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.

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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 daily) 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 cointment 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 conditions necessitated stopping cyclosporine. After that the patient was stabilised on calcipotriol, and after 1 month the skin condition improved and the patient was discharged.

**Fig. 1.** Erythrodermic skin and extensive scaling all over the body, at the moment of admission to hospital.
Corticosteroids (clobetasol propionate), a weak steroid, are useful if no response is observed after a few days. Also in case of the erythroderma has to be established. 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. Systematic 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 therapeutic 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. 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