

## CLINICAL REPORT

# Effect of Calcipotriol on Etanercept Partial Responder Psoriasis Vulgaris and Psoriatic Arthritis Patients

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**Patients who respond only partially to etanercept may require additional treatments that act synergistically to improve their therapeutic response while at the same time reducing the dose required and the risk of side-effects. The aim of this study was to evaluate the effectiveness of topical calcipotriol in etanercept partial responder patients. We enrolled 120 patients affected by psoriasis vulgaris and psoriatic arthritis. A 50 mg dose of etanercept was administered twice weekly for the first 12 weeks, followed by a 25 mg dose twice weekly for an additional 12 weeks. At week 12, for 45 patients who had not achieved PASI 50, calcipotriol cream was also prescribed twice daily for 4 weeks and then once daily for a further 8 weeks. At week 24, of the 45 patients in the group treated with etanercept plus calcipotriol, 14 (31.1%) had achieved PASI 75, and 23 PASI 50, while 8 (17.7%) had dropped out of therapy; of the 75 patients who continued etanercept in monotherapy with a 25 mg dose twice weekly for another 12 weeks, 71 (94.6%) had achieved PASI 50 and 57 (76.0%) PASI 75. The application of calcipotriol in etanercept partial responder patients had therefore helped 37 out of 120 patients (31%) achieve at least PASI 50. This is the first report about the controlled combination of topical calcipotriol and etanercept in a large group of psoriatic patients. The efficacy and cost-effectiveness of the combined treatment is evidenced by the good response shown at week 24 by a group of etanercept low-responder patients using drugs sparingly and limiting likely toxicity. *Key words: combined therapy; psoriasis; biologic drugs; analogue vitamin D.***

(Accepted June 5, 2008.)

Acta Derm Venereol 2009; 89: 288–291.

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Etanercept is a recombinant, entirely human, dimeric fusion protein, which functions as a tumour necrosis factor (TNF)- $\alpha$ -inhibitor by binding both free and receptor-bound TNF- $\alpha$  (1). TNF- $\alpha$  plays an important role in the cascade of reactions that causes the psoriasis inflammatory process (2, 3). The binding of etanercept to TNF- $\alpha$  renders it biologically inactive, resulting in a significant

reduction in inflammatory activity. Etanercept is indicated for the treatment of moderate-to-severe plaque psoriasis, psoriatic arthritis, rheumatoid arthritis, ankylosing spondylitis and juvenile rheumatoid arthritis (4–6).

Recent clinical trials have analysed the efficacy of biologics in combination with methotrexate or phototherapy (7, 8). A combined treatment is chosen to reduce the side-effects of systemic drugs, taking advantage of synergic mechanisms of action. Moreover, three clinical trials have reported that the addition of calcipotriol to systemic treatment such as methotrexate, acitretin and ciclosporin improves the therapeutic efficacy compared with a systemic monotherapy and minimizes side-effects by reducing either the dosage or the duration of treatment (9–11).

Another therapeutic strategy to increase efficacy is to combine a biologic agent with a topical anti-psoriatic agent in selected patients, as reported by van Duijnhoven and colleagues (12), who evaluated the effect of calcipotriol on epidermal cell populations in alefacept-treated psoriatic lesions.

Calcipotriol is a synthetic vitamin D3 analogue and an effective treatment for mild to moderate chronic plaque psoriasis, which binds to vitamin D receptor, a transcription factor in keratinocytes, fibroblasts, melanocytes and other cell types (13, 14). This binding induces keratinocytes terminal differentiation by the downregulation of the expression of two proliferation factors, early growth response-1 (EGR1) and polo-like kinase-2 (PLK2) (15). The protein levels of EGR1 and PLK2 are also decreased after local calcipotriol application. Calcipotriol is generally administered once or twice daily for long-term therapies. The maximum recommended weekly dosage of calcipotriol is 100 g; therefore its use is limited to cases where there is an involvement of 30% of body surface area or less (16).

Because of the different actions of etanercept and calcipotriol, it is interesting to speculate that the combination of both therapies may have a synergic result. The aim of the present study was to validate the effect of this combination in patients affected by different clinical variants of psoriasis vulgaris and/or psoriatic arthritis (17).

## PATIENTS AND METHODS

The study was carried out by our dermatology departments on 120 patients affected by psoriasis vulgaris and psoriatic arthritis,

75 males and 45 females, with a mean age of 48 years (age range 18–75 years). The mean baseline Psoriasis Area and Severity Index (PASI) was 8.26, including chronic plaque psoriasis, non-pustular psoriasis, palmo-plantar psoriasis, flexural psoriasis, seborrhoeic psoriasis and psoriatic arthritis (17). A 50 mg dose of etanercept was administered subcutaneously twice weekly for 12 weeks, followed by a 25 mg dose twice weekly for another 12 weeks (Fig. 1). A total of 45 patients with persistent psoriatic lesions who had not achieved PASI 50 at week 12 applied calcipotriol 0.005% cream locally twice a day for 4 weeks, and thereafter once a day for 8 weeks. Before starting, the patients had been in wash-out both for 4 weeks for systemic treatment and for 2 weeks for topical anti-psoriatic treatment.

