Low-dose (1.25 mg/kg) Cyclosporin A: Treatment of Psoriasis and Investigation of the Influence on Lipid Profile

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This study was designed to investigate the therapeutical efficacy of a comparatively low dose cyclosporin A (1.25 mg/kg/day) in the treatment of psoriasis and to assess the influence of cyclosporin A on lipid profiles. In the first, double-blind part of the study, 133 patients with moderate to severe psoriasis were randomized to receive a daily dose of 1.25 or 2.5 mg cyclosporin A/kg or placebo for a period of 10 weeks (period I). Subsequently, the patients entered a second open-label 12-week study (period II), in which the dosage could be increased up to 5.0 mg/kg/day. This was followed by a period of 4 weeks without treatment. After 10 weeks the percentage improvement from baseline in the Psoriasis Area and Severity Index (PASI) was 5.9% on placebo, 27.2% on 1.25 mg/kg/day and 51.0% on 2.5 mg/kg/day cyclosporin A. The final average dose at the end of study period II was 2.99 mg cyclosporin A/kg/day. At this time the PASI was reduced by at least 75% in 63.0% of the patients. From this group of good responders no patient relapsed (PASI >50% of baseline) during the four weeks after termination of active treatment. No significant effects of the drug on the lipid profiles were detected.

We conclude that 1.25 mg cyclosporin A/kg/day is superior to placebo in the treatment of psoriasis vulgaris and that a dose reduction to 1.25 mg/kg/day should be considered in patients responding well to a conventional dose between 2.5 and 5.0 cyclosporin A/kg/day. *Key words: PASI score; blood pressure; creatinine; cholesterol; triglycerides; lipoproteins; apolipoproteins.*

The increasing appreciation of the involvement of the immune system in psoriasis led to a number of studies showing an impressive effect of systemically administered cyclosporin A on severe chronic psoriasis (1, 2). However, when high doses are applied there is a concern about potential renal side effects of the drug. Therefore it is a common therapeutic strategy to start treatment with 2.5 mg/kg cyclosporin A daily, with subsequent dose alterations in order to find the minimum effective dosage (3). Even extremely low doses as 1.25 mg/kg/day cyclosporin A have shown some effect on severe psoriasis in recent studies (4–6). However, because of the lack of a placebo control it cannot be ruled out that these positive results were due to spontaneous variations in disease activity.

The primary objective of this randomized, double-blind, multicentre study in patients with moderate to severe psoriasis was to assess the efficacy of the extremely low dose of 1.25 mg/kg cyclosporin A daily compared with placebo and the positive control 2.5 mg/kg daily. In the second part of the study the long-term results with an optimized dose were assessed. Special emphasis was put on the monitoring of serum lipids, because an increase in serum triglyceride levels and serum cholesterol in patients receiving oral cyclosporin A for psoriasis has been reported previously (7–10).

MATERIALS AND METHODS

Patient selection

Patients who met the following criteria were included: age between 18 and 70 years, psoriasis vulgaris with an indication for systemic therapy, PASI score at the beginning of the study between 8 and 25. The PASI score represents a standardized and reproducible clinical rating system, which assesses the area of the body affected by psoriasis and the intensity of the main symptoms ranging from 0 to 72 (11). Informed written consent was obtained from all patients participating in the study.

General exclusion criteria included creatinine levels of more than 10% above the upper normal value, cholesterol ≥350 mg/dl, bilirubin and liver enzymes above 150% of the upper laboratory normal value of each centre, hyperkalaemia, hyperuricemia, hypertension (diastolic blood pressure >95 mmHg), leucopenia, thrombocytopenia, and concomitant therapy with potentially nephrotoxic agents or drugs which might influence the pharmacokinetics of the study drug.

In addition to general exclusion criteria, patients were not eligible for entry to the study if one of the following dermatological conditions was present: drug-induced psoriasis, erythrodermia, treatment with methotrexate, retinoids, photochemotherapy (PUVA) or cyclosporin A in the previous 4 weeks, specific topical treatment in the previous week, indispensable systemic treatment for psoriasis, concomitant treatment with cytostatic agents, corticosteroids, retinoids, PUVA, ultraviolet light radiation therapy. Pregnant or breast-feeding women were also excluded from the study.

