Failure of Combination Therapy with Acitretin and Cyclosporin A in 3 Patients with Erythrodermic Psoriasis

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Psoriatic erythroderma is a serious condition which requires a fast response to therapy, preferably during an in-patient treatment. Therapeutic options include various topical treatments and photo(chemo)-therapy, but in most cases systemic treatment is necessary [1]. Combination of cyclosporin A and methotrexate (MTX) resulted in serious adverse events after a short treatment period, and therefore is not recommended [2]. Combination of etretinate and MTX may lead to increased hepatotoxic risks, by increasing the MTX plasma levels [3,4]. Because of the different mechanisms of action and a different side effect profile combined treatment of cyclosporin A and retinoids might be successful.

Three patients with psoriatic erythroderma, who did not respond to monotherapy with acitretin in adequate dosages, were treated with combined therapy consisting of acitretin and cyclosporin A. They did not use co-medication known to interact with cyclosporin A metabolism or with nephrotoxic potentials. Serum creatinine level, liver enzymes, serum electrolyte levels, haematological parameters and

blood pressure were measured before initiating combination treatment and once weekly during therapy. Clinical scores were evaluated using the Psoriasis Severity Score modified according to Perkins et al. [5].

The individual dosages, clinical efficacy and side effects of each patient are summarised in table 1.

Case 1

A 58-year-old man was admitted because of a biopsy-proven psoriatic erythroderma. He had been treated with acitretin in a dosage of 0.5 mg/kg/day during 12 weeks. Because of lack of clinical improvement, combination therapy was started with cyclosporin A in a dosage of 3 mg/kg/day. After 1 week of combined treatment, acitretin was decreased to 0.3 mg/kg/day because of a retinoid-induced dermatitis. After 6 weeks the serum creatinine level was elevated > 40%, and the serum cholesterol level and the blood pressure were raised. No clinical improvement was achieved during 6 weeks treatment. Both therapies were stopped and MTX was started at a dosage of 7.5 mg/week. After 2 weeks the blood pressure and the cholesterol

level had normalised, the serum creatinine level normalised after 4 weeks. The erythroderma cleared in 5 months.

Case 2

An 83-year-old man with a history of psoriasis during 5 years was admitted with an erythrodermic psoriasis, which was treated subsequently with MTX during 2 weeks, prednisone during 2 weeks and acitretin 0.4 mg/kg/day during 3 weeks. These therapies were not successful. Cyclosporin A 3 mg/kg/day was combined with acitretin 0.4 mg/kg/day. After 4 weeks of combined treatment, only minimal clinical improvement was observed. The patient complained of dry lips and dry eyes. All serological parameters and the blood pressure were stable during therapy. Acitretin treatment was stopped and the cyclosporin A dose was raised to 5 mg/kg/day and combined with topical calcipotriol. This resulted in a good clinical improvement after 6 weeks.

Case 3

A 67-year-old man suffering from psoriasis for more than 40 years was admitted with an erythrodermic psoriasis. The psoriasis did not respond to local steroids or coal tar both in combination with acitretin 0.5 mg/kg/day during 8 months. Cyclosporin A (3 mg/kg/day) was started combined with acitretin 0.4 mg/kg/day. After 11 weeks of combination therapy the serum creatinine level was raised with 90% and the blood pressure had increased. The clinical response was unsatisfactory. Subsequently, both therapies were stopped and treatment with MTX 7.5 mg/week was initiated. However, 5 weeks later the patient had a cerebrovascular accident, complicated by fatal pulmonary embolism.

Considering the different modes of action and different side effect profiles, combination therapy of retinoids and cyclosporin A is a promising approach. However, because both retinoids and cyclosporin A are metabolised in the liver via a cytochrome P450-dependent system, a risk for interaction resulting in increased cyclosporin A levels is present. Recently, the effect of etretinate on the cyclosporin A metabolism was studied in an in vitro assay, using microsomes from normal human liver [6, 7]. With cyclosporin A levels of 5 µM and etretinate levels of 100 µM no metabolic interaction could be shown [6]. However, in a similar study with 100 µM etretinate and cyclosporin A levels up to 30 µM cyclosporin A metabolism was inhibited by 33-45% [7]. If this finding is of relevance in cyclosporin A treat-

