

Treatment of psoriasis with cyclosporin

Experience at Johannesburg Hospital

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Ten patients with moderate to severe plaque psoriasis were treated with cyclosporin A (CyA) for 2 - 19 months (mean 12 months). Initial dosages were 2,5 mg/kg/d in 6 patients and 5,0 mg/kg/d in 4. At 3 months the dosage was increased from 2,5 to 5,0 mg/kg/d in 4 patients in accordance with the study protocol. Subsequent dosages were adjusted according to clinical response and side-effects. Treatment was stopped owing to raised serum creatinine levels in 4 patients on the higher dose; levels returned to normal soon after this. The only other important side-effect was hypertension, which developed in 4 patients, in 2 of whom serum creatinine levels were raised. In all patients the psoriasis improved markedly within 2 months but relapsed, either while the dose of CyA was being tapered off or after treatment with the drug was stopped. Relapse was most rapid in patients with severe initial involvement. On a dosage of 2,5 mg/kg/d there was at least 50% clearance of the psoriasis and no evidence of renal side-effects.

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Cyclosporin A (CyA) is a powerful immunosuppressive agent which is used to prevent graft rejection in kidney, heart, liver and bone marrow transplantation.¹ It has also shown promising results in the treatment of several dermatological disorders.² CyA acts by inhibiting lymphokine production by activated T lymphocytes and is currently used in the treatment of psoriasis, a disease known to be mediated by T lymphocytes.³ Previous studies have shown CyA to be effective in the treatment of recalcitrant plaque psoriasis in dosages varying from 1 to 14 mg/kg/d, given for periods ranging from 1 to 25 months.⁴⁻⁶

The purpose of this study was to compare the efficacy and safety of CyA in a dosage of 2,5 mg/kg/d with a dosage of 5,0 mg/kg/d in treating psoriasis and to investigate the safety of long-term therapy.

Patients and methods

Ten patients were treated with CyA, 9 of whom (patients 1 - 9) were enrolled in a multicentre trial. The group

comprised 9 males and 1 female, ranging in age from 29 to 65 years (mean 44 years). All had moderate to severe psoriasis, which had been present for 10 - 31 years (mean 19 years). Response to conventional therapy had been inadequate. The duration of psoriasis and previous treatment are shown in Table I. The severity of the psoriasis was assessed before treatment and at each visit by means of the psoriasis area and severity index (PASI), in which four regions of the body are scored for erythema, induration and scaling.⁷ The results are shown in Table I. Exclusion criteria included hypertension, impaired renal or hepatic function, malignant disease and concomitant therapy with nephrotoxic drugs (e.g. aminoglycosides) or drugs known to interact with the pharmacokinetics of CyA (e.g. erythromycin and ketoconazole). All topical and systemic treatment for psoriasis was discontinued for 2 weeks before starting CyA. The only female patient had had a hysterectomy, obviating the need for contraception.

The patients were treated with CyA at a randomly selected starting dosage of either 2,5 mg/kg/d (6 patients, Nos 1, 3, 4, 5, 6 and 10) or 5,0 mg/kg/d (4 patients, Nos 2, 7, 8 and 9). The only topical treatment allowed was petroleum jelly. Patients were seen weekly for the first month and thereafter at intervals of 2 - 4 weeks depending on the state of the disease and the presence of side-effects.

Blood pressure was monitored and regular investigations included a full blood count, liver function tests, and measurement of urea and electrolyte, creatinine and urate levels. Urine was tested for the presence of protein and glucose. Creatinine clearance was measured at 6-monthly intervals.

At the end of 12 weeks the response to treatment was evaluated. According to the study protocol an adequate response was defined as a 75% decrease in the PASI or a score of less than 8,0. In those patients who had failed to respond to 2,5 mg/kg/d the dosage of CyA was increased to 5,0 mg/kg/d.

