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CYCLOSPORIN A IN THE TREATMENT OF SYSTEMIC LUPUS ERYTHEMATOSUS: RESULTS OF AN OPEN CLINICAL STUDY

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SUMMARY

In order to define the effects and safety of cyclosporin A (CsA) in systemic lupus erythematosus (SLE), we conducted an open clinical trial with 16 SLE patients. During an observation period of up to 64 months and an average treatment period of 30.3 months, 16 SLE patients, who did not have adequate disease control or experienced side-effects with their previous immunosuppressive therapy, were treated with CsA (3–5 mg/kg). In 3/16 patients, CsA treatment was discontinued because of side-effects, in two because of inefficacy and in 2/16 because of a pregnancy. Four out of 16 patients had a flare of disease during CsA therapy 7, 24, 36 and 40 months after initial response to therapy; one patient stopped CsA treatment after 54 months of successful disease control. Four out of 16 patients are still on CsA. The best beneficial effect was observed in 10 patients with proteinuria, which decreased from 4.7 ± 2.6 to 1.5 ± 1.1 g/24 h. In 3/3 patients with thrombocytopenia and 3/3 patients with leucocytopenia, platelets and leucocytes returned to normal values. The most frequent side-effects were hypertension and deterioration of renal function (3/16) and hypertrichosis (5/16). According to the preliminary results of this study, CsA was well tolerated and able to control disease activity over an extended time period. These data should encourage investigators to perform a multicentre controlled trial on CsA therapy in SLE.

KEY WORDS: Systemic lupus erythematosus, Therapy, Cyclosporin A, Proteinuria.

CYCLOSPORIN A (CsA) is the first immunosuppressive drug that, in contrast to compounds like cyclophosphamide, azathioprine or corticosteroids, does not cause a global inhibition of a wide range of immune functions, but selectively and reversibly inhibits only T-cell-mediated responses [1–4]. Because of its unique selectiveness, CsA has revolutionized the field of organ transplantation and is increasingly used in autoimmune diseases. Up to now, it has been used effectively in type I diabetes, psoriasis, uveitis, rheumatoid arthritis and recently in Crohn's disease and several types of nephropathies [1]. Despite its efficacy, there are only a few controlled trials in autoimmune diseases; also in systemic lupus erythematosus (SLE), there exist only a few reports about trials with this drug, which used either high dosages or had relatively short follow-up periods. This prompted us to start an open study over an extended period of time investigating the efficacy and safety of CsA treatment. Advantages and disadvantages of this therapy are discussed.

PATIENTS AND METHODS

To participate in the study, the patients had to (a) fulfil the 1982 revised criteria of the American College of Rheumatology (ACR) for the diagnosis of SLE [5], (b) have an active disease shown by inadequate disease control or by high doses of steroids necessary for disease control and/or (c) experience intolerable side-effects under their previous immunosuppressive therapy.

The exclusion criteria were as follows: (a) well-controlled disease with <12 mg/day prednisolone equivalent, without immunosuppressive or cytotoxic drugs; (b) life-threatening disease; (c) hypertension, not responding to antihypertensive drugs (defined by systolic pressure >160 mmHg and/or diastolic pressure >100 mmHg); (d) central nervous system (CNS) involvement, shown by infarction, haemorrhage, seizures, psychosis or altered mental function; (e) elevated serum creatinine levels (>1.6 mg/dl, normal 0.4–1.2 mg/dl); (f) treatment with CsA during the last 6 months; (g) additional treatment with nephrotoxic drugs; (h) history of malignancy; (i) uncontrolled infection; (j) malabsorption; (k) hereditary angioedema; (l) pregnancy or lactation; (m) serious, not SLE-related disease of the kidney, CNS, liver or another organ system; (n) non-compliance.