Study design

The study consisted of a screening phase followed by two successive treatment periods (study periods I and II) and a follow-up period. In the double-blind study period I, patients were randomized to oral treatment with either 1.25 mg or 2.5 mg cyclosporin A/kg/day or placebo over a time period of 10 weeks. During the open-label, 12-week study period II, the dose could be doubled to 2.5 mg and 5.0 mg/kg/day in the respective treatment groups, depending on the efficacy in terms of PASI score and tolerability. Criterium for doubling the dose was an increase in PASI of more than 50% compared to week 10. Patients who had received placebo during period I were treated with 2.5 mg cyclosporin A/kg/day, increasing to 5.0 mg/kg/day, if the PASI reduction was less than 10% in week 13 or less than 30% in week 16. The patients on 1.25 mg/kg during period I received 2.5 mg/kg in period II, if the PASI did not decrease by at least 60%. In accordance with the recommendations of the Consensus Conference on cyclosporin A for psoriasis, the maximum dose did not exceed 5 mg/kg/day (3). Study periods I and II were followed by a 4-week treatment-free follow-up period, which also included patients who did not complete the study.

At the two screening visits during week 2 and week 1 it was ascertained that the laboratory parameters were within the required limits. At the baseline visit, a complete physical examination was performed. Patients were reexamined at weeks 1, 3, 6 and 10 during

study period I, as well as at weeks 13, 16, 19 and 22 during study period II and at the end of the follow-up period at week 26. Blood pressure, weight, cyclosporin A trough-levels, adverse events and compliance were documented on all visits. At weeks 10 and 22, a final assessment of the treatment efficacy and tolerability was conducted. Analysis of triglycerides, total cholesterol, HDL- and LDL-cholesterol, apolipoproteins B, AI, AII and E as well as lipoproteins (a) and Al was performed at baseline and at weeks 10, 22 and 26. In addition, nutritional habits were documented.

Statistics

As the main measure of efficacy the PASI scores in the three treatment groups at the end of week 10 were tested by the Jonckheere-test for ordered alternatives. In case of a significant result in this test, the groups were compared pairwise with respect to response rates (PASI at week $10 \geq 75\%$ or $\geq 50\%$ or $\geq 25\%$ of baseline PASI, respectively) by Fisher's exact test. Group differences in serum lipids at baseline and in lipid changes during study period I were tested by the Kruskal-Wallis H-test and by the Wilcoxon U-test. Group differences at the end of study period II after posthoc stratification according to treatment with 2.5 mg/kg and 5.0 mg/kg were analysed by the Wilcoxon U-test. The sign test was applied to detect intragroup differences in the lipid profile during the course of the study.

Patients

One hundred and thirty-three patients (85 men and 48 women) with a mean age of 38.2 ± 11.6 years were screened in 17 centres. One hundred and twenty-eight patients fulfilling the required inclusion criteria entered study period I and were randomly assigned to treatment with cyclosporin A 1.25 mg/kg/day ($n=41$), cyclosporin A 2.5 mg/kg/day ($n=44$) or placebo ($n=43$). There was no significant difference between the three groups with respect to age-, sex- and body-mass-index-distribution and severity of psoriasis. Seventy-eight patients (60.9%) had been treated with methotrexate (19.5%), retinoids (21.1%), PUVA (50.8%) or corticosteroids (18%) before being enrolled in the study. One hundred and twenty patients completed study period I, 3 of whom did not enter study period II because of an improvement in PASI score of more than 60% from baseline when receiving placebo. Another 6 patients were withdrawn from study periods I and II because of protocol violations, 4 as a consequence of insufficient therapeutic response (to placebo) and 5 due to adverse events.

Dosage

In all patients from the placebo group the dose was increased after the end of study period I, leading to an average dose of 3.20 ± 0.72 mg cyclosporin A/kg/day at the end of period II. In 89.2% of the patients in the 1.25 mg treatment group the dose had to be increased due to insufficient response (average dose 2.71 ± 0.83 mg/kg/day) and in 41.0% of those in the 2.5 mg group the dose was increased (3.09 ± 0.93 cyclosporin A/kg/day in average).

