Acta Derm Venereol (Stockh) 1996; 76: 65–67

A Therapeutic Approach to Erythrodermic Psoriasis: Report of a Case and a Discussion of Therapeutic Options

C. J. M. VAN DER VLEUTEN, M. J. P. GERRITSEN, P. M. STEIJLEN, E. M. G. J. DE JONG and P. C. M. VAN DE KERKHOF

Department of Dermatology, University Hospital Nijmegen, Nijmegen, The Netherlands

In this case report a patient with therapeutically recalcitrant erythrodermic psoriasis is presented. After various attempts with several major therapies in this patient, the first substantial improvement was achieved using the combination of cyclosporine and calcipotriol, followed by the combination of UVB and calcipotriol. The therapeutic options for severe psoriasis are discussed, and since combined approaches seem to be an attractive alternative for severe psoriasis, mechanisms of synergy of combined therapeutic approaches are hypothesised. ***Key words: calcipotriol; cyclosporine; UVB; combination therapy.***

(Accepted August 30, 1995.)

Acta Derm Venereol (Stockh) 1996; 76: 65–67.

C. J. M. van der Vleuten, Department of Dermatology, University Hospital Nijmegen, P.O. Box 9101, NL-6500 HB Nijmegen, The Netherlands.

Erythrodermic psoriasis is a rare but dramatic condition. As a result of a trigger of any kind, psoriasis can become unstable and can extend until the whole skin is erythematous and scaly. In general, systemic treatment of erythrodermic psoriasis is inevitable, and patients should be admitted at the inpatient department.

Well-established therapeutic options for severe psoriasis, including erythrodermic psoriasis, are methotrexate, acitretin and cyclosporine. However, the therapeutic response in patients with erythrodermic psoriasis may be variable and sometimes disappointing. The search for the appropriate therapy is time-consuming. Often a combination of systemic and local therapies will provide the eventual remedy for the patient after several weeks of intensified supervision.

The aim of this report is to present a case, indicating the therapeutic problems during treatment of erythrodermic psoriasis.

CASE REPORT

An 83-year-old erythrodermic man was admitted to our hospital. At dermatological investigation generalised erythema and extensive scaling was observed all over the body (Fig. 1), face, scalp, palms and soles. Histopathological investigation of the skin showed a chronic, non-specific dermatitis without signs of lymphoma or psoriasis. At general investigation we saw a dyspnoeic man with oedema on both lower legs. The body weight was 63 kg. No enlarged lymphnodes were palpable. No additional abnormalities were observed except for pre-existent gallstones. Blood tests, X-thorax, ECG, CT-scan of thorax and abdomen, X-colon did not reveal any internal pathology. Especially no evidence existed for malignancy. Serum 1,25 $(OH)_2$ vitamin D_3 and 25 OH vitamin D_3 were 70 pmol/l and 50 nmol/l, respectively, which was in the normal range.

The patient had had psoriasis vulgaris for 5 years. The condition could be controlled up to 6 months prior to admission. A first exacerbation was treated with tar-UVB and calcipotriol, but 4 months later, the psoriasis flared again resulting in erythroderma. The patient was admitted to a hospital elsewhere and was treated with potent topical corticosteroids such as clobetasol 17-propionate and different systemic therapies, each of these only for a short period. Acitretin had been given for 3 weeks, methotrexate for 2 weeks and oral corticosteroids also for 2 weeks, without any substantial improvement. No factors were found that could have triggered this exacerbation of psoriasis. There was no history of infections or malignancy.