After giving informed consent, 16 patients were enrolled in an open clinical study. CsA was given orally at an initial dosage of 2.5–5 mg/kg/day divided into two daily dosages and reduced when hypertension occurred or creatinine was elevated to $\geq 130\%$ of the starting level. CsA was stopped at creatinine levels of $\geq 150\%$ or creatinine ≥ 2.0 mg/dl in spite of a dose reduction, refractory hypertension, serious infections, malignancy or if the patient wanted to stop treatment. Patients who did not benefit from the therapy within 6 months were permanently withdrawn. CsA serum levels were measured in a monoclonal radioimmunoassay for compliance control. The steroid dose was kept constant for at least 2 weeks until starting CsA

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treatment and then tapered with the aim of reaching a dosage of prednisolone equivalent to ⩽12 mg according to the clinical response. At the beginning and during the course of the trial, patients underwent clinical, laboratory and immunological evaluation. Disease activity according to the ECLAM score was recorded [6] immediately before the initiation of CsA therapy and at defined time points thereafter. In the course of treatment, patients were examined regularly, at least every 3 months, for possible side-effects. Urine and blood samples were collected at each visit for routine laboratory tests like erythrocyte sedimentation rate, blood cell count, liver function tests, levels of creatinine, creatinine clearance, blood urea nitrogen, uric acid, electrolytes, total serum protein and electrophoresis, 24 h protein excretion, urine sediment, immunoglobulins, complement C3, C4, antinuclear antibody (ANA) titres (determined by indirect immunofluorescence on Hep-2 cells), double-stranded (ds) DNA antibody titres (determined by Farr assay and *Crithidia luciliae* assay).

Statistical analysis

Descriptive statistics include means and standard deviation (S.D.). For calculating levels of significance, Student's paired *t*-test was used.

RESULTS

Patient characteristics

During 1989 and 1993, we enrolled 15 women and one man with definite SLE according to the revised ACR criteria in this study. The mean ± S.D. age was 31.8 ± 9.1 yr; the mean ± S.D. disease duration at the beginning of therapy was 6.1 ± 5.0 (range 1–18 yr). Seven patients had cyclophosphamide, three patients azathioprine, five patients chloroquine and 14 patients >12 mg/day prednisolone equivalent prior to CsA therapy without sufficient effect. The mean ± S.D. CsA dosage was 3.8 ± 0.9 mg/kg/day (2.5–5), the mean ± S.D. duration of treatment 30.8 ± 19.7 months, the minimum treatment interval was 6 months, the maximum up to now 64 months. Twelve patients had kidney involvement, five had CNS involvement, three had leucocytopenia and two had thrombocytopenia. In 10 patients with renal involvement, we could observe significant proteinuria (>1 g/24 h). The individual clinical manifestations and previous therapies at enrolment in the study are presented in Tables I and II.

TABLE I
ARA criteria of 16 SLE patients

Patient 1:	renal and CNS involvement, ANA, dsDNS-ab
Patient 2:	discoid and butterfly rash, lung involvement, arthritis, thrombopenia, ANA, dsDNS-ab
Patient 3:	renal and CNS involvement, ANA, dsDNS-ab, anaemia
Patient 4:	renal and CNS involvement, ANA, dsDNS-ab, anaemia
Patient 5:	renal involvement, discoid rash, ANA, dsDNS-ab
Patient 6:	renal involvement, butterfly rash, ANA, dsDNS-ab, anaemia
Patient 7:	renal involvement, butterfly rash, ANA, dsDNS-ab, anaemia, arthritis
Patient 8:	renal involvement, butterfly rash, ANA, dsDNS-ab, arthritis
Patient 9:	renal involvement, discoid and butterfly rash, ANA, dsDNS-ab
Patient 10:	renal involvement, discoid and butterfly rash, ANA, dsDNS-ab, thrombopenia, arthritis
Patient 11:	renal involvement, discoid and butterfly rash, ANA, dsDNS-ab, anaemia
Patient 12:	renal involvement, butterfly rash, ANA, dsDNS-ab, arthritis, oral ulcers
Patient 13:	renal involvement, ANA, dsDNS-ab, arthritis
Patient 14:	CNS involvement, discoid rash, arthritis, thrombopenia, ANA, dsDNS-ab
Patient 15:	renal involvement, ANA, dsDNS-ab, arthritis, thrombopenia, photosensitivity
Patient 16:	renal involvement, ANA, dsDNS-ab, arthritis

During the first 6 months of treatment, the dosages of steroids were tapered to 12 mg prednisolone equivalent per day or less (Fig. 1).

