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Remission of Ordinary Psoriasis Following a Short Clearance Course of Cyclosporin

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We set out to show that the assumption is incorrect that continuous treatment with cyclosporin is necessary in psoriasis, as this tenet forms a basis for current recommended treatment regimens.

Sixty patients with mild to moderate plaque psoriasis were allocated at random to treatment with oral cyclosporin 5 mg/kg/day (30 patients) or topical dithranol and ultraviolet B therapy (30 patients) for up to 16 weeks until clear (median time 6 weeks cyclosporin and 8 dithranol), and the times to relapse compared. The patients were seen monthly for up to 8 months, and the severity and the extent of psoriasis were assessed.

Relapse, defined as return of psoriasis to 50% of the area at the start of the trial or patient demand for further treatment, was not significantly different between the groups (hazard ratio 1.11, 95% CI 0.55–2.32). No patients suffered a rebound of severe disease and none relapsed in the first 8 weeks after stopping treatment. The relapse rate was higher following cyclosporin from 8 to 28 weeks after treatment and following dithranol from 28 to 34 weeks. The patients with arthritis had a higher median joint severity score at relapse than prior to treatment with cyclosporin. At the end of 8 months, 5 patients treated with dithranol and 8 patients with cyclosporin remained clear, 75% and 67% having relapsed.

We conclude that rapid relapse does not occur after clearance of mild to moderate plaque psoriasis with cyclosporin and the relapse rate was no different from dithranol treatment. ***Key words: relapse; dithranol; plaques; joints; nails.***

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Cyclosporin (CsA) is very effective in clearing psoriasis (1–4), but because of early reports of a rapid relapse (4–5) the belief took root that treatment has to be maintained continuously, and the consequent risk of toxicity therefore limited the use of the drug to severe disease. We believe this to be an error which arose because patients with severe and resistant disease were treated initially, and in these patients a rapid relapse would have occurred following withdrawal of any treatment (6). A pilot study (7) suggested that this explanation was likely to be correct and we have therefore done a formal study to test whether or not relapse is any different after clearance of ordinary plaque psoriasis with either cyclosporin or with dithranol and ultraviolet B.

MATERIAL AND METHODS

The study was an open randomised comparison of the effect of CsA and conventional short contact dithranol in patients with ordinary, mild to moderate plaque psoriasis.

Patients

The 60 patients studied (33 females, 27 males, aged 18–67) had been referred routinely to the outpatient clinic for treatment of their chronic plaque psoriasis. Patients with acute guttate psoriasis, and those who had required 3 or more treatment clearances for relapses in the previous year, were excluded. Other exclusion criteria were pregnancy, malignancy, epilepsy, concomitant treatment with nephrotoxic drugs or drugs known to interact with CsA, systemic treatment for psoriasis taken less than 2 weeks before the study, serum creatinine > 100 μmol/l, diastolic blood pressure >95 mmHg, hyperuricaemia and abnormal liver enzymes or bilirubin. The study was approved by the local ethics committee and all patients gave written, informed consent.

Thirty patients were randomised to treatment with CsA [median age 33 (range 18–61); duration of psoriasis 11.5 (1–40) years; median area involved 4.5% (range 1.5–35%)] and 30 to dithranol [age 34 (20–67); duration 12 (2–58); area 4.5% (0.9–15%)].

Five patients withdrew after randomisation but before starting treatment (1 CsA, 4 dithranol), 2 during dithranol treatment because of difficulty in attending daily and 3 during CsA treatment, 1 after 1 week because she objected to the frequent assessments and 2 because of dyspepsia after 2 and 14 weeks' treatment. A barium meal examination was normal on the latter patient.

Treatment

After screening, the patients were randomised, the code being available only to a hospital pharmacist who was otherwise uninvolved with the study. Oral CsA was given as two daily doses of 2.5 mg/kg until 2 weeks after the psoriasis had cleared. This dose was chosen with the aim of achieving clearance in 90% of patients (8). The dose was reduced by 25% if the serum creatinine increased by 30% over baseline, if serum bilirubin or liver enzymes increased 100% over baseline or if the diastolic blood pressure was consistently greater than 95 mmHg.