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Table 1. Clinical efficacy and side effects after combined therapy with acitretin and cyclosporin A (CyA) in 3 patients with erythrodermic psoriasis

Patient

Age

CyA-acitretin period, weeks

CyA dose mg/kg/day

Acitretin dose mg/kg/day

Initial PSS

PSS at the end

Side effects

58

83 67

4 II

0.3

0.4 0.4

44

66

33

55

55 33

retinoid dermatitis blood pressure ↑ serum creatinine ↑ serum cholesterol ↑ dry lips conjunctivitis

dry lips dry nose

serum creatinine ↑ blood pressure ↑

PSS = Psoriasis severity score.

Table 2. Review of the literature of combined therapy with retinoids and cyclosporin A (CyA) in psoriasis

a = Insufficient clinical response with retinoid monotherapy, introduction of CyA; b = insufficient clinical response with CyA monotherapy, introduction of retinoid; c = tapering of CyA combined with introduction of retinoid; E = etretinate; A = acitretin; + = good; ± = moderate; – = poor.

ment in which the normal trough and peak serum levels are far lower than 30 µM needs further study.

The results of combination therapy in in vivo studies in patients with chronic plaque or erythrodermic psoriasis previously described in the literature are summarised in table 2 [7-11].

The efficacy of combination therapy in plaque psoriasis is poor [9, 10]. Frequently reported side effects are retinoid dermatitis and raised serum creatinine levels. However, the 3 patients with erythrodermic psoriasis previously reported in the literature showed a satisfactory improvement [8, 11]. This is in contrast with the patients described here, who achieved poor clinical results.

Two patients showed cyclosporin A-induced side effects already after a short treatment period.

Because of

the relatively high age of our patients, they might be more susceptible to the development of side effects.

Although no decisive conclusions can be drawn regarding the value of combined treatment with acitretin and cyclosporin A in erythrodermic psoriasis, it proved not to be a major therapeutic force in our patients.

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Demonstration of Herpes Virus 8 in a
Lymphangioma-Like Kaposi's Sarcoma
Occurring in a Immunosuppressed Patient
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In April 1993, a 42-year-old Libyan man presented in the dermatology department with several lesions of the right foot. The lesions consisted of slightly raised reddish-brown plaques, 1.5 cm in diameter. The patient was in good health otherwise, and the physical examination was unremarkable, in particular there was no ankle edema or lymphadenopathy. The results of laboratory investigations were within the normal limits and HIV serology was negative. A biopsy of one of the lesions was taken. Histologically, it was composed of a proliferation of irregular lymphatic-like endothelial lined channels permeating the dermis. These channels were generally bloodless, and separated by dense collagen bundles (fig. 1). Spindle cells were rare or absent. Thus the diagnosis of lymphangioma-like Kaposi's sarcoma (KS) was suggested, and herpes virus [8] (HHV-8), a virus that has been suggested to play a role in various forms of KS, was demon-

Fig. 1. Typical pathological findings of lymphangioma-like KS: Irregular lymphatic-like endothelial lined channels, separated by dense collagen bundles. Note the absence of any area of spindle cell proliferation. HE $\times$ 20.

strated using the hot-start PCR technique from paraffin-embedded specimen, as previously described [1]. The lesion was positive for HHV-8, as shown by amplification of a 233-bp product (fig. 2) characteristic of the virus.

Lymphangioma-like KS is a rare and poorly understood entity. To date only several cases have been reported in the literature [2-7]. It is characterized by dilated lymphatic-like channels mimicking other primary lymphangiomatous tumors such as progressive lymphangioendothelioma, lymphangiectasis or lymphangioma or vascular tumors such as hemangioma, angiosarcoma or spindle cell sarcoma. Since spindle cells typical of KS are rare, as in our patient, this variant of KS remains conceptually debated. For some authors, it represents not true KS but a lymphatic tumor, whereas others consider it a distinctive variant of KS. We demonstrate here, for the first time, the presence of HHV-8 in lymphangioma-like KS. We as well as others have described this virus in various forms of KS including classic KS, endemic KS and KS occurring in immunosuppressed or HIV-infected patients [1, 7-12]. Naturally, our findings must be carefully investi-