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Clinical Trial with Cyclosporin A

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Six male patients with extensive psoriasis, resistant to conventional treatment, were treated orally with low-dose Cyclosporin A (CsA) (5 mg/kg/day). One patient had generalized pustular psoriasis, three psoriatic erythroderma, and two disseminated chronic plaque psoriasis. All patients, with the exception of one, were treated for at least twelve weeks. Nearly complete remission was obtained in four cases. In one patient the response was incomplete, while treatment in one case was suspended after two weeks because of the onset of cutaneous pyogenic infections and oral candidiasis. In each case a relapse was observed with the suspension of treatment. ***Key words: Psoriasis; Cyclosporin.***

CsA is an immunosuppressive agent which is commonly used for the prevention of transplanted organ rejection. Since 1979 (1) several studies have indicated that CsA can be effective in the treatment of psoriatic lesions (2, 3, 4). Such effectiveness has recently been confirmed in double-blind studies over a broad spectrum of case-reports, either with high (14 mg/kg/day) (5) or low dosage (mean dose 5.6 mg/kg/day) (6). The effectiveness of CsA has also been demonstrated in psoriatic erythroderma (7) and generalized pustular psoriasis (7, 8, 9).

The exact mechanism of action of CsA in psoriasis is still unknown. It has been shown that CsA has a selective inhibitory effect on the functions of helper and cytotoxic lymphocyte subpopulations (10). Moreover abnormalities of T-lymphocyte functions have been observed in psoriasis (11–15). It has therefore been suggested that the mechanism of action of CsA could be mainly immunological (16).

We undertook an open clinical trial on the use of CsA, at low oral dosage, in a few cases of psoriasis. We treated six male patients (Table I), selected according to the following criteria: 1) age ranging between 18 and 65 years; 2) clinical and histological diagnosis of psoriasis; 3) extensive psoriasis, present over a time of 2–26 years and resistant to traditional therapies (topical and systemic corticosteroids, methotrexate, PUVA and Re-PUVA, retinoids, dithranol).

Patients with infections, current or previous malignancies, impaired renal function (determined by serum urea nitrogen, creatinine, urine analysis, urea and creatinine clearances over 24 hours), impaired liver function (with significant alteration of serum transaminase, γ-GT, bilirubin), with high blood pressure ($\geqslant 150/100$) or under treatment with nephrotoxic drugs or drugs interfering with pharmacokinetics of CsA were excluded from the study. All patients gave informed consent prior to the beginning of the study.

CASE REPORTS

The initial dose of CsA (Sandimmune, Sandoz, 100 mg/ml) was 5 mg/kg/day for all patients, divided into two daily oral administrations. The CsA dose was then modified according to clinical course, CsA blood levels and side effects. All patients (except case 1) had suspended any other topical and systemic treatment, with the exception of mild emollients, for at least three weeks before CsA therapy.

The following parameters were checked before treatment and subsequently at weekly intervals: full blood count, serum glucose, urea nitrogen, creatinine, uric acid, bilirubin, transaminases, γ-GT, alkaline phosphatase, electrolytes, electrophoresis, urea and creatinine clearances with a 24-hour urine collection; blood pressure was also checked at the same times. Plasmatic levels of CsA were measured weekly with a Sandoz RIA-Kit.

A careful clinical evaluation was carried out before the beginning of treatment and subsequently at weekly intervals. A global score was given, according to severity on a scale from 0 (absence of lesions) to 100 (maximum severity and extension of lesions), taking to account either the spread of the lesions or characteristics of erythema, infiltration and scaling of individual plaques (Fig. 1).

Case 1

A 49-year-old man had suffered relapsing episodes of generalized pustular psoriasis for 17 years. In the past he had been treated with topical systemic steroids as well as methotrexate (MTX). At the beginning of CsA therapy he was already being treated with systemic corticosteroids. One week after the addition of CsA he showed a marked clinical improvement with reduction of erythema and disappearance of pustulation; his temperature normalized. Such improvement continued during the second week of therapy. At the beginning of the third week the appearance of severe oral candidiasis and ulcerative cutaneous pyogenic lesions caused suspension of therapy, with subsequent rapid pustular and erythrodermic relapse.