The ECLAM score ± S.D. decreased from 12.18 ± 4.64 to 8.18 ± 5.18 ($P < 0.005$) after 6 months and to 10.19 ± 6.44 ($P = 0.184$, n.s.) after the observation period (Table III). In two patients (patients nos 1 and 2), we stopped treatment after 8 and 6 months because of inefficacy. Fourteen patients have been responders now for 7–64 months. Responders were defined as patients with good disease control, no flare, <12 mg prednisolone per day and no other immunosuppressive drug. In four patients, we stopped treatment with CsA after 7, 36, 24 and 40 months (patients 6, 8, 14 and 16) because of a SLE flare after good initial response, in two other patients (patients nos 11 and 15) after 14 and 60 months of disease control because they became pregnant. Patient 16 with thrombocytopenia and anaemia, both normalized under CsA therapy, became pregnant after 31 months and remained on CsA therapy. All other symptoms of SLE, like proteinuria, fatigue, arthralgias and skin manifestations, had already improved rapidly after initiation of CsA. She had an uncomplicated pregnancy and gave birth to a healthy baby. During pregnancy she required four blood transfusions because of iron deficiency and antihypertensive therapy with beta-blockers. Directly after delivery, her renal function deteriorated during an SLE flare. CsA was stopped, steroid therapy was intensified and creatinine levels returned to normal.

Patient 7 had suffered from SLE since 1983 with arthralgia, alopecia and skin involvement. In 1987, diffuse proliferative glomerulonephritis was demonstrated in a kidney biopsy. In spite of treatment with cyclophosphamide, the patient developed a nephrotic syndrome with a proteinuria of 7.6 g/24 h. After plasmapheresis and CsA therapy, the proteinuria improved to <1 g/24 h. Disease activity was low. After 54 months of good disease control, the patient discontinued CsA treatment; 5 months later, she experienced an exacerbation of disease with an elevation of creatinine up to 3.7 mg/dl.

We observed two patients (patients nos 3 and 4) with refractory hypertension, which forced us to stop CsA after 15 and 12 months; a third patient had an elevation of creatinine to 120% and hypertension. Beside these events, we had no further major side-effects that required termination of CsA therapy. We observed hypertrichosis in five patients, mild paraesthesia in

TABLE II
Demographic data and medication

	Patient															
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Disease duration (yr)	18	2	1	3	6	6	5	1	2	6	8	5	16	7	10	1
Age (yr)	33	53	42	39	47	25	25	29	31	30	32	25	42	30	33	24
Steroids (mg)	20/24*	24/24	16/12	48/6	500/6	500/12	500/9	500/6	15/5	36/3	18/12	36/12	18/6	18/9	48/12	60/4
Chloroquine	+/−	+/+	−/−	−/−	−/−	+/−	+/−	−/−	+/−	+/−	+/−	+/+	+/+	−/−	+/−	−/−
Azathioprine	−/−	+/−	+/−	+/−	−/−	+/−	+/−	−/−	−/−	−/−	−/−	−/−	−	+/−	+/−	−/−
Cyclophosphamide	+/−	−/−	+/−	+/−	+/−	+/−	+/−	+/−	−/−	−/−	−/−	−/−	+/−	+/−	−/−	−/−
Plasmapheresis	−/−	−/−	+/−	+/−	+/−	+/−	+/−	+/−	−/−	−/−	−/−	−/−	+/−	−/−	−/−	−/−
Aspirin	−/−	−/+	−/−	−/−	−/−	−/+	−/−	−/−	−/−	−/−	+/+	−/−	+/−	−/−	−/+	−/+
Ca-channel blockers	−/−	−/+	−/+	−/+	−/+	−/+	−/+	−/+	−/−	−/−	−/−	−/−	−/−	−/−	−/−	−/−
β-Blocker	−/−	−/−	−/+	−/+	−/+	−/+	−/+	−/+	−/−	−/−	−/−	−/−	−/−	−/−	−/−	−/−
Diuretics	−/−	−/−	−/+	−/+	−/−	−/+	−/+	−/+	−/−	−/−	−/−	−/−	−/−	−/−	−/−	−/−
ACE inhibitors	−/−	−/−	−/−	−/−	−/+	−/−	−/−	−/−	−/−	−/−	−/−	−/−	−/−	−/−	−/−	−/−
Antiepileptics	+/+	−/−	−/−	−/−	−/−	−/−	−/−	−/−	−/−	−/−	−/−	−/−	−/−	−/−	−/+	−/−

*Steroid dosage and additional medication at study entry/at the end of the observation period are shown.