Calculating the mean dose at the end of study period II, patients received on average 2.99 ± 0.86 mg cyclosporin A/kg/day: 6.4% of all patients received a daily dose of 1.25 mg/kg, 56.4% were treated with 2.5 mg/kg/day and 37.3% were on 5 mg/kg/day.

RESULTS

Study period I

Whereas PASI score showed little change from baseline in the placebo group, the difference between the two treatment groups and the placebo group increased over the 10 weeks of therapy and became highly significant for both treatment groups vs. placebo (Table I). The results reveal a clear dose response relationship, with the higher cyclosporin A dosage level leading to a greater reduction of PASI score. Comparison of the percent change in PASI score in patients treated with 2.5 mg cyclosporin A/kg/day and placebo in study period I revealed a significant difference after the first week of treatment ($p < 0.01$).

While 76.2% and 44.7% of the patients receiving 2.5 mg and 1.25 mg cyclosporin A/kg/day, respectively, reached the cut-off point of a 25% improvement in PASI score from baseline in the responder analysis, this was only the case for 23.1% of the patients in the placebo group. Thus both dosages of the study drug proved to be superior to placebo. Further responder analysis with a cut-off point of 50% and 75% improvement in PASI score confirmed the above dose response relationship (Fig. 1).

Study period II

Responder analysis at the end of study period II with a cut-off point of $\geq 25\%$ reduction in PASI score indicated a successful treatment, with a response rate of 93.5% in all treatment groups. In most of the patients (82.4%), a $\geq 50\%$ reduction in PASI score was achieved, and the majority (63.0%) had a 75% decrease in PASI score.

Table I. *PASI scores: baseline, change from baseline in study period I and end of study period I*

		Placebo $n=39$		Cyclosporin A 1.25 mg/kg/day $n=40$		Cyclosporin A 2.5 mg/kg/day $n=41$	
		M	sd	M	sd	M	sd
	Baseline	15.6	5.1	16.7	5.7	15.1	5.0
Percental change (%)	1 week	−3.2	6.5	−4.3	9.8	−10.2[a]	15.3
	3 weeks	−7.3	19.2	−11.7	22.3	−22.9[a]	26.3
	6 weeks	−11.0	28.0	−22.1	29.0	−39.3[b]	28.8
	10 weeks	−5.9	36.1	−27.2[a]	34.6	−51.0[b]	30.9
	End of period I	14.9	7.9	11.8	6.8	7.6	6.2

M = mean, sd = standard deviation.
t-test for unequal variances.
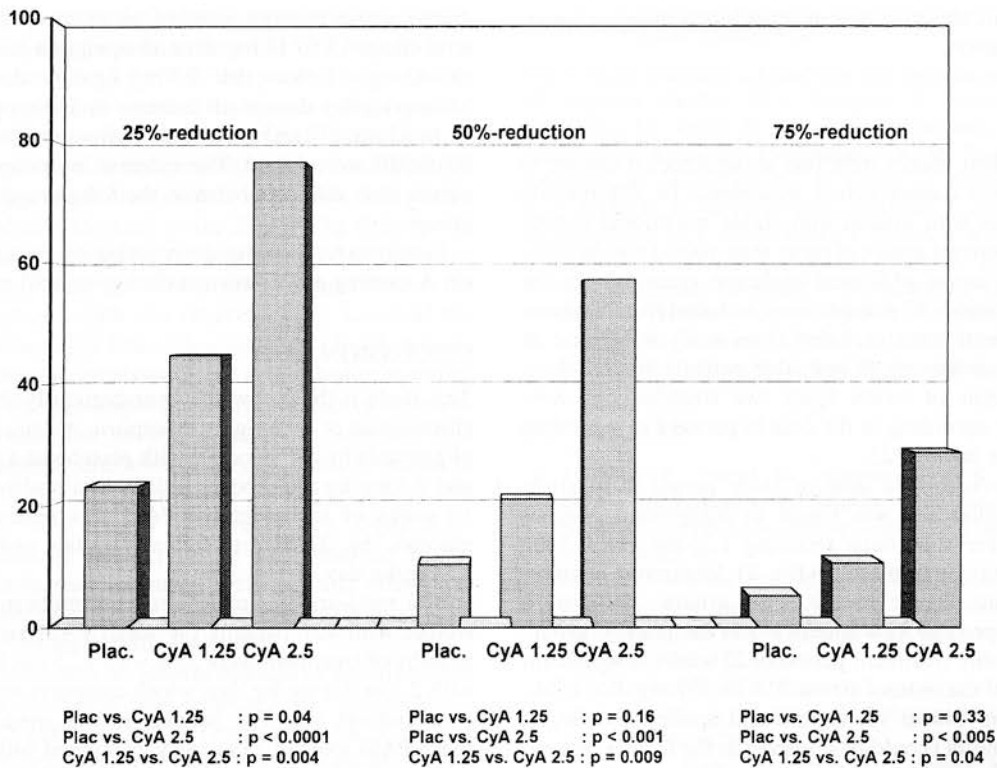[a] $p < 0.01$ vs. placebo.
[b] $p < 0.001$ vs. placebo.