Dithranol (2% to 8% with 0.5% salicylic acid in emulsifying ointment) was used in conventional short-contact therapy (9), the dithranol being applied daily for 15 min and then washed off. Treatment was administered on weekdays by clinic nursing staff skilled in the treatment of psoriasis and was preceded by a suberythemal dose of ultraviolet B. At weekends the patients treated themselves at home. A dithranol pomade was applied to the scalp overnight. The Ingram regimen, using dithranol in Lassar's paste (10), was used for patients not improving on the short-contact regimen. Treatment was considered a failure and stopped if there were any residual lesions after 16 weeks of either treatment.

Assessment of response

Visits for assessment were made twice before the treatment began and every 2 weeks thereafter until the rash was cleared and, after clearance, monthly until relapse or for 8 months. At each visit the area of involvement was assessed by the rule of nines and the scaling, erythema and degree of infiltration was graded (0–3). Individual nail involvement was scored (0–2), and itch and joint pain, swelling and handicap were scored as absent, mild, moderate or severe. To minimise observer variation of psoriasis extent scoring, assessment of the same patient was made periodically by two investigators. The average bias between the investigators was 118% (95% CI 95 to 146%), calculated from the mean log differences between paired measurements (11).

Clearance and relapse

Clearance was defined as the complete absence of visible or palpable lesions of psoriasis, but a few patients who had a residual fixed area less

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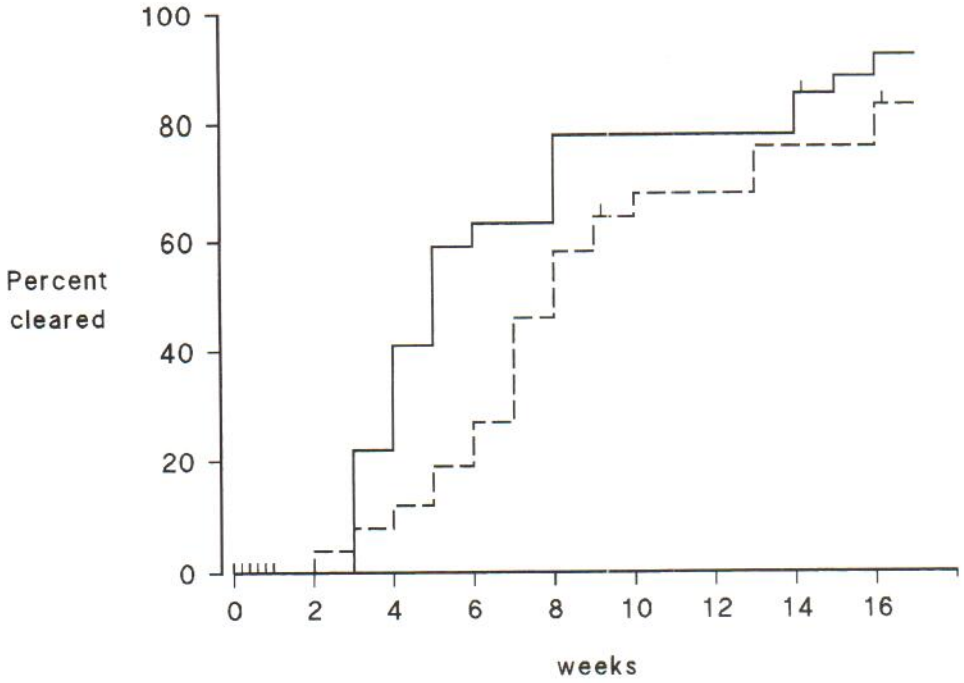

Fig. 1. Times to clearance with CsA (——) or dithranol (- - -); withdrawals shown (|).

than 2 cm diameter, unaffected by 2 weeks' further treatment, were also considered to have cleared. From the date treatment was discontinued the time of relapse was defined as a return of 50% or more of the severity of the rash before treatment, or the request by patients for further treatment even when the degree of relapse was less than 50%.

Blood pressure and chemistry

Blood was taken for measurement of creatinine, electrolytes, bilirubin, liver enzymes, uric acid and magnesium, and the blood pressure was measured at each assessment visit.