As the expression of psoriasis was extremely severe and unresponsive to various treatments, the patient was transferred to the university hospital. We started therapy with acitretin (20 mg/day) and hydrocortisone (1% in petrolatum) topically. Water-salt-balance normalised; furosemide 40 mg daily was given to control oedema and dyspnoea. Protein loss due to scaling was compensated with the appropriate diet. After 4 days the dose of acitretin was increased to 30 mg/day. Since there was no improvement, cyclosporine (3 mg/kg/day) was added after another 4 days. This resulted only in a minor improvement after 3 weeks; subsequently the dose of cyclosporine was increased to 4 mg/kg/day. After another week acitretin was stopped and cyclosporine was again increased to 5 mg/kg/day. The skin condition in the patient still did not improve. Then it was decided to start local calcipotriol on the right side of the body whilst continuing cyclosporine. The calcipotriol-treated side showed a remarkable improvement compared to the other side, which was treated with bland emollients (Fig. 2). After 1 week the whole body was treated on alternate days with calcipotriol twice daily up to 100 g per week. On the remaining days of the week bland emollients were applied. As the quantity of calcipotriol ointment approximated 100 g per week calcium and phosphate in the serum were measured at weekly intervals.

The condition of the skin improved markedly within 4 weeks. Meanwhile, after treatment with cyclosporine for 2 months, the serum creatinine increased and the patient developed a tremor of unknown origin, which could have been a side-effect of cyclosporine. These

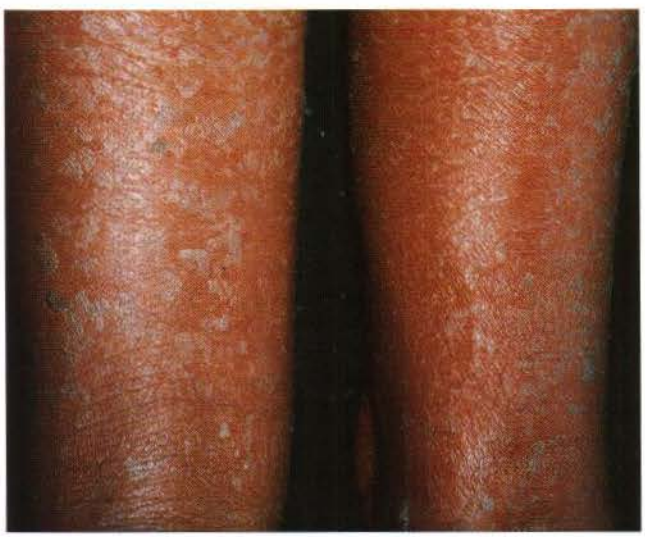

Fig. 1. Erythrodermic skin and extensive scaling all over the body, at the moment of admission to hospital.

 ISSN 0001-5555

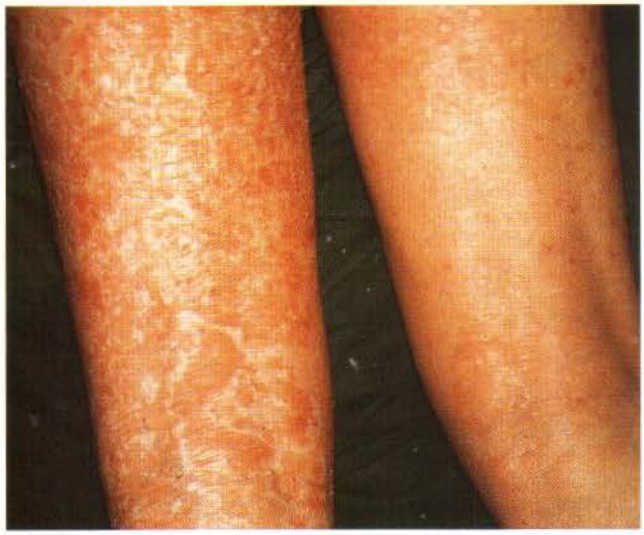

Fig. 2. Remarkable improvement on the right side of the body, due to calcipotriol on this side combined with systemic cyclosporine.

symptoms necessitated discontinuation of cyclosporine. As an alternative to cyclosporine, phototherapy with a low dose UVB in combination with local calcipotriol was started. The patient responded well to this treatment and was discharged from hospital in a reasonable condition after 1 month of phototherapy. Phototherapy in combination with local calcipotriol was continued at the out-patient department for about 4 months. So far the condition of the patient remains excellent, without any psoriatic lesion up till 6 months after discharge from hospital.