All patients signed a written informed consent before initiating treatment and the study was conducted in accordance with ethical guidelines of the Declaration of Helsinki.

The patients were visited and evaluated at week 0, 6, 12, 18 and 24 by the same investigator. Furthermore, a baseline profile was obtained for each patient before he or she began treatment, including a complete blood count, tests for hepatic and renal function and for calcaemia, a tine test and a chest X-ray.

## RESULTS

At week 12, a total of 38 patients (32%) had achieved PASI 75 and 37 (31%) PASI 50, whereas 45 patients (37%) had not achieved PASI 50. The mean PASI achieved was 3.5 (Table I).

From week 12, the 45 patients who had not achieved PASI 50 applied calcipotriol 0.005% cream twice daily for 4 weeks and then once daily for an additional 8 weeks.

At week 24, of the 45 patients, 14 (31.1%) had achieved PASI 75 and 23 (51.1%) PASI 50, while 8 (17.7%) had dropped out of therapy. The end-point mean PASI was 1.83.

The local application of calcipotriol in etanercept partial responders had therefore helped 37 patients (31%) achieve at least PASI 50.

We observed a reduction in erythema, scaling and itching. The drug was well tolerated and proved to be

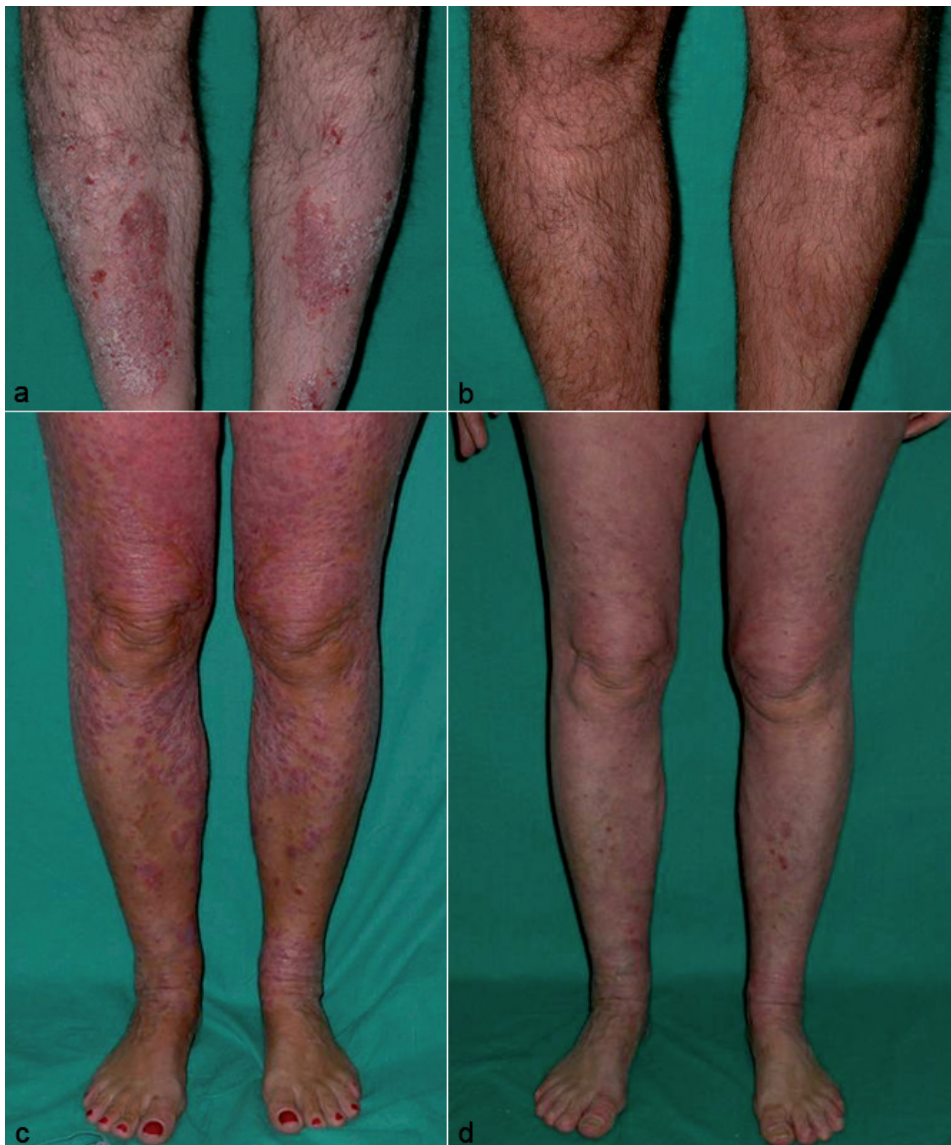


Fig. 1. Two patients with psoriatic lesions on the lower limbs at week 12 (a and c) and at week 24 (b and d).