Fig. 1. Percentage of responders according to different responder criteria at the end of week 10.

Study period III (Relapse analysis)

Four weeks after termination of active therapy, 81.3%, 62.6% and 28.0% of the patients still had PASI reductions of $\geq 25\%$, $\geq 50\%$ and $\geq 75\%$, respectively.

Interestingly in the subgroup of good responders the disease remained under satisfactory control without treatment for at least 4 weeks. When relapse was defined as an increase to $\geq 50\%$ of baseline PASI after a $\geq 75\%$ decrease, no relapse could be observed until the end of the study.

Safety and tolerability

Adverse events. Adverse events were reported for 63 out of 133 patients. The most frequent adverse event was influenza-like symptoms in 16 patients, in all cases with an uncertain or non-existent relationship to the study medication. Other frequent adverse events were headache (12 patients), abdominal pain (8 patients), nausea (6 patients) and pyrosis (4 patients). In 5 patients gingival hypertrophy, paraesthesia and diarrhoea were observed. In study period I, a clear dose relationship could be detected with 4 adverse events in the placebo group, 14 in patients receiving 1.25 mg/kg cyclosporin A and 30 in patients receiving 2.5 mg/kg cyclosporin A. On placebo, 1.25 and 5 mg/kg/day cyclosporin A no patient discontinued because of adverse events, whereas adverse events at least contributed to the withdrawal of 5 patients on 2.5 mg/kg/day (increase in blood pressure, heartbum, rhinitis, epididymitis and orchitis, upper airway infection, fever).

Blood pressure. During study period I systolic blood pressure increased by 1.1 mmHg with placebo, by 2.4 mmHg with 1.25 mg and by 3.7 mmHg with 2.5 mg cyclosporin A/kg/day. Changes in diastolic blood pressure were -0.1 mmHg with placebo, 1.8 mmHg with 1.25 mg and 4.4 mmHg with 2.5 mg cylcosporin A/kg/day.

After long-term treatment with up to 2.5 mg cyclosporin A/kg/day, systolic blood pressure was increased at week 22 by 3.5 mmHg and diastolic blood pressure by 3.8 mmHg. At the same time the increase in the 5-mg group was 3.4 mmHg for systolic blood pressure and 4.6 mg/Hg for diastolic blood pressure. Within 4 weeks after termination of cyclosporin therapy the blood pressure had returned to near-baseline levels. Among the patients with baseline values of <95 mmHg for diastolic blood pressure, only 5 developed hypertension with at least 2 diastolic measurements of >95 mmHg. Systolic blood pressure values of >160 occurred in 3 patients but could not be confirmed on the next visit.

Creatinine and laboratory test analysis. In contrast to blood pressure there was no dose-dependent overall increase in serum creatinine, either in study period I or in study period II. In 11 of 133 patients (8.3%), serum creatinine increased by 30% or more on at least one occasion. However, in 4 patients this elevated creatinine level appeared only once and decreased without dose reduction or even on an increased cyclosporin dose. Two patients fulfilled the criterion of a creatinine increase of $\geq 30\%$ due to the isolated extremely low baseline values of 61.0 µmol/l and 50.4 µmol/l. In the remaining 5 patients a creatinine increase of $\geq 30\%$ was found at the last visit of active treatment in week 22. Although these increased values could not be reproduced, a relationship with cyclosporin A seems probable. The final creatinine values in these 5 patients were in the range between 97.2 and 140.6 µmol/l, with a maximum increase of 73%. Two of these patients were on 2.5 mg and 3 on 5.0 mg cyclosporin A/kg/day. No patient discontinued the study prematurely because of renal side-effects. Furthermore, the cyclosporin A therapy caused no

clinically relevant abnormalities of other biochemical or hematological parameters.

