Oral Cyclosporin A Is Effective in Clearing Persistent Pustulosis Palmaris et Plantaris

M. M. H. M. MEINARDI, M. A. de RIE and J. D. BOS

Department of Dermatology, University of Amsterdam, Academic Medisch Centrum, Amsterdam, The Netherlands

In a prospective open study, seven patients with persistent pustulosis palmaris et plantaris were treated with oral Cyclosporin A (CsA). Clinical efficacy was assessed on a semi-quantitative 0–4 point scale for erythema, desquamation, induration and pustulation. CsA controlled skin lesions in doses ranging from 1.1 to 6.1 mg/kg body weight/day. Clinical side effects included renal impairment, nausea and tiredness. Rapid recurrence of the skin lesions was observed on withdrawal of insufficient treatment with the drug.

(Accepted May 22, 1989.)

Acta Derm Venereol (Stockh) 1990; 70: 77–79.

M. M. H. M. Meinardi, Department of Dermatology, University of Amsterdam, Academic Medisch Centrum, Meibergdreef 9, 1105 AZ Amsterdam, The Netherlands.

Cyclosporin A, introduced as an immunosuppressant acting specifically on activated CD4-positive T helper lymphocytes, effectively suppresses severe forms of psoriasis vulgaris (1, 2, 3). Its specific inhibition of CD4-positive T cells has substantiated the T-cell hypothesis of psoriasis (4–7). In high dosages (12 mg/kg/day) CsA also suppressed pustulation in a case of von Zumbusch generalized pustular psoriasis (8). Lower doses (7 mg/kg/day) appeared not effective in another case of von Zumbusch (9). Such high dosages are inevitably at risk for side effects such as hypotension and renal dysfunction, especially when treatment has to be continued for longer periods of time. As regards dose-dependent side effects, we were interested to treat patients with persistent pustulosis palmaris et plantaris (PPP) with low dosages of CsA. PPP is characterized by symmetrical erythematous and scaly plaques with sterile pustules restricted to the palms and soles. Although a relationship with psoriasis is not uniformly accepted, PPP presents itself relatively common with other forms of psoriasis. Treatment of choice includes potent topical corticosteroids under occlusion and oral etretinate (10, 11). We selected 7 patients with PPP resistant to both treatment modalities for treatment with oral CsA.

METHODS

Selection of patients
Seven patients, 5 males and 2 females (aged 43–69) with severe PPP were selected for oral CsA treatment upon resistance to conventional therapy (including topical corticosteroids and oral etretinate). We excluded patients with a malignancy or a history of malignancy, impaired renal function (serum creatinine >100 μmol/l), liver enzymes more than twice the upper limit of the normal range and hypertension (diastolic blood pressure >95 mmHg, systolic blood pressure >160 mmHg). An exception was made for patient no. 7, who suffered from terminal renal insufficiency. All patients had evidence of (mild) psoriasis elsewhere on the body. Patients 1 and 3 had associated psoriasis arthropathica. Oral treatment was discontinued for 4 weeks and topical treatment for 2 weeks prior to the study. Informed consent was obtained from all patients.

Clinical evaluation was restricted to the palms and soles. A 0–4 point scale (0 = absent, 1 = trace, 2 = mild, 3 = mild/severe, 4 = severe) for erythema, desquamation, induration and pustulation was used (i.e., a maximum score of 16). Laboratory investigations included serum creatinine, potassium, magnesium, liver functions and routine hematological screening and were performed at week 0, after the third week of treatment and every 6 weeks thereafter. Blood pressure was recorded at each visit.

Phase 1
Oral CsA treatment (Sandimmune®, 100 mg/ml) was started on 2.5 mg/kg body weight/day. Evaluation was carried out at week 0, 3, 6, 9, 12. If at week 6 the antipsoriatic efficacy of CsA appeared sufficient (score 75% of baseline), patients directly entered phase 2 for subsequent dose adjustment according to clinical efficacy. In cases of insufficient response to 2.5 mg/kg/day, doses were increased to 5 mg/kg/day for another 6 weeks. These patients entered phase 2 at week 12 for subsequent dose adjustment.

Phase 2
In phase 2, doses were adjusted to maintain a complete or near complete stable remission of palms and soles as described earlier (12). Topical corticosteroids (betamethasone dipropionate 0.05%) were allowed on psoriatic skin lesions elsewhere on the body.

RESULTS

Data on phase 1 are presented in Table 1. At week 9, in patients 2, 5, 6 and 7 the initial CsA dose of 2.5
mg/kg/day appeared insufficient and was increased to 5 mg/kg/day. The other patients (nos. 1, 3 and 4) entered phase 2. The mean score at the beginning of phase 1 (12.7) was reduced by 48% to 6.6 at the beginning of phase 2.

Minimally effective doses in phase 2 are summarized in Table II. After temporary exacerbations (e.g. due to emotional stress, concomitant illness) PPP again could be controlled by its original minimally effective dose. PPP in patient 7 could at first be controlled by 5.4 mg/kg/day. After 19 months of treatment, however, CsA had to be slowly increased to 6.1 mg/kg/day, on which his PPP has remained stable until now.

