Comparison of Calcipotriol Monotherapy and a Combination of Calcipotriol and Methylprednisolone Aceponate Therapy in Psoriasis Patients

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Background: **Complete clearance of the lesions by using calcipotriol alone have not been reported commonly in the treatment of psoriatic patients. Moreover, lesional and perilesional irritation are reported in some patients using calcipotriol, which may result in premature termination of the treatment due to impairing the compliance.**

Objective: **A clinical study was conducted to determine whether, in the topical treatment of psoriasis, a combination of calcipotriol cream and methylprednisolone aceponate was more effective than calcipotriol monotherapy.**

Methods: Twenty-one psoriasis patients who had the symmetric lesions on the right and left lower legs were enrolled in the study. A combination of calcipotriol cream and methylprednisolone aceponate therapy was done on the left lower legs, whereas calcipotriol alone was applied on the right lower legs twice daily. PASI score and adverse events were recorded at each visit (1, 2, 3, 4, 6 week). The overall therapeutic result was also assessed by the physician and patients.

Results: **The initial PASI score was 7.09 on both legs. After 6 weeks, the mean PASI score was 3.85 on the left leg, and 5.70 on the right leg ($p<0.05$). In the physician°Øs global assessment, the percentage of patients who showed the improvement of more than half of lesions was 29% in the monotherapy and 62% in the combination therapy area. Two patients complained of mild itching sense on monotherapy, but there was no specific side effect on combination area.**

Conclusion: **The combination therapy was more effective, as assessed by all evaluated variables. Furthermore, this combination reduces the adverse effects caused by long-term use of topical corticosterois as well as the irritation associated with calcipotriol.**

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Key Words : Calcipotriol, Methylprednisolone aceponate, Combination, Psoriasis

Calcipotriol, the first vitamin D_3 analogue, was introduced into antipsoriatic therapy in the early 1990s and since then it has been used for mild and moderate plaque-type psoriasis. Many clinical studies report the favourable effect of calcipotriol or other calcitriols on the various clinical features of psoriasis[1-3]. Clinical comparisons of calcipotriol with topical steroids showed that about two-thirds of patients responded with a marked improvement in psoriatic lesions[4]. But, complete clearance of the lesions by using calcipotriol alone have not been reported commonly. Moreover, lesional and perilesional irritation are reported in about 12 to 20.1% of

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patients using calcipotriol[5]. The irritation is mild in most patients, but may result in premature termination of the treatment due to impairing the compliance.

The object of our study was to determine whether a combination of calcipotriol cream and methylprednisolone aceponate (moderate-potent topical steroid) is more effective and tolerable than calcipotriol cream monotherapy.

MATERIALS AND METHODS

1. Materials

A total of 21 patients that attend the psoriasis clinic at Seoul National University Hospital, Seoul, Korea were asked to take part in the study. Only patients with chronic plaque type psoriasis which had symmetric lesions on both lower extremities were included. Patients with lesions exceeding 30% of total body surface area or who had received any systemic antipsoriatic or UV therapy during previous 4 weeks were excluded, as were pregnant or nursing women and those who were youngsters less than 18. Table 1 contains the relevant data concerning age, sex, and the initial PASI (Psoriasis Area and Severity Index) score of lower extremities.

2. Study Design

The study was conducted as a randomized comparison between monotherapy with 0.005% calcipotriol cream (Daivonex, Leo Pharmaceutical Products, Ballerup, Denmark® and a combination of calcipotriol and methylprednisolone aceponate 0.1% cream (Advantan®, Schering, Germany). After 4-week wash-out in which the patients were allowed to apply an emollient only, calcipotriol cream was applied on right lower extremities twice daily whereas calcipotriol cream (morning) and methylprednisolone aceponate cream (evening) were applied on left lower extremities once daily respectively. The end-point of treatment was the complete clearance or development of unacceptable adverse effects.

Table 1. Patients profile enrolled in the study

number	21
Age (years)	37.0 ± 13.6
Sex (male / female)	9 / 12
Initial PASI (only on unilateral lower leg)	7.09 ± 2.04

Table 2. Criteria of response to therapy

Grade	Criteria
0	No change
1	Minimal improvement -slightly less scale and/or erythema
2	Definite improvement -partial flattening of all plaques - less scale and erythema
3	Considerable improvement -nearly complete flattening of all plaques, border of plaques still palpable
4	Clearing-complete flattening of plaques may be outlined by pigmentation

3. Clinical assessment

Patients were examined before the start of the therapy, and at 1,2,3,4,6 weeks after the start of treatment. At each visit, the severity of the psoriasis was evaluated according to the psoriasis area and severity index (PASI).