Statistics

Survival curves showing the clearance and relapse rates were drawn. A reflection method was used to calculate confidence limits for the median times for clearance and relapse (12). The logrank test was used to calculate hazard ratios to compare the clearance rates and to compare the relapse rates with CsA and dithranol treatment, and 95% confidence limits for these ratios were calculated (13). The terms relapse rate and clearance rate refer to the ratios of observed divided by expected events in the two treatment groups. The times to clear and relapse of the components of the rash, erythema, infiltration and desquamation and the times to clear and relapse of the rash in each body site were also compared using the logrank test. The severity scores for overall joint and nail involvement before, at the end of treatment and at relapse were

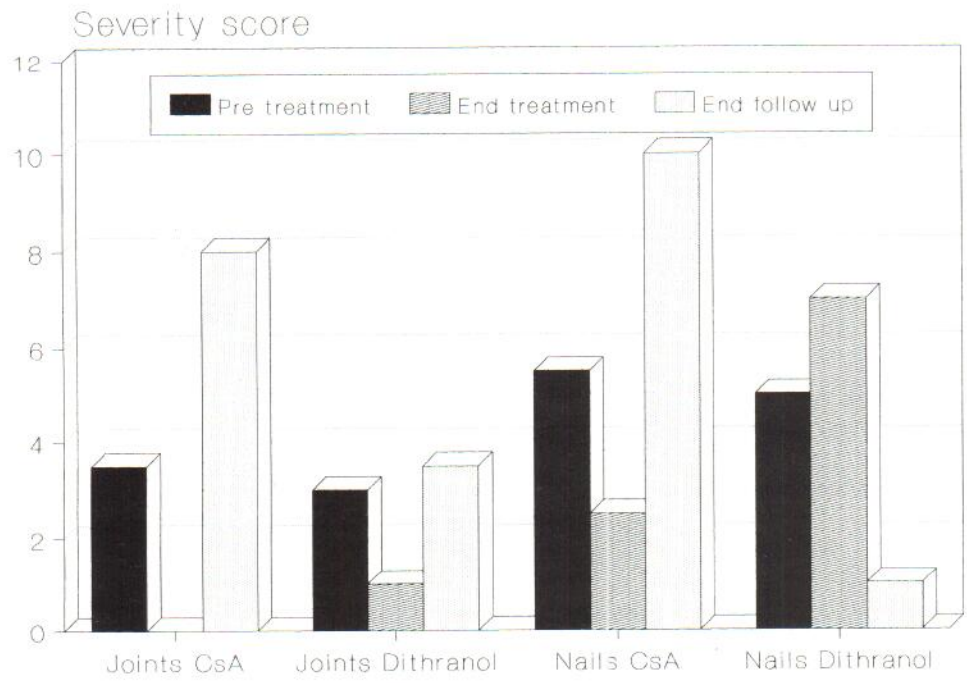

Fig. 2. Median nail and joint severity scores for affected patients, before treatment, at the end of treatment and at the end of follow-up.