Gradual tapering off of the dose of CyA was started at the end of month 7 in patients on 5,0 mg/kg/d and the end of month 12 in patients on 2,5 mg/kg/d. Treatment with the drug was stopped at the end of the 16th month in uncomplicated cases and after 19 months when the dosage had been increased from 2,5 mg to 5,0 mg/kg/d because of inadequate response. CyA was withdrawn earlier in those patients who developed significant side-effects necessitating withdrawal of the drug (Table I). Patients were studied for 3 months after cessation of treatment to confirm the reversal of any side-effects and to observe any relapse of the psoriasis.

Results

The dosage of CyA and the duration of treatment in each patient is shown in Table I. Four patients (Nos 1, 4, 8 and 9) completed a full treatment period of 16 months. Two patients (Nos 5 and 10) in whom the dose of CyA was increased from 2,5 to 5,0 mg/kg/d because of inadequate response improved satisfactorily on the higher dose and treatment was continued for 19 months. CyA was discontinued in the remaining 4 patients owing to side-effects after periods varying from 8 to 47 weeks.

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Table I. Results of treatment of psoriasis with CyA

Patient No.	Age/sex	Duration of psoriasis (yrs)	Previous systemic treatment	CyA		PASI			Creatinine (mmol/l)*		Side-effects and adverse events
				Dosage (mg/kg/d)	Duration (mo.)	Base-line	Lowest	Improvement (%)	Base-line	Highest	
1	65/M	25	Etretinate	2,5	16	28,2	3,4	88	88	137	Hypertrichosis
2	34/M	13	MTX, PUVA, steroids, dapsone, etretinate	5,0	8	36,9	7,2	81	70	176†	Gum hypertrophy, raised bilirubin
3	38/M	16	PUVA, steroids	2,5 + 5,0	5	43,2	8,4	81	106	203†	Hypertension
4	51/M	31	Steroids	2,5	16	41,4	3,9	91	101	124	Hypertension, raised bilirubin and liver enzymes
5	41/M	13	Etretinate, MTX, steroids	2,5 + 5,0	19	21,7	6,0	72	85	114	Hypertrichosis, raised bilirubin
6	54/M	17	MTX, PUVA, etretinate, azathioprine, dapsone, clofazamine	2,5 + 5,0	11	54,2	28,4	48	92	147†	Squamous cell carcinoma, raised bilirubin
7	29/M	10	Etretinate	5,0	2	24,0	10,9	55	78	170†	Hypertension
8	32/F	20	Etretinate, MTX	5,0	16	19,4	1,2	94	88	98	Raised bilirubin
9	45/M	21	Etretinate, PUVA, steroids	5,0	16	24,0	5,0	79	106	140	Raised bilirubin
10	51/M	20	Etretinate, PUVA, MTX, steroids	2,5 + 5,0	19	32,1	2,6	92	114	155	Hypertrichosis, gum hypertrophy, hypertension, furunculosis

* Normal level < 130 mmol/l.

† Treatment stopped owing to persistently raised creatinine levels.

M = male; F = female; MTX = methotrexate.

The baseline PASI scores before treatment and the lowest scores during treatment are shown in Table I. It can be seen that the reduction in the PASI varied from 48% to 94%. After 6 months the mean PASI score for the 7 patients remaining in the trial was 77% lower than at the start. Patients taking CyA at a dosage of 5,0 mg/kg/d responded more rapidly than those on 2,5 mg/kg/d. The former group showed a 74% improvement in their psoriasis by 12 weeks, compared with a 54% improvement in those taking 2,5 mg/kg/d (Fig. 1). Although there had been a marked improvement in their psoriasis, 4 of the 6 patients on an initial dosage of 2,5 mg/kg/d had failed to improve sufficiently to meet the protocol requirements. At the end of 12 weeks the dosage was therefore increased to 5,0 mg/kg/d. Two of these 4 patients (Nos 3 and 6) were subsequently removed from the study owing to the development of side-effects while on the higher dose. Of the 4 patients on an initial dose of 5,0 mg/kg/d, 2 (Nos 8 and 9) completed 16 months of treatment with excellent clearing of their psoriasis. CyA was discontinued in patients 2 and 7 owing to rising serum creatinine levels which persisted in spite of reductions in the dose of CyA.

