1.98±1.08			2.49±1.01		
	Control (n=90)	0.88±0.83	3.994	0	1.47±1.03	3.523	0.001	1.90±1.10	4.14	0
Degree of inflammation	Treatment (n=132)	0.94±0.88			1.55±1.04			1.98±1.00		
	Control (n=90)	0.71±0.69	2.064	0.04	1.11±0.94	3.228	0.001	1.51±0.96	3.51	0
Degree of infiltration/ hypertrophy	Treatment (n=132)	1.12±0.82			1.82±0.93			2.38±0.83		
	Control (n=90)	0.67±0.76	4.167	0	1.38±0.99	3.372	0.001	1.82±0.93	4.656	0
Degree of lichenification	Treatment (n=132)	1.02±0.87			1.69±0.90			2.15±0.97		
	Control (n=90)	0.69±0.82	2.805	0.005	1.33±0.92	2.862	0.005	1.87±1.03	2.096	0.037
Area of target lesions	Treatment (n=132)	0.82±1.01			1.74±1.25			3.05±1.17		
	Control (n=90)	0.40±0.65	3.467	0.001	1.16±1.13	3.565	0	2.08±1.46	5.244	0.001

Comparison of the recurrence rates between the two groups within the 4-week, treatment-free period

The recurrence rate was lower (13.56%) in the treatment group compared with control group (21.43 %), but there were no significant difference between the two groups (P>0.05) (Table 9).

Table 9: Comparison of the recurrence rate between the two groups within the 4-week, treatment-free period

Group	Yes	Non	Total	Incidence (%)	*P*
Treatment	8	51	59	13.56	0.431*
Control	3	11	14	21.43	

*Fisher exact test

Adverse events

Two cases in the treatment group reported AEs such as burning, tingling sensation or pruritus. The incidence of adverse events was 1.52 % in the treatment group. There were no adverse events in the control group. However, the difference between the groups was not statistically significant (P>0.05).

DISCUSSION

The study results throw light on therapeutic applications of calcipotriol betamethasone ointment in patients with chronic eczema. Currently, corticosteroids remain one of the most valuable available treatments to be used to treat eczema[21]. However, corticosteroids have poor efficacy in the treatment of chronic hypertrophic and lichen lesions[22]. Long-term external use could lead to skin atrophy, telangiectasia, tachyphylaxis, and easy recurrence further making the disease persistent, unhealed and even sensitive for repeated attacks[23]. Calcipotriol is a vitamin D analog; in recent years, more literature suggests that calcipotriol offers an effective alternative form of treatment for inflammatory skin diseases with the characteristics of skin infiltration hypertrophy and varying degrees of lichenification[14,] including recalcitrant hyperkeratotic palmoplantar eczema[18].

In this study, nearly 60% of the patients received long-term glucocorticoid hormone therapy or other treatments. Most of them had poor efficacy and converted to refractory chronic eczema. After 4 weeks of treatment either with calcipotriol betamethasone ointment (treatment group) or halometasone/triclosan cream (control group), the cure rates were 44.70% and 15.56% (P<0.001), respectively. The effective rates were 83.33% and 55.56 % in the respective groups (P<0.001).

At weeks 1, 2, and 4 after treatment, decrease in the scores was significantly higher in the treatment group (P<0.005). Calcipotriol betamethasone ointment in the treatment of refractory chronic eczema quickly relieved the signs and symptoms, including itching, inflammation, infiltration / hypertrophy, and moss like cover. These results demonstrated the clinical efficacy of calcipotriol betamethasone over halometasone/triclosan cream.

Calcipotriol has a high binding affinity to the vitamin D receptor (VDR) for the biologically active form of vitamin D3: 1, 25-hydroxy vitamin D3 (calcitriol)[14]. Previous studies[24,25]suggested the biological effects of calcitriol included regulation of epidermal cell

proliferation and differentiation, inhibition of vascular proliferation, and regulation of cytokines. Vitamin D3 analogs induce terminal differentiation of epidermal keratinocytes without changing their keratin gene expression *in vitro*[14]. Thus, some scholars[14] speculated that calcipotriol could improve disorders of histological elements, such as hyperkeratosis, acanthosis, parakeratosis, and epidermal hyper proliferation by modifying the epidermal growth pattern through the stimulation of terminal differentiation and the simultaneous inhibition of proliferation.

Histopathological manifestations of chronic eczema are mainly due to the epidermal psoriasis-like hyperplasia, acanthosis cell layer thickening, hyperkeratosis or parakeratosis, and superficial dermal perivascular lymphocytic infiltration. In chronic eczema patients with epidermal psoriasis-like hyperplasia hypertrophy, infiltration and lichenification of the lesions could be significantly alleviated after calcipotriol betamethasone ointment therapy. In addition, to the above biological effects *in vitro* studies showed that calcipotriol may reduce the development of Th1 cells and expression of Th1-type cytokines INF-γ, causing wide range of effects on immunoregulation and immunosuppression[26,27]. In animal model experiments, immunization through calcipotriol-treated skin induces CD4 (+) CD25 (+) regulatory T cells (Treg) that prevent subsequent Ag-specific CD8 (+) T cell proliferation and IFN-gamma production[28]. Calcipotriol induced Treg is capable of inhibiting the induction and elicitation of protein contact hypersensitivity[28]. Topical calcipotriol treatment also induces the expression of receptor activator of NF-kappa-B ligand (RANKL) by keratinocytes, a tumor necrosis factor (TNF) family member involved in modulation of skin dendritic cells [28]. *In vitro* study demonstrated that 1, 25-