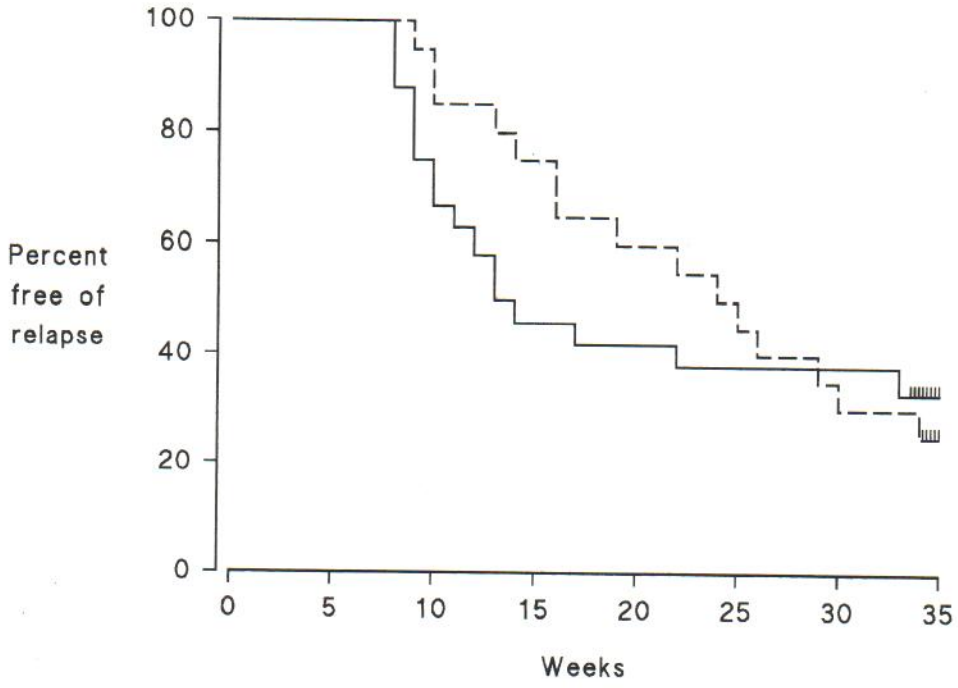

Fig. 3. Times to relapse after clearance of psoriasis with CsA (——) or dithranol (- - -). Each of the marks (1) at 35 weeks represents a patient who had not relapsed.

compared using a Wilcoxon test, and 95% confidence intervals were calculated using the CIA program version 1.1 (BMJ publications UK). Changes in blood pressure and chemistry were compared using paired Student's *t*-tests and 95% confidence intervals were calculated. Ninety-five per cent confidence intervals describe the range within which the result might occur with a probability >0.05.

RESULTS

Response to treatment

Complete regression of the rash occurred in 24 out of 26 patients treated with CsA and 20 out of 24 treated with dithranol who completed the protocol (Fig. 1). The median clearance time was 8 weeks (90% CI 6 to 10 weeks) with dithranol, compared with 6 weeks (90% CI 4 to 9 weeks) with CsA. The rate of clearance was faster with CsA than with dithranol but this was not significant. The ratio of the clearance rates for CsA:dithranol was 1.57 (95% CI 0.83 to 2.97).

Forty-eight of the patients complained of itch (23 CsA, 25 dithranol), and this improved with both treatments with a median time to regression of 4 weeks with CsA and 5 weeks with dithranol treatment. The rate of clearance of itch was faster with CsA but this was not significant; the ratio of clearance rates for CsA:dithranol was 1.50 (95% CI 0.68 to 3.29).

Nine of the patients treated with CsA had joint symptoms with a median baseline score of 3.5 (Fig. 2); 1 withdrew before further assessment but the remainder all improved, with a median decrease in severity score of 3.5 (96.1% CI 2 to 5); 5 of the patients treated with dithranol had joint symptoms (median score 3) which worsened in 1 and improved in 4.

Thirteen patients randomised to CsA had psoriatic nail disease, of whom 3 withdrew before further assessment. Of the remainder (median baseline score 5.5), 8 improved, 1 was unchanged and 1 worsened (median decrease in severity score 4.5; 95.1% CI 0 to 8). Sixteen patients randomised to dithranol had a nail dystrophy treated with dithranol; 1 withdrew before further assessment; of the remainder (median score 5), 8 improved, 2 were unchanged and 5 worsened (median score change 0, 95.2% CI −3 to 2.5).

Failure to respond

Two patients failed to clear with CsA; 1 was found to have been dispensed a lower dose than prescribed and the other had not maintained the dose schedule. Four patients failed to clear with dithranol treatment.

Time to relapse

All patients who cleared were followed up until relapse or until 8 months had elapsed. Relapse of psoriasis in the 24 patients cleared by CsA and the 20 patients cleared by dithranol is shown in Fig. 3. Rapid relapse was not seen after either treatment. The initial rate of relapse was greater after CsA treatment than after dithranol, 50% having relapsed at 13 weeks (90% CI 10 to 33 weeks) after CsA compared with 24 weeks (90% CI 15 to 30 weeks) after dithranol. At 8 months 67% had relapsed following clearance with CsA and 75% following clearance with dithranol. There was no significant difference between the relapse rates; the ratio of the relapse rates for CsA:dithranol was 1.11 (95% CI 0.55 to 2.32).

The proportion of patients who relapsed on symptomatic criteria was similar after each treatment (31% CsA, 40% dithranol: difference 9%; 95% CI −24% to 42%). The patients who requested further treatment did so when the psoriasis extent was less severe after CsA (mean: 27% of baseline score) than after dithranol (mean: 35% of baseline score); however, the difference (8%) was not significant (95% CI −10% to 27%).

The rate of recurrence of itch was faster following CsA but this was not significant. The ratio of itch relapse rates for dithranol:CsA was 0.622 (95% CI 0.306 to 1.27).