Case 2

The patient was a 64-year-old man. He had been affected by plaque-type psoriasis for 26 years. A progressive transformation into psoriatic erythroderma occurred in the last year.

Table I. *Clinical data on patients*

Patient	Age (yrs)	Duration of psoriasis (yrs)	Type	Previous treatments
1	49	17	Generalized pustular	MTX, corticosteroids
2	64	26 (erythroderma in the last year)	Erythrodermic	Etretinate, Re-PUVA, corticosteroids
3	60	25 (erythroderma in the last year)	Erythrodermic	Corticosteroids, Re-PUVA, etretinate
4	48	20	Erythrodermic	MTX, RE-PUVA, corticosteroids
5	31	2	Vulgaris (widespread)	PUVA, topical corticosteroids
6	38	11	Vulgaris (widespread)	Dithranol, Re-PUVA

Systemic corticosteroid therapy and etretinate either alone (for 9 months) or in association with PUVA (for 3 months) had been carried out during the last two years. During the first two weeks of therapy the patient showed a slight improvement, while at the end of the third week a marked reduction of erythema and scaling became evident, although infiltrative and scaling areas of the lumbar-sacral region and of the folds persisted. By the end of the eighth week, the clinical picture improved dramatically with the disappearance of the erythroderma. Only a few guttate elements on the back of the feet and a very slight furfuraceous scaling of the flexor surfaces of the limbs and the lumbar-sacral area was still evident. A complete remission was obtained by the 11th week and the therapy was suspended six weeks later. Three weeks after suspension of therapy a mild erythrodermic relapse occurred which became severe two weeks later.

Case 3

A 60-year-old patient had been affected by psoriasis vulgaris for 25 years. A progressive worsening and evolution towards erythroderma occurred over the last year. Topical and systemic corticosteroid therapy, Re-PUVA and etretinate had been used previously. After three weeks of therapy a marked improvement with a reduction in erythema, scaling and palmoplantar hyperkeratosis could be seen. In the subsequent weeks the clinical picture slowly improved. At the end of the 11th week the CsA dose was reduced because of an ingravescent leukopenia, while the clinical picture continued to improve. By the 15th week, there was an almost total disappearance of psoriatic manifestations. Therapy was suspended at the 19th week: only small psoriatic patches on the elbows remained. Ten weeks after suspension of therapy there was a re-appearance of psoriatic plaques on the scalp and limbs, without a tendency to erythroderma. During treatment there was a tendency to leukocytopenia with neutropenia (minimum value 3200 WBC/μl), probably drug-induced, as normalization occurred four weeks after suspension of the therapy. A mild and irregular alteration of total serum bilirubin (maximum value 2.5 mg/dl) was detected.

Case 4

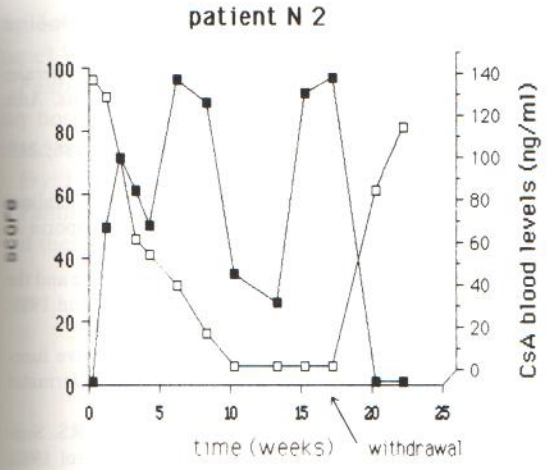
A 48-year-old patient had been affected by psoriasis for 2[illegible] years, with relapsing episodes of erythroderma. He had be[illegible] previously treated with MTX, Re-PUVA, topical and syste[illegible]ic corticosteroids. At the beginning of therapy the clini[illegible] picture was generalized exfoliative erythroderma, with s[illegible]verely involved general conditions (sideropenic anaem[illegible] dysprotidaemia, weight loss, dystrophic ulcers). After a sli[illegible] improvement of the clinical picture, CsA was administe[illegible] because of the persisting erythrodermic state. A slight modi[illegible]cation of erythroderma during the first six weeks of ther[illegible] was obtained. By increasing the CsA dose to 6 mg/kg/da[illegible] further, more noticeable improvement was observed, last[illegible] until the suspension of therapy (12th week), even though th[illegible] erythema never disappeared completely. A complete erythr[illegible]dermic relapse was observed two months after suspensio[illegible]