During the various treatments, apart from the transient increase of serum creatinine and the temporary tremor during cyclosporine, no side-effects occurred. Serum calcium and phosphate remained in the normal range.

DISCUSSION

Before deciding on the strategy of the treatment, the underlying cause of the erythroderma has to be established. Histopathological investigation is not always specific (1). The history of a previous skin disease is an important clue to the diagnosis; 25% of the cases are associated with psoriasis. Drugs, neoplasia and eczema account for the majority of the other known causes. In a substantial part of the cases no obvious cause is found (2). In case the nosological identity of the erythroderma remains unknown, further internal investigation is required to exclude paraneoplasia (3).

As erythroderma is a serious condition, fast improvement is urgently wanted. Topical treatments with potent corticosteroids may be useful; however, as the patient described in this report had already been treated elsewhere with potent corticosteroids (clobetasol 17-propionate), a weak steroid preparation was prescribed in order to prevent systemic complications. Systemic treatment is often necessary but is sometimes changed if no response is observed after a few days. Also in the present case, various short treatments were initiated without allowing a sufficient treatment period for an anti-psoriatic result. One may argue that the period of 1-week acitretin monotherapy might have been too short to induce a significant improvement. However, the severity of the erythroderma required a fast therapeutical effect, hence the combined approach.

Combinations of the major therapies for psoriasis are an attractive option, since some combinations allow a lower dose than that used in monotherapy, which reduces side-effects. The combination of methotrexate and etretinate is controversial in view of hepatotoxicity (4,5); the combination of etretinate and cyclosporine has been used with success in psoriasis (6,7). From a theoretical point of view, the immunosuppressive effect of cyclosporine and the differentiation modulating effect of retinoids is a promising combination. Oral retinoids have also been combined successfully with UVB or PUVA (re-PUVA) (8,9). The combination of two immunosuppressive therapies like methotrexate and cyclosporine is not recommended (10).

Another practical approach is the combination of systemic and topical therapy. After various attempts with several major therapies in this patient, including the combination of cyclosporine and acitretin, the first substantial improvement was achieved using the combination of calcipotriol and cyclosporine. In the past emollients, tars and topical steroids have been used in combination with systemic therapies (11). Nowadays, the vitamin D_3 analogue calcipotriol is available. Its beneficial effect as a monotherapy in mild to moderate chronic plaque psoriasis has been well established (12). However, calcipotriol might irritate the skin in about 20% of the patients (13). In particular patients with erythrodermic psoriasis are susceptible to low doses of irritants. On the other hand, patients with unstable and erythrodermic psoriasis have been reported to respond well to calcipotriol (14,15). In the present case the maximum quantity of 100 g calcipotriol ointment per week was not exceeded. As serum vitamin D_3 levels were normal, it was excluded that this patient might have had a vitamin D_3 deficiency.

The skin is the site of production of vitamin D_3 and target of its active metabolite: 1α,25-dihydroxyvitamin D_3 (16). Vitamin D_3 receptors, member of the steroid-hormone-receptor super-family, are found in the epidermis (17). The therapeutic mode of action of vitamin D_3 and its analogues in psoriasis is partly via these receptors, which regulate gene transcription, and partly through non-genomic mechanisms (18). Calcipotriol inhibits proliferation and induces terminal differentiation in cultured human keratinocytes (19). *In vivo* these effects are observed as well (20). Immunomodulating effects of calcipotriol are also described: inhibition of T-cell proliferation in response to interleukin 1 *in vitro* (21) and reduction of interleukin 6 in a psoriatic plaque *in vivo* in response to calcipotriol (22).