Lipid analysis

Analysis of patient diaries indicated an unexpected change in nutritional habits during active treatment. To differentiate between patients with altered and stable nutritional habits, increase of cholesterol intake of more than 100% from baseline was introduced as an additional exclusion criterion. On the basis of this criterion, 35 patients were excluded from analysis. Another 3 patients were excluded from analysis because of missing data, thus leaving 89 evaluable patients in week 0.

For the analysis of serum lipids two stratifications were applied, namely according to the dose in period I or according to the final dose in week 22.

Stratification according to dose in study period I. In study period I, no difference was found in lipoprotein analysis between the three subgroups receiving 1.25 mg and 2.5 mg cyclosporin A/kg/day or placebo (Fig. 2). Intragroup comparison revealed no change in the three groups; however, a decrease in lipoprotein AI was detected in the placebo group.

During the entire treatment period of 22 weeks, a significant increase in total cholesterol (from 214 to 231 mg/dl), LDL-cholesterol (from 144 to 156 mg/dl) and apolipoprotein AII (from 37 to 41 mg/dl) could be observed in the former placebo group, in which most of the patients were subsequently treated with 2.5 mg cyclosporin A/kg/day. Patients initially in the 1.25 mg/kg/day treatment group showed a decrease in lipoprotein AI (from 58 to 49 mg/dl). For patients receiving the 2.5 mg dosage in study period I, an increase in apolipoprotein AII (from 38 to 42 mg/dl) was found.

Stratification according to the final dose in week 22. With this stratification, intragroup comparisons of the changes during active therapy revealed an increase of VLDL-cholesterol (from 13 to 17 mg/dl) and apolipoprotein AII (from 38 to 42 mg/dl) for the 2.5 mg/kg/day dosage. For the 5.0 mg/kg/day dosage an increase in apolipoprotein B (from 75 to 85 mg/dl) and a decrease in lipoprotein AI (from 54 to 50 mg/dl) were found. The increase in apolipoprotein B was significantly different between the 5 mg group and the 2.5 mg group.

In summary, these results revealed no evidence of cyclosporin A causing any consistent change in lipid metabolism.

DISCUSSION

This study is the first which unambiguously shows the clinical effectiveness of 1.25 mg/kg cylosporin A daily in the treatment of psoriasis by comparing it with placebo as a negative control and 2.5 mg/kg cyclosporin A daily as a positive control. After 10 weeks of treatment the PASI was reduced by 5.9% on placebo, by 27.2% on 1.25 mg/kg/day and by 51.0% on 2.5 mg/kg/day.

In a meta-analysis of 5 European multicentre dose-finding studies with 457 patients the mean PASI reductions after 3 months of treatment were 35% with 1.25 mg/kg/day and 57% with 2.5 or 3.0 mg/kg/day, which compares very well with our own findings (1). The patients in this meta-analysis had a mean PASI score of 25 at entry, compared with approximately 16 in our study, but a subgroup analysis showed equal efficacy of 2.5 mg/kg/day in patients with PASI scores of ≤ 25 and those of ≥ 25 (1). However, one must be careful when drawing conclusions because of the methodological shortcomings of historical comparisons.