The PASI scores of lower extremity was summed up as follows; PASI score of lower leg= 0.4 × area × (erythema + scale + thickness). The initial mean PASI score was calculated by averaging the PASI scores of bilateral lower legs. Additionally, the physician rated the global assessment according to five grade. The grading system consisted of no change (Grade0), minimal improvement (Grade1), definite improvement (Grade2), considerable improvement (Grade3), and clearing (Grade4) (Table2). At the end of therapy, all the patients were asked which therapy was preferred and the physician also decided which was more efficient.

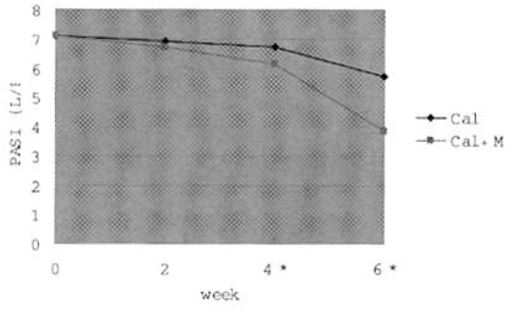
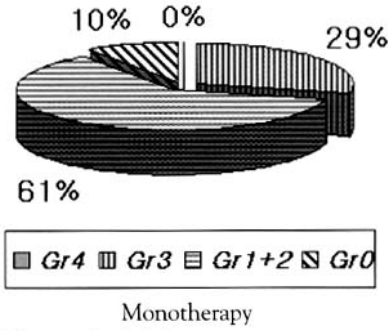


Fig. 1. The change of PASI of lower extremities during the treatment
Cal : calcipotriol , M : methylprednisolone aceponate * $p < 0.05$



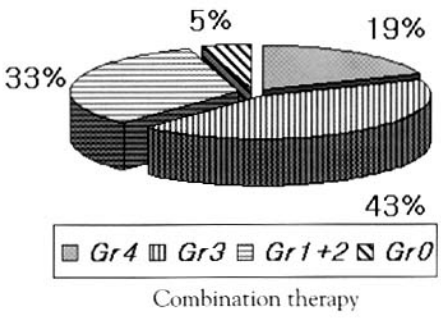


Fig. 2. Physician's global assessment
Grade 0 : no change
Grade 2 : definite improvement
Grade 4 : clearing

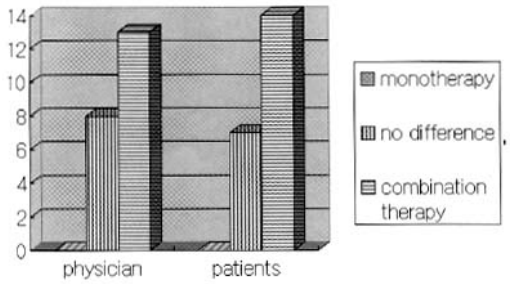


Fig. 3. The preference of therapy.

All adverse events were recorded at each visit.

4. Statistical methods

Mann-Whitney U test was performed to evaluate the differences between the monotherapy and the combination therapy area (SPSS® 9.0 version, USA). Wilcoxon Matched-Pairs Signed-Ranks test was performed to analyse the reduced PASI of both extremities. P value of less than 0.05 was regarded as significant.

RESULTS

Figure 1 shows the change of PASI on lower extremities during treatment. The initial mean PASI score was 7.09 on both legs. There was no significant difference between two areas at 2 weeks. After 6 weeks, the mean PASI score was 3.85 on the left leg, and 5.70 on the right leg ($p<0.05$). In the physician's global assessment (Fig 2), there was no clearance group on the monotherapy area whereas 19% (n=3) showed clearance response on the combination area. The portion which showed considerable improvement was 29% (n=6) on the monotherapy and 43% (n=9) on the combination therapy area respectively. Therefore, the percentage of patients who showed the improvement of more than half of lesions (Grade 3,4) was 29% (n=9) in the monotherapy and 62% (n=13) in the combination therapy area ($p<0.05$). When the patients were asked which therapy was preferred and the physician also decided which was more efficient of the two therapy regimen, 14 (66.7%) patients preferred the combination therapy and the physician decided that the combination therapy was more effective in 13 (61.9%) patients. No patients or physicians preferred monotherapy. (Figure 3). All adverse events were recorded at each visit. Two patients complained of mild itching sense and erythema on monotherapy, but there was no specific adverse effect on combination area.