TABLE III
Duration and dosage of CsA therapy, reasons for discontinuation, ECLAM score and creatinine levels

	Patient															
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
CsA dosage (mg/kg/day)	3.0	3.0–3.2	5.0–3.5	5.0	5.0–3.5	5.0	5.0–3.4	4.6	2.5	3.0	3.0	3.0	5.0–3.0	5.0	5.0–3.0	3.0
Duration of therapy (months)	8	6	15	12	32	7	54	36	31	36	14	54	64	24	60	40
Reason for discontinuation	Inefficacy	Inefficacy	RR	RR	Creatinine	Flare	Non-compliance	Flare	–	–	Pregnancy	–	–	Flare	Pregnancy	Flare
ECLAM score																
Before	21	11	20	15	16*	13*	8*	8*	8	7	9	11	9	11	9	19
After 6 months	15	10	12	16	9	19	4	2	3	6	6	4	6	11	3	5
At the end of therapy observation	15	10	13	18	13	19	9	11	3	3	6	6	7	24	3	9
Creatinine (mg/dl)																
Before	1.4	1.0	1.4	1.6	1.5	0.8	0.9	1.1	1.2	0.8	0.9	0.7	0.8	1.0	1.0	0.8
After 6 months	1.4	1.0	1.4	1.7	1.6	1.8	1.0	1.2	1.1	0.7	1.0	0.8	0.8	1.0	0.9	0.9
At the end of therapy/ observation	1.4	1.0	1.6	1.8	2.1	1.8	1.0	3.2	0.9	0.8	1.0	0.7	0.9	2.4	0.8	3.2

*Note that patients 5–8 received pulse steroid and plasmapheresis therapy within 2 weeks before CsA was given. In these cases, the ECLAM score represents the disease activity immediately before the start of CsA medication. RR = Riva Rocci.

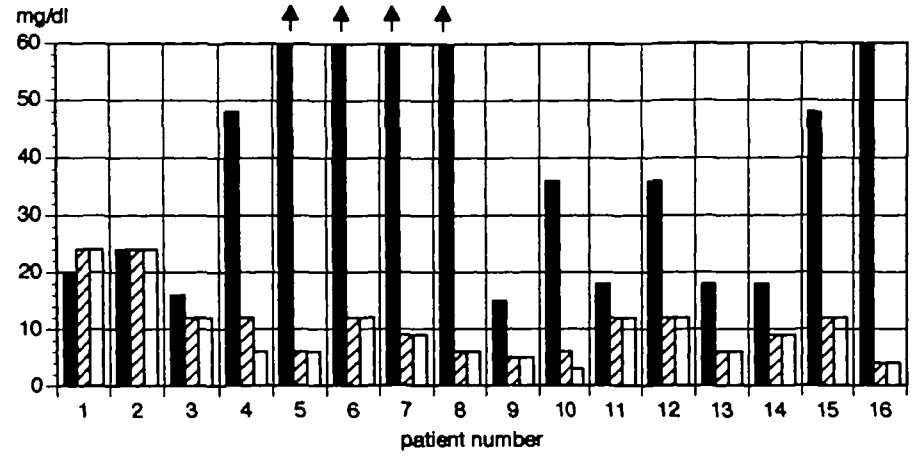

FIG. 1.—Daily prednisolone dosage (mg/day) before (black bars) and after 6 months of CsA therapy (hatched bars), and at the end of the observation period (open bars). Patients 5–8 had plasmapheresis and pulse prednisolone starting 2 weeks before CsA therapy.

three patients, gingival hypertrophy was seen in three patients and initial tremor in two patients.