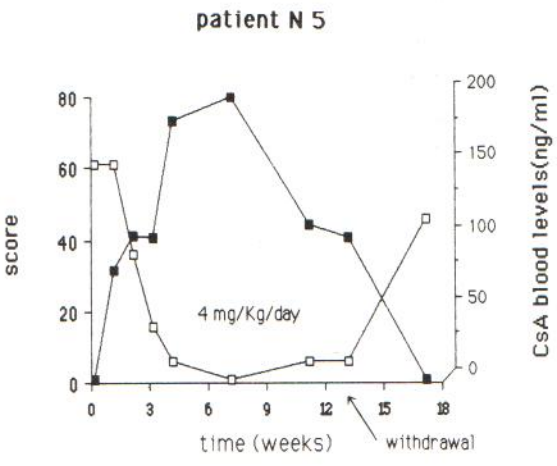
Case 5

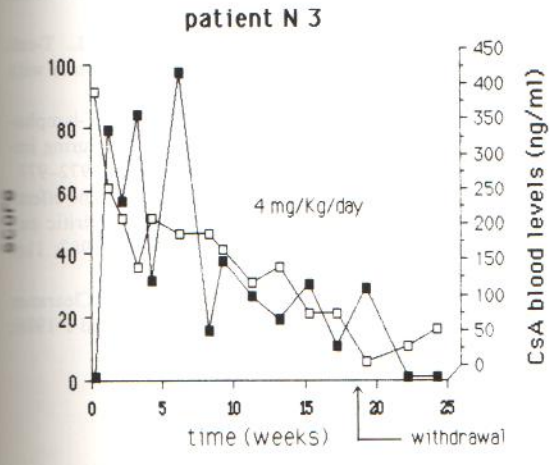
A 31-year-old patient had been affected by chronic plaq[illegible] psoriasis for 2 years, previously treated with PUVA a[illegible] topical steroid therapy. On the first clinical examination h[illegible] showed typical psoriatic plaques spread over the trunk, limb[illegible] and scalp. A dramatic improvement, characterized by redu[illegible]tion of thickness of the plaques and disappearance of scali[illegible] was evident after 15 days of therapy. The lesions almo[illegible] completely cleared up after 4 weeks and the regression last[illegible] during the whole treatment (13 weeks). A relapse in plaq[illegible]form psoriasis occurred 4 weeks after suspension.

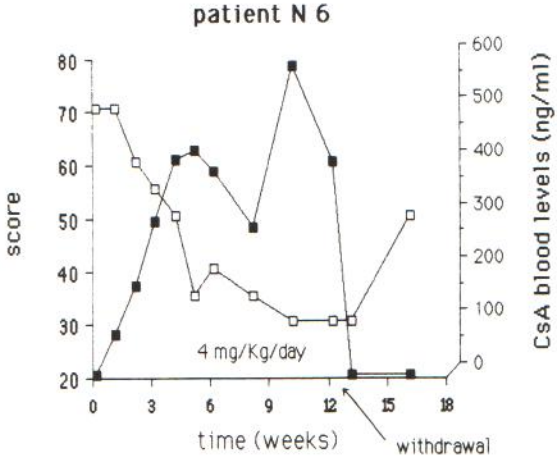
Case 6

A 38-year-old patient, affected by chronic plaque psoriasis f[illegible] 11 years, had been previously treated with local (dithran[illegible] and general (Re-PUVA) therapy unsuccessfully. At the begi[illegible]ning of treatment, he showed large psoriatic plaques on th[illegible] trunk, limbs and scalp, as well as a marked onychopathy o[illegible] the hands and feets. CsA therapy caused a constant an[illegible] progressive improvement of the manifestations, more stri[illegible]ing on the hyperkeratosis and onychopathy, while the eryt[illegible]