Of the 6 patients with joint symptoms who cleared with CsA, 2 remained unchanged and 4 worsened after treatment was

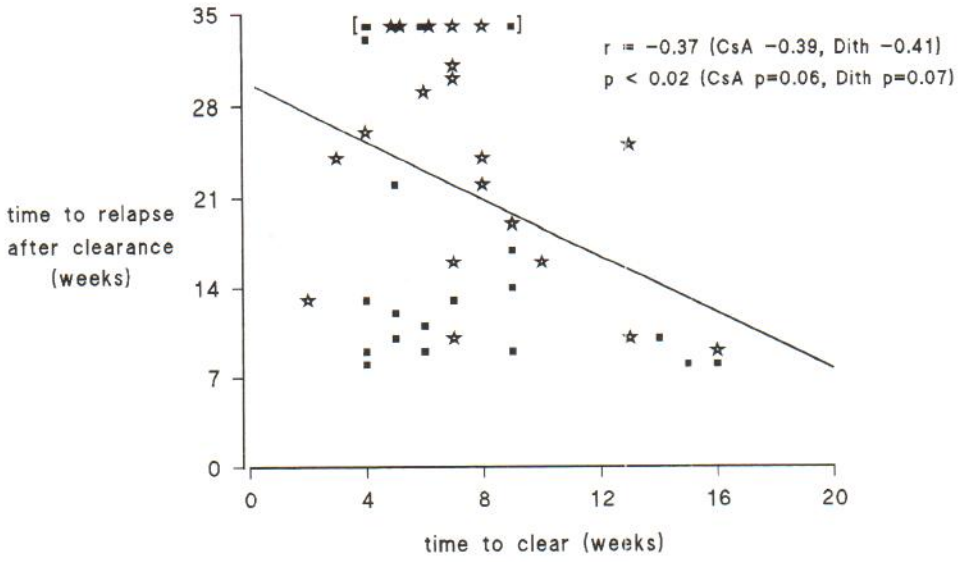

Fig. 4. Clearance times for patients treated with CsA (■) and dithranol (★) are plotted against the times to relapse. The 13 patients who had not relapsed at 35 weeks are included in brackets.

stopped (Fig. 2). By the end of follow-up the median increase in score was 4 (96.9% CI 0–9). The 4 patients with joint symptoms who cleared with dithranol all worsened after stopping treatment.

Eight patients with a nail dystrophy cleared with CsA; 1 was unchanged and 7 worsened after stopping treatment (Fig. 2). The median increase of the nail severity score by the end of follow-up was 5 (96.1% CI 2 to 9.5). Of the 10 patients with a nail dystrophy who cleared with dithranol, 1 was unchanged, 7 improved and 2 worsened after treatment was discontinued; the median improvement in score at the end of follow-up was 4 (95.8% CI 0 to 8).

Relationship of response and relapse to site and treatment. There were no significant differences between the clearance rates or the relapse rates of the rash in different body sites or of the components of the rash (erythema, desquamation and induration) either within or between the two treatment groups.

Relationship between times to clear and relapse. The patients who took more than 8 weeks to clear with CsA relapsed quickly. A similar trend was seen with dithranol treatment. When the times to clearance of both treatment groups were plotted against the times to relapse, there was a weak but significant negative correlation between the time to clearance and the time of follow-up, due to the patients who were slow to clear (Fig. 4).

Table I. *Safety data*

Mean baseline values and percentage changes from baseline (±95% confidence intervals) of blood pressure (mmHg) and blood tests [mg/dl (μmol/l)].

	Baseline	End of treatment	4 weeks after treatment
Creatinine			
CsA	0.88 (77.3)	+7.5±6.1*	+3.1±4.5
Dithranol	0.89 (78.0)	+2.3±4.6	+2.9±4.4
Urate			
CsA	5.2 (317)	+7.3±5.4*	−2.8±3.8
Dithranol	5.2 (320)	+5.1±3.8*	+4.4±5.3
Magnesium			
CsA	(781)	−9.2±4.2*	−3.5±3.7
Dithranol	(804)	−2.6±2.6	−2.5±3.6
Systolic BP			
CsA	126	+1.6±4.3	−1.9±4.8
Dithranol	120	−5.0±4.7*	+0.2±6.1
Diastolic BP			
CsA	79	+2.6±6.3	−2.0±5.7
Dithranol	75	−3.2±6.3	+0.5±7.3

* = $p<0.05$

Blood pressure and chemistry

Clinically important changes in liver enzymes and bilirubin did not occur. One patient receiving CsA required a 25% dose reduction after 2 weeks' treatment due to a high blood pressure recording (150/100 mmHg) which subsequently returned to normal. The mean changes in blood pressure were not significant except for a fall in systolic blood pressure with dithranol treatment which subsequently rose to pretreatment levels (Table I).