Side effects (see Table I)

Renal function

Eight patients developed raised serum creatinine levels while taking CyA; in 6 of these the dosage was reduced. In 4

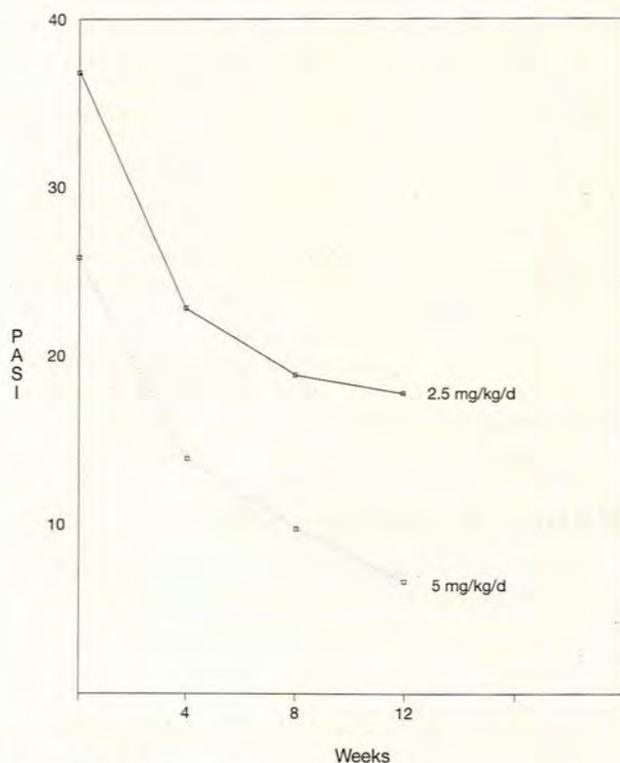


Fig. 1. Mean PASI scores in patients on CyA.

of these patients creatinine levels failed to return to normal in spite of two 25% reductions and the CyA was discontinued. Two of these patients (Nos 3 and 7) were taking indomethacin for arthritis. Creatinine levels returned to normal during a 3-month follow-up period in patients 3, 6 and 7. In patient 2, who was last seen 1 week after CyA was discontinued, the creatinine level was already normal at that time. No patient on 2,5 mg/kg/d required a reduction in dosage because of raised creatinine levels.

Hypertension

A persistent rise in blood pressure occurred in 4 patients — 3 on 5,0 mg/kg/d (Nos 3, 7 and 10) and 1 (No. 4) on 2,5 mg/kg/d. Antihypertensive treatment with the calcium channel blocker nifedipine was instituted. At the time of developing hypertension 2 of these patients (Nos 3 and 7) had elevated creatinine levels which eventually necessitated cessation of CyA treatment. In the remaining 2 patients (Nos 4 and 10) the hypertension was controlled by nifedipine and the CyA was continued for the full study period. The blood pressure returned to normal in all 4 patients after CyA was discontinued and no further antihypertensive therapy was required.

Liver function

A transient increase in total bilirubin occurred in 6 patients. In 5 of these cases the increase was in the unconjugated fraction and returned to normal in spite of continued treatment. In 1 patient (No. 4) an increase in conjugated bilirubin occurred after a period of excessive alcohol intake and was associated with a concomitant increase in liver enzymes (transaminases and gamma-glutamyl transferase).

Squamous cell carcinoma

Five months after starting treatment with CyA, while experiencing satisfactory improvement of his psoriasis, patient 6 developed a small superficial squamous cell carcinoma on his right forearm which was easily removed by cauterisation and curettage. The study protocol required that CyA be discontinued when the lesion developed. Subsequent treatment of the psoriasis with etretinate was ineffective. Re-treatment with CyA resulted in a moderate improvement, but the drug was discontinued after a further 7 months owing to raised serum creatinine levels. No new skin lesion developed during a follow-up period of 18 months.

Hypertrichosis

An increase in body hair was noted by 3 patients, all of whom had marked male pattern alopecia, which remained unchanged. Hair growth reverted to normal soon after CyA was discontinued.