dihydroxyvitamin D (3) had significant additive effect on dexamethasone-mediated inhibition of lymphocyte proliferation[29]. This hormone also has additive effects on inhibition of T (H) 1 cytokine production when combined with dexamethasone[29]. Psoriasis is a common T cell–mediated autoimmune disorder, involving keratinocyte proliferation and altered differentiation as well as abnormal apoptosis[30]. Eczema is another Th1 cell–mediated type IV allergy disease[31] so immunoregulation and immunosuppressive effects of calcipotriol could be helpful for treatment.

A study conducted by Holm EA et al[14] showed calcipotriol has anti-inflammatory effects, and play an important role in the treatment of keratosis lichenoides chronica, pityriasis rubra pilaris, seborrheic dermatitis, erythema annulare centrifugum, verrucous epidermal nevus etc. In another *in vitro* study, calcipotriol showed marked anti-proliferative effect on hematopoietic stem cells, thus inhibiting the number of cells involved in inflammatory response, and inhibiting the synthesis of growth-promoting lymphokines directly or indirectly[32]. A recent study showed S 100A7 psoriasin is markedly overexpressed not only in psoriasis but also in many epidermal inflammatory diseases such as atopic dermatitis, mycosis fungodies, Darier's disease, and other chronic inflammatory diseases[30]. Treatment of psoriasis with vitamin D analog calcipotriol interferes with S100-mediated positive feedback loop by suppressing the increased production of psoriasin (S100A7) and koebnerisin (S100A15) and their Th17-mediated regulation in epidermal kerainocytes. Thus, targeting the S100-amplification loop could be a beneficial anti-inflammatory approach in psoriasis and other chronic inflammatory skin diseases[34].

In this study, within the 4-week treatment-free period, the recurrence rate was low (13.56%) in treatment group compared with control group (21.43%); however, it was not statistically significant. The treatment group reported common AEs such as burning, tingling sensation or pruritus but the incidence was not statistically significant compared with control group. Treatment-related AEs were generally similar with other studies[35-37].

CONCLUSION

This study confirms the remarkable therapeutic effects of calcipotriol betamethasone ointment in the treatment of chronic eczema. However, large-scale randomized, double-blind, placebo or positive drug parallel controlled studies are required to further study the efficacy of calcipotriol betamethasone ointment in the treatment of chronic eczema or reduction in the recurrence rate.

REFERENCES

1. Bieber T. Mechanisms of Disease: Atopic Dermatitis. N Engl J Med 2008; 358:1483–94.
2. Williams H, Flohr C. How epidemiology has challenged 3 prevailing concepts about atopic dermatitis. J Allergy Clin Immunol 2006; 118:209–13.
3. Bian Zhao. China Clinical Dermatology (1st ed). Nanjing, Jiangsu science and technology press, 2010; 725-732.
4. Veien NK, Larsen PO, Thestrup-Pedersen K, Schou G. Long term intermittent treatment of chronic hand eczema with mometasone furoate. Br J Dermatol 1999; 140:882-6.
5. Sehgal VN, Srivastava G, Dogra S. Tacrolimus: approved and unapproved dermatologic indications/usages physician's sequential literature survey part 2. Skinmed 2008; 7:73-7.
6. Groves R. Development of calcineurin blocking non-steroid topical immunosuppressants for effective management of eczema. J Dermatolog Treat 2003; 14:135.
7. Sehgal VN, Pahwa M. Pimecrolimus, yet another intriguing topical immunomodulator. J Dermatolog Treat 2007; 18:147-50.
8. Veien NK, Menne T. Treatment of hand eczema. Skin Therapy Lett 2003; 8:4-7.
9. Reitamo S, Granlund H. Cyclosporin A in the treatment of chronic dermatitis of the hands. Br J Dermatol 1994; 130:75-8.
10. Thestrup-Pedersen K, Andersen KE, Menne T, Veien NK. Treatment of hyperkeratotic dermatitis of the palms (eczema keratoticum) with oral acitretin. A single-blind placebo-controlled study, Acta Derm Venereol 2001; 81:353-5.
11. Schiener R,Gottlober P, Muller B et al. PUVA-gel vs PUVA-bath therapy for severe recalcitrant palmoplantar dermatoses. A randomized, single-blinded prospective study. Photodermatol Photoimmunol Photomed 2005; 21:62-7.
12. Polderman MC, Govaert JC, LeCessie, Pavel S. A double-blind placebo-controlled trial of UVA-1 in the treatment of dyshidrotic eczema. Clin Exp Dermatol 2003; 28:584-7.
13. Lindelof B, Wrangsjo K, Liden S. A double-blind study of Grenz ray therapy in chronic eczema of hands. Br J Dermatol 1987; 117:77-80.
14. Holm EA, Jemec GB.The therapeutic potential of calcipotriol in diseases other than psoriasis. Int J Dermatol 2002; 41:38-43.
15. Zvulunov A, Grunwald MH, Halvy S. Topical calcipotriol for treatment of inflammatory linear verrucous epidermal nevus. Arch Dermatol 1997; 133:567-8.
16. Chang SE, Jung EC, Hong SM, et al. Keratosis lichenoides chronica: marked response to calcipotriol ointment. J Dermatol 2000; 27:123-6.
17. Khoo BP, Tay YK, Goh CL. Calcipotriol ointment vs. betamethasone 17-valerate ointment in the treatment of lichen amyloidosis. Int J Dermatol 1999; 38:539-41.
18. Kiyofumi E. Topical vitamin D_3 derivatives in treating hyperkeratotic palmoplantar eczema: a report of five patients. J Dermatol 2005; 32:381-6.
19. Saraceno R, Andreassi L, Ayala F, et al. Efficacy, safety and quality of life of calcipotriol/betamethasone dipropionate (Dovobet) versus calcipotriol (Daivonex) in the treatment of psoriasis vulgaris: a randomized, multicentre, clinical trial. J Dermatolog Treat 2007; 18:361-5.
20. Vakirlis E, Kastanis A, Ioannides D. Calcipotriol/betamethasone dipropionate in the treatment of psoriasis vulgaris. Ther Clin Risk Manag 2008; 4:141-8.