Laboratory data

Eleven patients had C3 levels below 70 mg/dl. The mean + S.D. levels before treatment and 6 months later were 62.2 ± 25.7 and 85.4 ± 29.7 mg/dl, respectively ($P < 0.05$) (Fig. 2). In all but one patient, C3 levels normalized within this time. After 3 months, leucocytopenia as well as the thrombocytopenia, seen in five patients, had already returned to normal (Fig. 3). In patient 10, previous splenectomy had not

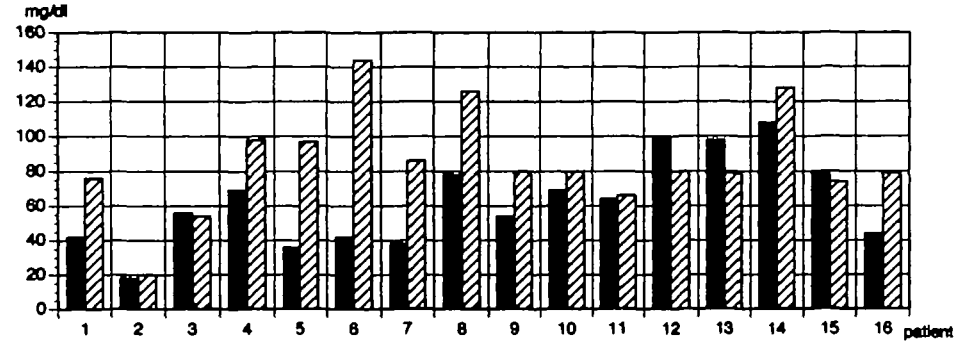

FIG. 2.—Complement C3 serum levels before (black bars) and 6 months after initiation of CsA therapy (hatched bars); $P < 0.05$.

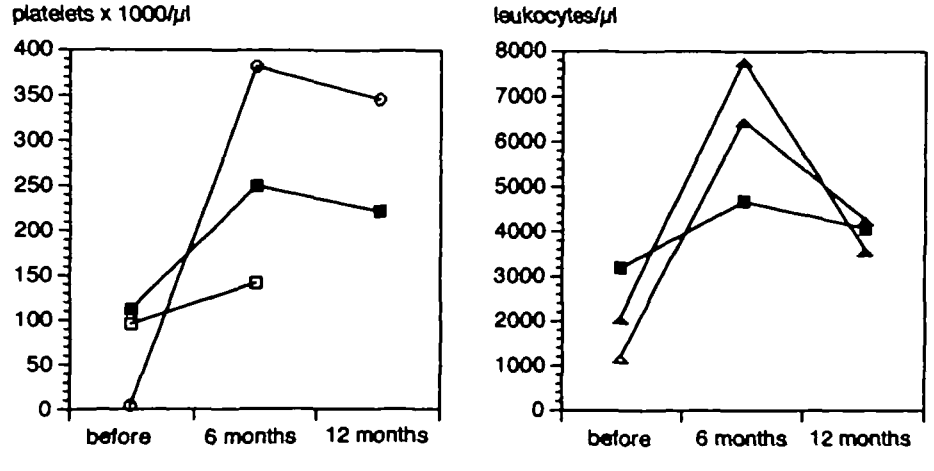

FIG. 3.—Normalization of platelet and leucocyte counts in five different SLE patients during CsA therapy. Patient 2 (open square), patient 10 (open circle), patient 16 (black square), patient 1 (black triangle), patient 3 (open triangle).