DISCUSSION

There have been a few reports[6,7] that showed the efficacy of a combination therapy of calcipotriol and topical steroid. A combination of topical once daily calcipotriol (morning) plus halobetasol (afternoon) was superior to either twice daily calcipotriol or twice daily halobetasol in a 2-week study in patients with plaque psoriasis. After 2 weeks, recipients in the combination therapy g-

roup had significantly greater reductions in mean overall psoriasis severity score and in subscale scores of plaque elevation compared with calcipotriol monotherapy. But, there was no difference in erythema and scaling scores between the combination therapy group and halobetasol alone[6]. In another study, a combination of once daily calcipotriol plus once daily betamethasone valerate 1mg/g provided more marked reductions in mean overall psoriasis severity scores than twice daily calcipotriol ointment alone after 4 weeks of therapy[7]. In addition, pulse therapy with calcipotriol ointment twice daily (weeks 1 and 3) plus betamethasone dipropionate once daily (weeks 2 and 4) was superior to betamethasone dipropionate monotherapy in reducing overall disease severity[8].

As in other studies, a combination of calcipotriol and methylprednisolone aceponate is also thought to have a synergistic effect because they may interact with different receptor subtypes.

In the view of adverse effects, many studies including our research have shown that fewer local side effects reported in combination therapy than in monotherapy. The most common local adverse effect associated with calcipotriol in short term studies were irritation (12 to 20.1% of patients)[5]. The irritation is especially common on the lesional skin and even once-daily application is not known to reduce this response. There have been some reports[6-8] that indicated the decrease of irritation by using topical steroid. But most of the combined steroids were relatively potent ones. Our study showed that the steroid with moderate potency is sufficient to reduce the skin irritation of calcipotriol.

Although the topical steroids can improve the effects of calcipotriol and reduce the local adverse effects, there are a few opposite views to combining the steroids in all calcipotriol-using psoriasis patients. The calcipotriol monotherapy may induce clearance in some patients, and the irritational response is often mild and transient. Moreover, the long-term use of topical steroid, or in excessive quantities, can make a detrimental effect on the skin in various ways[9]. In conclusion, we think that the combination therapy with a mid potency steroid is beneficial for patients who have a suboptimal response to calcipotriol monotherapy.

REFERENCES

1. Kragballe K, Beck H-J, Sogaard H: Improvement of psoriasis by a topical vitamin D_3-analogue (MC-903) in a double-blind study. Br J Dermatol 119: 223-30, 1988.
2. Kragballe K: Treatment of psoriasis by the topical application of the novel cholecalciferol analogue calcipotriol (MC 903). Arch Dermatol 125: 1647-52, 1989.
3. Nieboer C, Verburgh CA: Psoriasis treatment with vitamin D3-analogue MC903. Br J Dermatol 126: 302-3, 1992.
4. Kragballe K. Vitamin D and derivatives. In Dubertret L (ed.) Psoriasis. Brescia: ISED, 1994: 124-34.
5. Scott LJ, Dunn CJ, Goa KL: Calcipotriol ointment: A review of its use in the management of psoriasis. Am J Clin Dermatol 2(2): 95-120, 2001.
6. Lebwohl M, Siskin SB, Epinette W: A multicenter trial of calcipotriene ointment and halobetasol ointment compared with either agent alone for the treatment of psoriasis. J Am Acad Dermatol 35(2 Pt 1): 268-9, 1996.
7. Ruzicka T, Lorenz B: Comparison of calcipotriol monotherapy and a combination of calcipotriol and betamethasone valerate after 2 weeks' treatment with calcipotriol in the topical therapy of psoriasis vulgaris: a multicenter, double-blind, randomized study. Br J Dermatol 138: 254-8, 1998.
8. Singh S, Reddy DCS, Pandey SS: Topical therapy for psoriasis with the use of augmented betamethasone and calcipotriene on alternate week. J Am Acad Dermatol 43(1 Pt 1): 61-5, 2000.
9. Barnetson RS. White AD: The use of corticosteroids in dermatological practice. Med J Aust 156: 428-31, 1992.