The same problem is faced when comparing the responder rates at the end of this study with other published data. Nevertheless, in the study of Christophers et al., where treat-
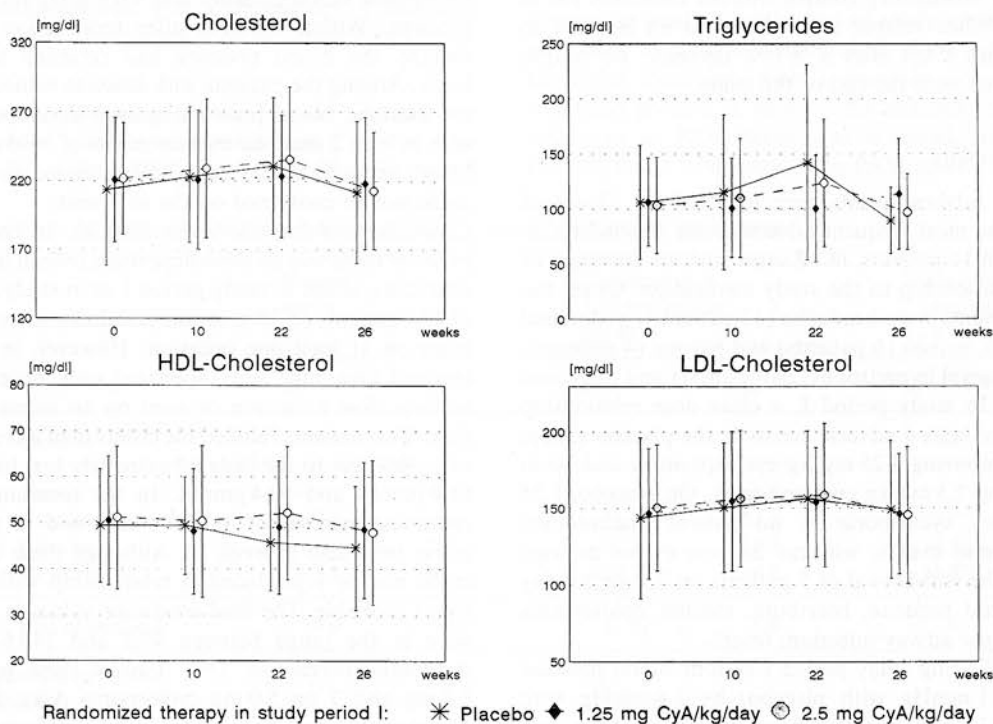

Randomized therapy in study period I: ✳ Placebo   ◆ 1.25 mg CyA/kg/day   ◎ 2.5 mg CyA/kg/day

Fig. 2. Serum lipids during the course of the study. The groups correspond to the initial randomisation.

ment duration and responder criteria were relatively similar to ours, 67.8% of the patients achieved a 75% reduction in PASI score compared with 63% of the patients in our study (5). The patients in Christophers' study had a higher initial PASI, and again the degree of percentage PASI reductions on cyclosporin A seems to be independent of the baseline PASI value. The average final dose in that study was 3.02 mg/kg daily, which is almost identical to the 2.99 mg/kg daily in our study. Our observation that no patient with a PASI reduction of ≥75% relapsed during 4 weeks after termination of the drug is in accordance with the observation of Levell et al., who found no relapse (≥50% of baseline area) in 24 patients with mild to moderate psoriasis within 8 weeks after stopping treatment (12). This prolonged antipsoriatic effect of cyclosporin A after termination of active treatment suggests that intermittent treatment schedules with cyclosporin A should be evaluated.

In accordance with former observations, a slight dose-dependent increase in blood pressure was observed in our study (13). This increase occurred early on, and afterwards the blood pressure remained stable throughout the study and returned to baseline levels within 4 weeks.

Interestingly, there was no general increase in serum creatinine, and serum creatinine was increased by ≥30% above baseline in only 5 patients (3.8%). This may be due to the low dose used in this study and the careful dose adaptation. This observation shows that our patients were at little risk of developing relevant structural alterations of the kidneys. According to the International Kidney Biopsy Register of Cyclosporin in Autoimmune Disease (Psoriasis), the probability of developing morphologic alterations of the kidneys was about 1% in our patients (14).