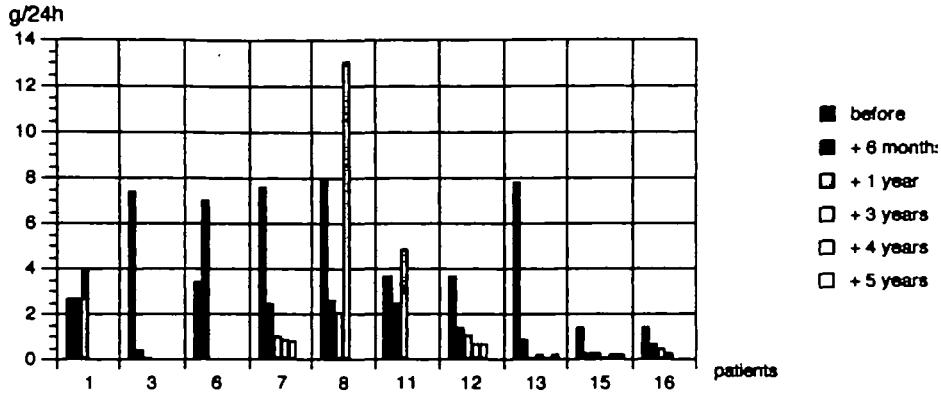

FIG. 4.—Amount of proteinuria in SLE patients before and during CsA therapy; $P < 0.005$.

led to normalization of platelets, but CsA therapy did. The levels of IgG, IgA and IgM remained unchanged and there was no significant change in ANA or dsDNA antibody titres ($P = 0.18$, n.s.).

The decrease in proteinuria in 9/10 patients from 4.7 ± 2.6 to 1.5 ± 1.1 g/24 h (Fig. 4) was impressive ($P < 0.005$) and remained stable except for patients with a disease flare. In all but one patient, serum creatinine did not increase more than 20% of the initial level after 1 yr of CsA. The only patient (no. 6) with a creatinine increase of >100% after 6 months had clear signs of an exacerbation of SLE. Three out of eight patients (nos 8, 14 and 16) with CsA treatment of 2 yr or more had a disease flare with elevation of serum creatinine of >100% because of nephritis and, as a consequence, their therapeutic regimen was changed. A renal biopsy was performed in one of those patients (patient 8) and there were no signs of CsA-induced damage like tubulopathy or arteriolopathy (Table III).

DISCUSSION

A variety of abnormalities of regulatory T-cell functions and of B-cell reactivity have been described in SLE [7]. For many years, the inhibition of T-helper cell function has been a promising therapeutic approach in murine lupus models [8]. CsA reversibly inhibits T-helper cell function by blocking the intracellular signalling cascade of T-cell activation and transcription of T-cell-specific cytokines, such as interleukin-2 or γ-interferon [1, 2].

Trials of CsA application in NZB/W F1 mice could demonstrate a prolongation of life spans of the female and a decrease of DNA antibody production in male mice [9–11]. For human SLE, there exist several uncontrolled studies with high [12–16] and low [17–27] doses of CsA with short observation periods and case reports [20, 24]. Isenberg *et al.* [12, 13] were the first to describe five SLE patients who were treated for up to 7 weeks with 10 mg/kg/day CsA. Treatment was terminated because of various side-effects, including renal toxicity and angioedema. Transient nephrotoxicity was observed by Deteix and Feutren *et al.* [15, 16, 19] in 7/16 patients and hypertension in 7/12 patients treated with a dose of up to 10 mg/kg. In SLE as well as in rheumatoid arthritis, the efficacy of CsA has been seriously compromised by its nephrotoxicity, which was probably related to the high dosages used initially [28–31]. Over the last few years, lower CsA dosages with fewer side-effects but maintained efficacy of the drug were used in autoimmune diseases.

Only in four studies are the results of low-dose CsA treatment for >2 yr described [17, 18, 21–23, 25]. However, in three out of these four studies a combination of various immunosuppressive therapies was used [17, 18, 21, 22, 23]. Miescher and Miescher [17] conducted their first study with 3–6 mg/kg/day CsA in 1985. They treated 20 SLE patients in total, but only eight patients for a period of 6 months or more. They observed a significant rise in serum creatinine during the first 2–4 months, especially in those patients with reduced kidney function. In 15 of 20 patients, they had good disease control; proteinuria ameliorated markedly in all but one patient. In 1987, Miescher *et al.* [17, 18] published additional results in 14 SLE patients treated over a period of 17–42 months with a combination of high-dose fluocortolone and monthly alternating CsA and azathioprine. In 12/14 patients, they observed a significant reduction of the disease activity score. The extent of proteinuria decreased in all patients. Kidney biopsies, performed after 17 months, did not reveal any significant acute or chronic CsA toxicity. In 1988 and 1989, Miescher *et al.* and Favre *et al.* [18, 21, 22] published further data, which did not demonstrate any CsA nephrotoxicity after 2 yr of continuous treatment. Hussein *et al.* [25] observed similar results in five patients during an observation period of 5–35 months. Tokuda *et al.* [27] and Gerkely *et al.* [26] recently published results of a 5 month CsA trial in 10 and six patients. They also could not observe any nephrotoxicity but, consistent with our results, normalization of C3 and improvement of disease activity score [27].