Table I. Clinical responses at weeks 12 and 24

	Week 12 (50 mg twice weekly) <i>n</i> = 120			Week 24 (25 mg twice weekly) <i>n</i> = 75		
	PASI >75	PASI 50–75	PASI <50 <sup>a</sup>	PASI >75	PASI 50–75	PASI <50
Etanercept monotherapy	38 (31.7%)	37 (30.8%)	45 (37.5%)	57 (76%)	18 (24%)	0
Etanercept plus calcipotriol cream Combined treatment from week 12 to week 24.				PASI <50 <i>n</i> = 45		
				14 (31.1%)	23 (51.1%)	8 (17.8%)

<sup>a</sup>These patients were switched to the combination therapy.

a valid therapeutic agent in cases where an associated topical treatment was necessary.

Of the 75 patients who continued etanercept in monotherapy, 71 had achieved PASI 50 and 57 PASI 75 at week 24 (Table I).

## DISCUSSION

In the literature, some clinical trials recommend using a combined therapy to treat moderate to severe psoriasis, as has been demonstrated with traditional systemic drugs with biologics and with topical medications, either in cases with a lower response rate or to reduce toxicity (8–11, 18, 19).

The rationale for a combined therapy in psoriasis is that a synergistic action could increase efficacy while lowering individual drug dosages. Legat et al. (20) described an accelerated and improved clearance of psoriasis in patients treated with alefacept by adding phototherapy as compared with alefacept monotherapy.

Regarding the use of biologic treatment and topical therapy in psoriatic patients, in the literature to date there has been only one anecdotal study reported on the use of a combined treatment of alefacept (anti-LFA2) and calcipotriol cream in psoriatic patients. It showed that calcipotriol had an additional effect on the epidermal cell population in psoriatic lesions in patients treated with alefacept and that the combined treatment (alefacept-calcipotriol) induced a faster clinical improvement than alefacept monotherapy (12).

On the basis of this data and our previous experience of etanercept monotherapy, we decided to validate the addition of calcipotriol cream in a trial of etanercept partial responder patients.

In psoriatic lesions, TNF- $\alpha$  is produced locally and stimulates the release of other chemokines and the expression of adhesion molecules on keratinocytes and on endothelial cells. TNF- $\alpha$  amplifies and maintains the inflammatory process causing other inflammatory cells to be recruited into the plaque and in synovia. Etanercept mimics the activity of naturally occurring soluble TNF- $\alpha$  receptors and prevents TNF- $\alpha$  from binding to its receptor. By inhibiting TNF- $\alpha$  through etanercept, the inflammatory process is impaired (2). Calcipotriol is a

vitamin D3 derivate that binds to the vitamin D receptor, a ligand-activated transcription factor, in target cells identified as keratinocytes and lymphocytes. The vitamin D analogues inhibit the proliferation of epidermal T cells, the accumulation of polymorphonuclear leukocytes and the activity of Langerhans' cells in psoriatic lesions and stimulate the cell differentiation of keratinocytes (16). The rationale for the use of these two different drugs is related to their activity on different cells involved in the psoriasis pathogenesis. Furthermore, the efficacy and safety of biologics has been demonstrated in several clinical trials, but their long-term safety has not yet been verified (21).

Regarding the recommendations on the use of etanercept, it is well known that in patients who achieve PASI 75 after 3 months of treatment at 50 mg twice weekly, the dosage will be reduced (25 mg twice weekly) for the maintenance period. If PASI improvement is less than 50% after 3 months, it could be reasonable to shift to other treatments or to reduce the dosage to limit the drug toxicity while adding a drug with a different mechanism of action (22).

In our clinical experience, in the group of etanercept partial responder (PASI < 50) patients (37%), the addition at week 12 of calcipotriol cream and the reduction of the etanercept dosage (to 50 mg/week) allowed a good clinical outcome. Of these patients, we observed that 31.1% had achieved PASI 75 by the end of our study (week 24). Persistent psoriatic lesions localized on the limbs, which had had a low response to etanercept monotherapy, had responded well when etanercept was combined with calcipotriol. Moreover, the PASI reduction was maintained for several weeks after treatment was stopped.

The rationale for studying a combined treatment was based on three considerations: first, the existence of a moderate number of patients with a lower response rate to etanercept who complained of the discomfort caused by persistent lesions; secondly, the improvements noted in patients who had already been treated with etanercept when a topical treatment was used; and finally, the usefulness of a combined treatment in terms of reducing the risk of side-effects and lowering the cost of biologics. Larger, longer-term studies are required to support our

preliminary results. Furthermore, in future trials it could be useful to give the topical medication in combination with a biologic drug at the start of therapy in order to accelerate the therapeutic response.

Clinical experience with biological therapies in dermatology is relatively limited and their long-term safety is uncertain. In future studies, it would be very interesting to investigate new combinations of biologics with conventional drugs in order to improve efficacy, limit toxicity and reduce costs.

*The authors declare no conflicts of interest.*

## ACKNOWLEDGEMENT

The authors wish to thank Diana Saltarelli for editing assistance.

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