In 1 patient the serum creatinine increased on CsA by more than 30% after 8 weeks' treatment, but this reversed after a 25% dose reduction. There was a significant mean rise in the serum creatinine with CsA treatment by 7.5% of the mean pretreatment value of 0.88 mg/dl, which reversed after treatment was discontinued (Table I).

There was a significant mean rise in the serum urate with both CsA and dithranol treatment, compared to the mean pre-treatment values by 7.3% and 5.1%, respectively, and a mean fall in the serum magnesium by 9.2% and 2.6%, respectively.

DISCUSSION

This study shows that a rapid relapse does not occur after clearance of ordinary mild to moderate plaque psoriasis with

CsA, and that the rate and severity of relapse does not differ greatly from that following dithranol treatment.

As in previous studies, the response to both CsA and dithranol was good and there were few unwanted effects: minimal toxicity was seen in some of the patients treated with CsA and some of the patients were burnt by the dithranol, but none of these effects were problematic. The patients all had ordinary and localised psoriasis; none were selected other than by a pre-defined set of exclusion criteria which would not have affected the therapeutic outcome. Because dithranol-treated skin is easily recognised, the study could not be done blind, but the patients were randomised to the two different treatment regimens and the response was assessed independently by two clinicians experienced with the semi-quantitative clinical methods used. The drop-outs were not likely to have biased the results, and the number of patients completing both treatments and the magnitude of the therapeutic responses were sufficient to define the therapeutic effects we set out to study. We therefore have reasonable confidence that we would have been able to detect clinically significant differences in response and relapse after CsA and dithranol. Differences were found in rate of response and initial relapse, but overall there was little difference between the two therapies, and the proportion of patients in remission 8 months after treatment was comparable. Furthermore there was no difference in the severity of relapse in the two groups, and "rebound" to a severity worse than before treatment was not seen after CsA or dithranol. These findings are consistent with our pilot study (7) and show no evidence of an enhanced propensity to relapse, let alone "rebound", after treatment of ordinary psoriasis with CsA. Psoriatic nail and joint disease improved during cyclosporin treatment but then deteriorated to more severe disease after treatment was stopped; however, the relatively small number of patients affected limits the interpretation of this finding.

Thus, as originally suggested (6), the rapid relapse initially reported after treatment of psoriasis with CsA must be a reflection of the severity of the disease originally treated and not the treatment. The idea that CsA has a particular propensity to elicit a relapse when it was stopped was always more intriguing than likely, because such a unique property of the drug implies a capacity to remove the rash whilst maintaining its eruptive potential (5). Our present findings with CsA are similar to those from studies in which we compared the response of ordinary uncomplicated psoriasis to dithranol and PUVA (14, 15) and found that after clearance relapse occurred at about 10% per month, so that most patients require one to two courses of treatment a year.

Our demonstration that stopping CsA treatment does not provoke a relapse has important therapeutic implications for CsA and its newer analogues. Since it is now clear that the drug does not have to be given continuously, the consequent risk of toxicity may no longer require the justification of severe resistant disease. CsA treatment does not need to be limited to such patients, but could be given like dithranol, tar or PUVA to patients with minor disease who respond rapidly and relapse slowly. Whether such treatment should be used must depend, of course, on whether the decrease in toxicity from the reduced cumulative dose of intermittent therapy will prove sufficient, especially with use of a dose and duration less than that which we used. In this respect our finding of a lower rate of relapse in patients responding by 8 weeks requires confirmation because it suggests that this should be the period of initial treatment.

The purpose of the present study, however, was not to establish a new therapeutic regimen but to show that the basis for the existing treatment recommendations with CsA (16) is incorrect. Clearly CsA will maintain its place in the therapy of severe resistant psoriasis but, in addition, the efficacy and toxicity of a new therapeutic strategy should now be studied for those patients with ordinary plaque psoriasis who can be controlled by one or two short low-dose courses a year.

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