Patients with proteinuria seem to benefit most [17, 21, 22, 26]. In our series, 9/10 patients with proteinuria improved promptly after starting CsA. Until now, it has been uncertain whether this reduction of proteinuria reflects a disease-modifying, immunosuppressive effect of CsA or just a decrease in the

glomerular filtration rate. The pathophysiology of increased serum creatinine, body weight and blood pressure is obviously due to vasoconstriction of the afferent glomerular arteriole [32] and is fully reversible as long as the serum creatinine elevation is $<30\%$ of baseline values [29, 33, 34]; in two patients, we stopped CsA because of severe hypertension that was refractory to treatment with antihypertensive drugs. As demonstrated in a large histopathological study with 192 patients, treated with CsA for various autoimmune diseases with a mean initial dosage of 8.2 ± 2.8 mg/kg/day for 4–39 months, there was no permanent nephrotoxicity in those patients treated with low-dose CsA (<5 mg/kg/day) and without an increase in serum creatinine of $>30\%$ of the patient's baseline value [34]. Fathman and Myers [35] commented that the increase in renal blood flow and the glomerular filtration rate after withdrawal of the vasoconstrictor CsA does not prove any reversal of renal tissue damage. They point out that 9% of heart transplant recipients develop end-stage renal disease after 10 yr of CsA treatment and warn of long-term treatment. In our patients, we observed a sudden deterioration of renal function in one patient after 6 months and in three patients after 2 yr or more. All these patients had signs of disease exacerbation and renal function improved with better control of SLE activity. We conclude, as a preliminary result from our study, that we did not see any chronic progressive deterioration of renal function under long-term CsA therapy (>1 yr). Therefore, CsA might be a valid alternative medication in SLE patients, when other immunosuppressants cannot be used or had been ineffective. In 80% of our patients, we achieved long-term control of disease with low-dose CsA and additional low-dose steroid treatment without major side-effects that necessitated interruption of our treatment protocol. Taking into account the highly variable natural course of this disease, however, only controlled multicentre trials will give us final and valid information to compare the efficacy and toxicity of CsA and other immunosuppressive agents. An advantage of CsA is that it does not influence polymorphonuclear leucocytes or macrophages and therefore carries a low risk of infections [36]. As has been shown for transplant patients, the rate of infections as a side-effect of immunosuppressive therapy, which are responsible for up to 50% of deaths in SLE, might also be reduced in patients with autoimmune diseases on CsA therapy [1]. We did not observe any severe infection during CsA therapy. In spite of its immunosuppressive effects, CsA does not increase the incidence of solid neoplasms like cyclophosphamide [37]; however, the incidence of lymphoma may be increased [38]. Currently, CsA is not recommended for use during pregnancy in autoimmune diseases [39]. However, its lack of teratogenic potency [1, 38], and several case reports about sucessful pregnancies and deliveries [24, 25] in SLE patients on CsA, could make it a potentially useful drug for patients who do not have satisfactory disease control during pregnancy with steroids alone.

Just as CsA has revolutionized the field of organ transplantation, it also has proven effective in some autoimmune diseases. Drug toxicity has become less of a problem with lower initial dosage and early tapering of dose in the event of a significant rise in creatinine. Therefore, CsA might also come to be regarded as a potent immunosuppressive disease-controlling drug in SLE. Similar criteria for CsA medication as those established in an international consensus report for the use in rheumatoid arthritis [39, 40] should be applied in SLE.

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