Thus, a mean total reduction of PPP of 91% was obtained in all patients. Topical corticosteroids at least partially suppressed any psoriatic skin lesions elsewhere on the body.

Side effects
In 3 patients (nos. 1, 3 and 5) tiredness related to CsA intake was severe enough to impede on normal daily activities. Another 3 patients (nos. 2, 4 and 6) experienced nausea from 1 hour after CsA intake.

In 1 patient (no. 4) a rise in serum creatinine from 88 µmol/l to 127 µmol/l was noted during his 6th month of CsA treatment. Subsequent reduction of the dose from 3.3 to 2.7 mg/kg/day lowered serum creatinine to a stable 100 µmol/l. To date, 7 months later, no further rise in serum creatinine has been observed.

No rises in blood pressure were observed. Minor side effects included mild hypertrichosis in 2 patients.

DISCUSSION
In 7 patients with severe PPP resistant to standard treatment (including etretinate) oral CsA, in dosages ranging from 1.1 to 6.1 mg/kg/day, appeared highly effective in suppressing the skin lesions in all patients.

Histologically, PPP is characterized by large intraepidermal pustules filled with neutrophils. As in psoriasis, where a mononuclear infiltrate precedes the appearance of neutrophils, the pustules are preceded by epidermal spongotic vesicles containing mostly mononuclear cells (13). Beneath the slightly acanthotic epidermis, an inflammatory infiltrate can be seen in much the same way as in psoriatic plaques.

The impressive efficacy of orally administered CsA in psoriasis has refreshed the attention to immunologically mediated processes in psoriatic skin lesions. Although the hidden stratum corneum hypothesis (14) is difficult to explain by a direct effect of CsA, as are the remarkable beneficial effects on pusulation in PPP, these effects might well be mediated indirectly. Inhibition of the CD4-positive T cell by CsA may lead to decreased stimulation of keratinocytes, which may lead to a decreased production of LTb (15). Reduction of LTb, a potent attractant of neutrophils, may explain indirectly the suppression of pusulation as was observed in our patients. In fact, while in vitro CsA did not affect chemotaxis, nor oxidative metabolism, nor microbial activity of human polymorphonuclear leukocytes (16), in vivo migration of PMNs into a polyethylene chamber decreased significantly during CsA treatment of psoriasis patients (17).

In conclusion, in our patients, oral CsA did control persistent PPP. Withdrawal of the drug, however, rapidly led to the same extent of the disease as before CsA treatment. Because of the known side effects of long-term treatment with oral CsA, blood pressure and renal function should be carefully monitored, and dosage over 5 mg/kg/day should be avoided. Additionally, in patients who have been treated with PUVA or UVB, CsA is mentioned as a factor that can

Table II. Long-term treatment of PPP with CsA

<table>
<thead>
<tr>
<th>Pat.</th>
<th>Duration of CsA treatment (months)</th>
<th>Minimally effective dose (mg/kg/day)</th>
<th>Max. dose (mg/kg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>25</td>
<td>1.1</td>
<td>2.5</td>
</tr>
<tr>
<td>2</td>
<td>5</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>3</td>
<td>8</td>
<td>2.8</td>
<td>2.8</td>
</tr>
<tr>
<td>4</td>
<td>13</td>
<td>2.7</td>
<td>3.3</td>
</tr>
<tr>
<td>5</td>
<td>10</td>
<td>4.7</td>
<td>4.7</td>
</tr>
<tr>
<td>6</td>
<td>6</td>
<td>5.3</td>
<td>5.3</td>
</tr>
<tr>
<td>7</td>
<td>31</td>
<td>6.1</td>
<td>6.1</td>
</tr>
</tbody>
</table>
increase the risk of developing squamous cell tumours (18, 19). Thus, in spite of its efficacy in recalcitrant PPP, oral CSA should be reserved for disabling forms of PPP in patients who are unresponsive to or intolerant of standard therapies.

REFERENCES


Multiple Familial Eccrine Spiradenoma with Cylindroma

S. WRIGHT1 and J. RYAN2

1 Department of Dermatology, The Royal Free Hospital, School of Medicine and
2 Department of Morbid Anatomy, The London Hospital, London, England

This report documents an association between multiple eccrine spiradenoma and multiple cylindromas in three generations of one family and provides further evidence to support previous contentions that these tumours are derived from a pluripotential basal cell. We propose that eccrine spiradenoma may be inherited as an autosomal dominant. Key words: Eccrine sweat gland; Basal cell; Autosomal dominant.

(Accepted May 28, 1989.)
Acta Derm Venereol (Stockh) 1990; 70: 79–82.

S. Wright, Department of Dermatology, The Royal Free Hospital, School of Medicine, Rowland Hill Street, London NW 3, England.

Eccrine spiradenoma is almost invariably present as a solitary tumour, most commonly located on the chest and face (1). Multiple eccrine spiradenoma have occurred in individual patients (2) and in association with multiple cylindromas and trichoepitheliomas in three members of one family (3); an association

Acta Derm Venereol (Stockh) 70