In literature both cyclosporine (23) and UVB (24,25) have been combined successfully with calcipotriol in psoriatic patients. In particular low-dose cyclosporine (2 mg/kg/day) in combination with calcipotriol proved to be an effective and safe approach (23). From a theoretical point of view it is attractive to speculate that calcipotriol-cyclosporine is a useful combination. The modes of action of cyclosporine and 1α,25-dihydroxyvitamin D_3 and its analogues are thought to be complementary (26–28). Recently several investigators have demonstrated the synergistic effects of both anti-psoriatic therapies. Calcipotriol can potentiate the immunosuppressive effect of cyclosporine in mixtures of human lymphatic and epidermal cells (29). The effect of cyclosporine on interleukin 2 is increased by calcitriol (26–28). On the other hand, the differential effect of both treatments on epidermis and immune system might explain the synergistic effect (30,31). When

cyclosporine treatment was not possible anymore in our patient due to increase of serum creatinine, UVB in combination with calcipotriol was applied successfully. In literature there is still no clearness about synergy of UVB and calcipotriol in psoriasis (24,25). But the remarkable effect of the combination in this patient suggests that in some cases synergism might occur.

In the case of erythrodermic psoriasis, the therapeutic strategy often includes systemic treatment. Options are monotherapy with acitretin, cyclosporine or methotrexate. The choice depends on indications and contraindications in the individual patient. In the present case of persisting erythroderma, combination therapy of cyclosporine plus calcipotriol and subsequently UVB plus calcipotriol proved to be a successful approach.