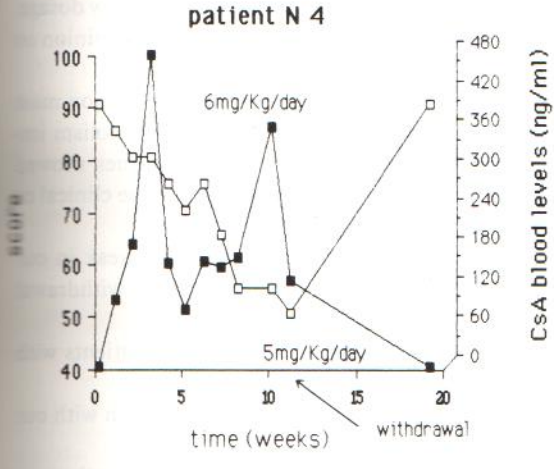


Fig. 1. Clinical score (0–100) (white square) and CsA levels (black square) during treatment in patients 2, 3, 4, 5, 6.

ma persisted during the whole treatment (12 weeks). A complete relapse of psoriatic plaques was observed 4 weeks after suspension of therapy.

DISCUSSION

Our study deals with the use of CsA in six patients affected by different forms of psoriasis. Therefore response to therapy has been influenced by this inhomogeneity. However, the use of the drug in low dosage has made it possible to obtain good remissions in all subjects tested, independent of the type of psoriasis. In particular, in patient 5 an almost complete remission had already been obtained by the 4th week. In patient 4 the partial clinical result obtained by the end of therapy is to be considered satisfactory, taking in account the general conditions at the beginning and

the almost absolute refractoriness to all the other therapies. In patient 1, who had been treated with steroid therapy unsuccessfully, addition of CsA caused a marked improvement in two weeks. The suspension of treatment in this case was motivated by the appearance of infective muco-cutaneous complications, probably induced by the combined immunosuppressive effect of the two drugs.

Four weeks was the mean time necessary to obtain a significant clinical response with this dosage. Clinical improvement continued during the subsequent weeks in all patients, even though to a different extent. With the suspension of treatment a relapse in all patients within a four-week period was observed. In some cases relapse was less severe compared to initial clinical manifestations, and manageable by conventional therapies. Case 3 presented a plaque-form relapse instead of the erythroderma present before CsA therapy.

A correlation between clinical response and plasmatic levels of CsA was not observed, as already reported (5, 17). The effectiveness of CsA therapy seems to be relatively influenced by the dose.

A low incidence of side-effects with the doses used in this trial was observed. Namely, no renal function alterations were detected. A slight elevation in serum total bilirubin values (up to 2.5 mg/kg/day) was observed in patient 3. In patients 3 and 5 a progressive mild leukocytopenia with neutropenia occurred but rapidly cleared up after withdrawal of therapy. A slight rise in blood pressure values in patient 6 did not require suspension of treatment.

In conclusion, our limited experience confirms the effectiveness and excellent tolerability of CsA in low systemic dosage for either chronic plaque psoriasis or erythrodermic forms resistant to conventional therapies.

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DISCUSSION

Carlesimo: In a patient with recalcitrant arthropathic psoriasis and stomach ulcer, C. was given for 6 weeks + Cimetidine 800 mg/day + etretinate at low dosage: the response was a good one. What is your opinion on this kind of combination?

Finzi: I think a C. + etretinate combination must be used with great precaution (lipid metabolism impairment). Your C. blood levels sometimes showed high peaks (over 600–700/ml). Did you see clinical or laboratory side-effects in these cases?

Fantini: Side-effects were scanty and weak in our patients and regressed in a few weeks after withdrawal of C.

Scarpa C.: Did you monitorize your patients with PASI score?

Fantini: We preferred to monitorize them with our own particular clinical score from 0 to 100.

Rebora: C. plasma levels seem to vary greatly even with a fixed dosage. Did your patients take the drug at

regular intervals? Was the intake of food always the same? What about alcohol intake?

Fantini: Compliance seemed fairly good even in day hospital regime. Accumulation by fat tissue and blood release may vary of course.

Fry: How did you measure C. plasma levels?

Fantini: We used RIA monoclonal assay with normal therapeutic range between 50 and 200 ng/ml.

Fry: What did you do with the patient with whom you had to stop C. because of his Candida infection?

Fantini: Pustular psoriasis relapsed in a couple of weeks as the patient refused any further treatment, and went home.