Former studies have indicated an increase in serum triglycerides (7–10) and in serum cholesterol (7). These studies were neither placebo-controlled nor were the nutritional habits recorded in specific diaries as in our study. By this diet surveillance we were able to take changes in food intake into account when interpreting lipid effects of cyclosporin A. Our study did not confirm a cyclosporin-specific increase in serum triglycerides or cholesterol. The reason for this discrepancy, compared with other studies, may be that in the double-blind, placebo-controlled part of our study, only doses up to 2.5 mg/kg daily were used, which were much lower than the average dose in the studies of Stiller et al. (7) or Grossmann et al. (8). Probably as a consequence of this, the observed lipid changes in our study were much lower than in these studies. Furthermore, we found increases in cholesterol and triglyceride serum levels in the placebo group as well, which may be caused either by biological variation or by the vehicle consisting of olive oil and Laprafil (Pegliol-5-oleat), which has been shown to increase cholesterol and triglyceride levels. Moreover, we excluded patients with relevant baseline hyperlipidemia, perhaps the major risk factor for cyclosporine-induced lipid changes (7, 8). Although our study failed to provide a clear answer about the effects of low-dose cyclosporine on serum lipids, it would not have failed to detect the significant effects reported for high-dose cyclosporine.

REFERENCES

1. Timonen P, Friend D, Abeywickrama K, Laburte C, v. Graffenried B, Feutren G. Efficacy of low-dose cyclosporin A in psoriasis: results of dose-finding studies. Br J Dermatol 1990; 122, Suppl. 36: 33–40.
2. Mahrle G, Schulze HJ, Färber L, Weidinger G, Steigleder GK. Low-dose short-term cyclosporine versus etrinate in psoriasis: improvement of skin, nail, and joint involvement. J Am Acad Dermatol 1995; 32: 78–88.
3. Mihatsch MJ, Wolff K. Report of a meeting: consensus conference on cyclosporin A for psoriasis, February 1992. Br J Dermatol 1992; 126: 621–623.
4. Reitamo S, Erkko P, Remitz A, Lauerma AI, Montonen O, Harluja K. Cyclosporine in the treatment of palmoplantar pustulosis: a randomized, double-blind, placebo-controlled study. Arch Dermatol 1993; 129/10: 1273–1279.
5. Christophers E, Mrowietz U, Henneicke HH, Färber L, Welzel D. Cyclosporine in psoriasis: a multicenter dose-finding study in severe plaque psoriasis. J Am Acad Dermatol 1992; 26: 86–90.
6. Tegelberg-Stassen MJAM, Lammers AM, van Vloten WA, Meinardi MMHM, de Rie MA, Bos JD, et al. Responsiveness of moderate psoriatic skin lesions to 1, 2 or 3 mg/kg/ day cyclosporin A: a multicenter study. Eur J Dermatol 1992; 2: 147–150.
7. Stiller MJ, Pak GH, Kenny C, Jondreau L, Davis I, Wachsmann S, et al. Elevation of fasting serum lipids in patients treated with low-dose cyclosporine for severe plaque-type psoriasis. An assessment of clinical significance when viewed as a risk factor for cardiovascular disease. J Am Acad Dermatol 1992; 27: 434–438.
8. Grossman RM, Delaney RJ, Brinton EA, Carter DM, Gottlieb AB. Hypertriglyceridemia in patients with psoriasis treated with cyclosporine. J Am Acad Dermatol 1991; 25: 648–651.
9. Mrowietz U, Färber L, Bachmann H, Christophers E. Hypertriglyceridemia in patients with psoriasis treated with cyclosporine. J Am Acad Dermatol 1992; 27: 491–492.
10. Krupp P, Monka C. Side-effect profile of cyclosporin A in patients treated for psoriasis. Br J Dermatol 1990; 122, Suppl. 36: 47–56.
11. Fredriksson T, Pettersson U. Severe psoriasis – oral therapy with a new retinoid. Dermatologica 1978; 157: 238–244.
12. Levell NJ, Shuster S, Munro CS, Friedmann PS. Remission of ordinary psoriasis following a short clearance course of cyclosporine. Acta Derm Venereol (Stockh) 1995; 75: 65–69.
13. Feutren G, Abeywickrama K, Friend D, von Graffenried B. Renal function and blood pressure in psoriatic patients treated with cyclosporin A. Br J Dermatol 1990; 122, Suppl. 36: 57–70.
14. Feutren G, von Dach C, Krayenbuehl J, Rodriguez F, von Graffenried B, Nüsch E. International kidney biopsy registry of Sandimmun in autoimmune diseases (psoriasis). Sandoz Pharma Ltd, May 1993. Document No. 603–271.