REFERENCES

1. Zip C, Murray S, Walsh NM. The specificity of histopathology in erythroderma. J Cutan Pathol 1993; 20: 393–398.
2. Boyd AS, Menter A. Erythrodermic psoriasis. Precipitating factors, course, and prognosis in 50 patients. J Am Acad Dermatol 1989; 21: 985–991.
3. Nicolis GD, Helwig EB. Exfoliative dermatitis. A clinicopathologic study of 135 cases. Arch Dermatol 1973; 108: 788–797.
4. Beck HI, Foged EK. Toxic hepatitis due to combination therapy with methotrexate and etretinate in psoriasis. Dermatologica 1983; 167: 94–96.
5. Tuyp E, MacKie RM. Combination therapy for psoriasis with methotrexate and etretinate. J Am Acad Dermatol 1986; 14: 70–73.
6. Brechtel B, Wellenreuther U, Toppe E, Czarnetzki BM. Combination of etretinate with cyclosporine in the treatment of severe recalcitrant psoriasis. J Am Acad Dermatol 1994; 30: 1023–1024.
7. Korstanje MJ, Bessems PJ, van de Staak WJ. Combination therapy ciclosporin-etretinate effective in erythrodermic psoriasis [letter]. Dermatologica 1989; 179: 94.
8. Lowe NJ, Prystowsky JH, Bourget T, Edelstein J, Nychay S, Armstrong R. Acitretin plus UVB therapy for psoriasis. Comparisons with placebo plus UVB and acitretin alone. J Am Acad Dermatol 1991; 24: 591–594.
9. Saurat JH, Geiger JM, Amblard P, Beani JC, Boulanger A, Claudy A, et al. Randomized double-blind multicenter study comparing acitretin-PUVA, etretinate-PUVA and placebo-PUVA in the treatment of severe psoriasis. Dermatologica 1988; 177: 218–224.
10. Korstanje MJ, van Breda Vriesman CJ, van de Staak WJ. Cyclosporine and methotrexate: a dangerous combination. J Am Acad Dermatol 1990; 23: 320–321.
11. Farber EM, Nall L. Erythrodermic (exfoliative) psoriasis. Cutis 1993; 51: 79–82.
12. Berth Jones J, Hutchinson PE. Progress in self treatment for psoriasis vulgaris. J Clin Pharmacol Ther 1992; 17: 217–222.
13. Kragballe K, Gjertsen BT, De Hoop D, Karlsmark T, van de Kerkhof PC, Larkö O, et al. Double-blind, right/left comparison of calcipotriol and betamethasone valerate in treatment of psoriasis vulgaris [published erratum appears in Lancet 1991 Apr 20;337(8747):988]. Lancet 1991; 337: 193–196.
14. Berth Jones J, Bourke J, Bailey K, Graham Brown RA, Hutchinson PE. Generalised pustular psoriasis: response to topical calcipotriol. BMJ 1992; 305: 868–869.
15. Gray JD, Bottomley W, Layton AM, Cotterill JA, Monteiro E. The use of calcipotriol in HIV-related psoriasis. Clin Exp Dermatol 1992; 17: 342–343.
16. Texereau M, Viac J. Vitamin D, immune system and skin. Eur J Dermatol 1992; 2: 258–264.
17. Milde P, Hauser U, Simon T, Mall G, Ernst V, Haussler MR, et al. Expression of 1,25-dihydroxyvitamin D3 receptors in normal and psoriatic skin. J Invest Dermatol 1991; 97: 230–239.
18. Bittiner B, Bleehen SS, MacNeil S. 1 alpha,25(OH)2 vitamin D3 increases intracellular calcium in human keratinocytes. Br J Dermatol 1991; 124: 230–235.
19. Binderup L, Bramm E. Effects of a novel vitamin D analogue MC903 on cell proliferation and differentiation in vitro and on calcium metabolism in vivo. Biochem Pharmacol 1988; 37: 889–895.
20. de Jong EM, van de Kerkhof PC. Simultaneous assessment of inflammation and epidermal proliferation in psoriatic plaques during long-term treatment with the vitamin D3 analogue MC903: modulations and interrelations. Br J Dermatol 1991; 124: 221–229.
21. Muller K, Svenson M, Bendtzen K. 1 alpha,25-dihydroxyvitamin D3 and a novel vitamin D analogue MC 903 are potent inhibitors of human interleukin 1 in vitro. Immunol Lett 1988; 17: 361–365.
22. Oxholm A, Oxholm P, Staberg B, Bendtzen K. Expression of interleukin-6-like molecules and tumour necrosis factor after topical treatment of psoriasis with a new vitamin D analogue (MC 903). Acta Derm Venereol (Stockh) 1989; 69: 385–390.
23. Grossman RM, Thivolet J, Claudy A, Souteyrand P, Guilhou JJ, Thomas P, et al. A novel therapeutic approach to psoriasis with combination calcipotriol ointment and very low-dose cyclosporine: results of a multicenter placebo-controlled study. J Am Acad Dermatol 1994; 31: 68–74.
24. Kragballe K. Combination of topical calcipotriol (MC 903) and UVB radiation for psoriasis vulgaris. Dermatologica 1990; 181: 211–214.
25. Kerscher M, Volkenandt M, Plewig G, Lehmann P. Combination phototherapy of psoriasis with calcipotriol and narrow-band UVB [letter]. Lancet 1993; 342: 923.
26. Gupta S, Fass D, Shimizu M, Vayuvegula B. Potentiation of immunosuppressive effects of cyclosporin A by 1 alpha,25-dihydroxyvitamin D3. Cell Immunol 1989; 121: 290–297.
27. Gepner P, Amor B, Fournier C. 1,25-dihydroxyvitamin D3 potentiates the in vitro inhibitory effects of cyclosporin A on T cells from rheumatoid arthritis patients. Arthritis Rheum 1989; 32: 31–36.
28. Fournier C, Gepner P, Sadouk M, Charreire J. In vivo beneficial effects of cyclosporin A and 1,25-dihydroxyvitamin D3 on the induction of experimental autoimmune thyroiditis. Clin Immunol Immunopathol 1990; 54: 53–63.
29. Bagot M, Charue D, Pamphile RP, Revuz J. Calcipotriol potentiates the immunosuppressive effects of cyclosporine A in allogeneic reactions [Abstract]. J Invest Dermatol 1991; 96: 1023.
30. Furue M, Gaspari AA, Katz SI. The effect of cyclosporin A on epidermal cells. II. Cyclosporin A inhibits proliferation of normal and transformed keratinocytes. J Invest Dermatol 1988; 90: 796–800.
31. Bagot M, Charue D, Lescs MC, Pamphile RP, Revuz J. Immunosuppressive effects of 1,25-dihydroxyvitamin D3 and its analogue calcipotriol on epidermal cells. Br J Dermatol 1994; 130: 424–431.