21. Sehgal VN, Srivastava G, Aggarwal AK, Sharma AD. Hand dermatitis/ eczema: current management strategy. J Dermatol 2010; 37:593-610.
22. Cheng W, Feng WL, Yang J. Clinical efficacy of 0.1% tacrolimus ointment in the treatment of chronic eczema. Practical Medical Technical Journal 2008; 15:47
23. Xie ZQ, Li LF, Chen XR. Treatment of localized chronic eczema with topical calcipotriene in combination with halcinonide. Integrated Traditional Chinese and Western Dermatology and Venereology 2003; 2:53-4.
24. Morimoto S, Yoshikawa K, Kozuka T, et al. An open study of Vitamin D3 treatment in psoriasis vulgaris, Br J Dermatol 1986; 115:421-9.
25. Van de Kerkhof PC. Biological activity of vitamin D analogues in the skin, with special reference to antipsoriatic mechanisms. Br J Dermatol 1995; 132:675-82.
26. Mattner F, Smiroldo S, Galbiati F, et al. Inhibition of Th1 development and treatment of chronic-relapsing experimental allergic encephalomyelitis by a non-hypercacemic analogue of 1,25-dihydroxyvitamin D3. Eur J Immunol 2000; 30:498-508.
27. Piemonti L, Monti P, Sironi M, et al. Vitamin D3 affects differentiation, maturation, and function of human monocyte-derived dentritic cells. J Immunol 2000; 164:4443-51.
28. Ghoreishi M, Bach P, Obst J, Komba M, Fleet JC, Dutz JP. Expansion of antigen-specific regulatory T cells with the topic vitamin D analog calcipotriol. J Immunol 2009; 182:6071-78.
29. Jirapongsananuruk O, Melamed I, Leung DY. Additive immunosuppressive effects of 1,25-dihydroxyvitamin D3 and corticteroids on TH1, but not TH2, responses. J Allergy Clin Immunol 2000; 106:981-5.
30. Bolognia JLS, Jorizzo JL, Rapini RP, Zhu XJ,Wang BX,Sun JF,Xiang HL. Dermatology. 2nd ed. Beijing: Peking University Medical Press; 2010 p.10
31. Lu LM, Chen KT. Research Progress on the mechanism of eczema. Asia-Pacific Traditional Medicine 2007; 3:76-9.
32. Scott-Mackie P, Hickish T, Mortimer P, Sloane J, Cunningham D. Calcipotriol and regression in T-cell lymphoma of skin. Lancet 1993; 342:172.
33. Eckert RL, Broome AM, Ruse M, Robinson N, Ryan D, Lee K. S100 proteins in the epidermis. J Invest Dermatol 2004; 123:23-33.
34. Hegyi Z, Zwicker S, Bureik D, et al. Vitamin D analog calcipotriol suppresses the Th17 cytokine-induced proinflammatory S100 "alarmins" psoriasin (S100A7) and koebnerisin (S100A15) in psoriasis. J Invest Dermatol 2012; 132:1416-24.
35. Remitz A, Reitamo S, Erkko P, Granlund H, Lauerma AI. Tacrolimus ointment improves psoriasis in a microplaque assay. Br J Dermatol 1999; 141:103-7.
36. Murdoch D, Clissold SP. Calcipotriol: A review of its pharmacological properties and therapeutic use in psoriasis vulgaris. Drugs 1992; 43:415-29.
37. Scott LJ, Dunn CJ, Goa KL. Calcipotriol ointment: A review of its use in the management of psoriasis. Am J Clin Dermatol 2001; 2:95-120.