Gingival hyperplasia

This occurred in 2 patients (Nos 2 and 10), 4 and 10 weeks respectively after starting treatment. In both the gums soon returned to normal after careful attention to oral hygiene.

Discussion

In 1979, while treating 4 patients with severe psoriatic arthritis with CyA, Mueller and Herrmann⁹ noted that all showed rapid clearing of psoriatic skin lesions. Since then CyA has been shown to be effective in treating psoriasis in open^{9,10} and double-blind trials.^{11,12} However, in most patients the psoriatic lesions relapse soon after the drug is withdrawn,^{5,9,12} and long-term maintenance treatment may be required for adequate control.

The most important side-effects involve the kidneys. After short-term therapy the hypertension and nephrotoxicity as measured by serum creatinine levels and the glomerular filtration rate (GFR) are reversible after treatment has been stopped.¹³ Renal biopsies were done on 8 patients after continuous treatment with an average dose of 3,3 mg/kg/d for a mean duration of 5 years. Six patients had features consistent with CyA nephrotoxicity. In 2 the changes were considered severe enough to stop treatment.¹³ Patients should be carefully monitored and safety guidelines must be followed^{13,15} in order to minimise the risk of renal changes. Measurement of the GFR should ideally be done before treatment with CyA is started.^{13,15} Nephrotoxic compounds and potassium-sparing diuretics must be avoided whenever possible, because they increase the risk of renal side-effects.¹⁶ When the trial was started concomitant use of non-steroidal anti-inflammatory drugs was not proscribed. It has recently been recommended that this combination should be avoided.^{13,15} Three of our patients were taking indomethacin for arthritis and in 2 of them CyA had to be withdrawn because of raised creatinine levels.

Hypertension occurs in about one-third of patients treated with CyA for psoriasis.¹³ Although the exact mechanism is not known, an important factor is intrarenal vasoconstriction which can be antagonised by calcium channel blockers. If a calcium channel blocker is required nifedipine or isradipine should be used, because they do not interfere with CyA blood levels.¹⁵

Transient elevation in liver enzyme and bilirubin levels may occur during treatment with CyA.¹⁶ According to Fradin *et al.*¹⁷ hyperbilirubinaemia occurs in up to 50% of patients taking CyA, but they do not state whether it occurs in the conjugated or unconjugated fraction. In 5 of our patients transient elevation of unconjugated bilirubin levels occurred without any abnormalities in liver enzymes. This may be explained by interference by CyA with the hepatic uptake or conjugation of bilirubin.¹⁸

CyA is metabolised in the liver by the cytochrome P450 enzyme system. Drugs such as ketoconazole and erythromycin, which inhibit these enzymes, tend to increase CyA levels very rapidly, increasing the risk of side-effects. The combination of methotrexate and CyA results in decreased elimination and increased blood levels of each drug with a risk of serious side-effects.¹⁹

Patients treated with immunosuppressive drugs may be at an increased risk of developing malignant disease. Krupp and Monka²⁰ reported that of 842 patients treated with CyA for psoriasis 6 developed malignant or pre-malignant skin lesions, 6 solid organ tumours and 5 lymphoproliferative disorders. These neoplasms were considered unlikely to be related to the use of CyA. Our patient who developed skin cancer while on CyA had a severely sun-damaged skin and

previous treatment for his psoriasis had included the potential carcinogens PUVA, methotrexate and azathioprine. Long-term follow-up of patients who have received CyA in addition to other immunosuppressive therapy will show whether CyA is a significant additional risk factor for the development of malignant disease.

This study supports previous findings that CyA is effective in the treatment of psoriasis. A dosage of 5,0 mg/kg/d was more effective than 2,5 mg/kg/d but carried a greater risk of side-effects. CyA can safely be administered to patients with psoriasis, provided the guidelines are observed.^{14,15} Since chronic plaque psoriasis is not a life-threatening disease, use of CyA must be considered only after the benefits and risks have been carefully weighed. The aim of treatment of psoriasis should be to control the disease and not to achieve total clearing of the lesions. Small persistent lesions should be treated with topical therapy rather than an increased dose of CyA.

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