Q J Med 1998; **91**:573–580

Long-term treatment of lupus nephritis with cyclosporin A

L.S. TAM, E.K. LI, C.B. LEUNG, K.C. WONG, F.M.M. LAI[1], A. WANG, C.C. SZETO and S.F. LUI

From the Department of Medicine and Clinical Therapeutics, and [1]Department of Anatomical and Cellular Pathology, The Chinese University of Hong Kong, Prince of Wales Hospital, Hong Kong

Received 2 March 1998 and in revised form 18 May 1998

Summary

We evaluated the efficacy and safety of long-term treatment with cyclosporin A (CSA) in type IV lupus nephritis. Seventeen patients with biopsy-proven WHO type IV lupus nephritis were enrolled in a prospective, open study. Twelve of the 17 completed 48 months of treatment with CSA and prednisolone. Three patients required the addition of azathioprine, at 12, 38 and 47 months, respectively, for cutaneous disease flare with refractory rashes. One patient was lost to follow-up at 40 months. The mean $\pm$ SD duration of treatment was 43.2 $\pm$ 10.1 months (range 15.7–48 months). A significant reduction of proteinuria and a significant rise in serum albumin were noted 1 month after initiation of treatment. Improvement was maintained throughout the study except for three patients who relapsed with recurrence of nephrotic syndrome. There were no significant changes in serum creatinine level or creatinine clearances throughout the study. Repeat renal biopsy at 12 months following treatment with CSA showed histological improvement, with WHO type II changes in all 17 patients accompanying significant reduction in activity indices. Patients with baseline haemoglobin (Hgb) levels $<$12 g/dl showed significant improvement. Serum C3 and C4 levels were not changed significantly. Corticosteroid-sparing effects were noted. Side-effects included hypertension, gum hypertrophy and mild hirsuitism, but were not serious. Combination therapy using CSA and prednisone is effective and safe for long-term treatment in lupus patients with WHO type IV nephritis.

Introduction

Lupus nephritis is one of the most common visceral manifestations of systemic lupus erythematosus (SLE), and is a major cause of morbidity and mortality. The optimal therapy for treatment of the more aggressive type of nephritis, such as WHO type IV nephritis is still not well established. Ideally, therapy should be effective, with minimal side-effects, and convenient to administer. Many centres worldwide have favoured the NIH regimen with 'pulse' intravenous cyclophosphamide (IVCY) and corticosteroid for patients with type IV nephritis.[1] This regimen, however, was disappointing in our population.[2] In addition, side-effects including premature ovarian failure and infections were common. For this reason, alternative immunosuppressants with less severe side-effects, such as cyclosporin A (CSA), have been used in trials in the treatment of patients with SLE. CSA inhibits T cells, suppresses the production of helper factors inducing overactivity of B cells, and attenuates the immune-mediated injury in SLE patients.[3–5] In animal studies, it has prolonged the survival of diseased mice better than other treatments such as IVCY.[6] Many reports have shown CSA to be effective in treating various disease manifestations in SLE, including lupus nephritis.[7–14] Some studies included patients with different renal histological groups, whilst others did not follow patients for a long enough period to allow assessment of long-term efficacy and outcome. We therefore undertook this study to look at the efficacy and safety of CSA in

Address correspondence to Dr E.K. Li, Department of Medicine and Clinical Therapeutics, The Chinese University of Hong Kong, Prince of Wales Hospital, Shatin, Hong Kong

the long-term treatment of lupus patients with WHO type IV lupus nephritis.

Methods

Patients

All patients fulfilled the American College of Rheumatology 1982 revised criteria for the classification of SLE.[15] The patients were recruited from a combined rheumatology and nephrology out-patient clinic for this prospective, non-randomized study. Enrolled in the study were SLE patients with histologically-proven WHO type IV nephritis who (i) had never received cyclophosphamide or other immunosuppressants; or (ii) had failed to respond to cyclophosphamide or other immunosuppressants as defined by persistent proteinuria of >2 g/24 h and/or serum albumin of <30 g/l, and had been taken off these medications for at least three months prior to the study.

We excluded patients with: (i) uncontrolled infections; (ii) CNS manifestations; (iii) recurrent fever related to the disease; (iv) known neoplastic diseases; (v) an intention to become pregnant during the treatment period; or (vi) previous treatment with CSA.

Treatment regimen

CSA (Sandimmun Neoral, Sandoz) was given initially at 5 mg/kg/day divided into two doses. Dosage was adjusted aiming for trough plasma level of 250–400 μg/l, and was slowly tapered to 2.5 mg/kg/day after 6 months. This dosage was maintained unless there was a relapse. The CSA dosage was reduced by 0.5 mg/kg/day if the serum creatinine level increased by 30% or more from the baseline value. Prednisolone was given at 0.5 mg/kg/day at the start of treatment and then decreased by 2.5 mg/day every 2 weeks until reaching a maintenance dose of 5–10 mg daily after 6 months.

Clinical assessment

All patients were seen twice-monthly in the first 4 months and thereafter monthly, when complete examinations were performed and they were questioned about side-effects of the drugs. At each visit, we recorded body weight, blood pressure, complete blood count, serum creatinine level, serum albumin level, liver function tests, (bilirubin, alanine aminotransferase, aspartate aminotransferase), C3 and C4 complement components, levels of CSA in the blood (measured by radioimmunoassay using monoclonal antibody) and 24-h urine samples tested for protein and creatinine clearance. A second renal biopsy was performed in all patients at 12 months. Renal tissue was prepared according to standard techniques for immunohistological and electron microscope examination. Renal biopsy specimens were classified according to World Health Organization criteria.[16] In addition, specific histological features of activity and chronicity were semiquantitively graded, based on the scheme put forward by the National Institutes of Health (NIH).[17]

Statistical analysis

Results obtained at baseline, 6 and 12 months, and then yearly up to 4 years were used in data analysis, using paired *t* tests unless otherwise stated.

Results

Patients characteristics

Between 1991 and 1993, 17 consecutive patients (16 female, 1 male) with a definite diagnosis of SLE according to the revised ACR criteria were enrolled into the study (Table 1). The mean $\pm$ SD age was 37.0 ± 7.1 years (range 26–52 years). The duration of disease (from the first definitive diagnosis up to the time of CSA treatment) was 73.1 ± 58.1 months (range 1.7–206.5 months). Nine of the 17 patients had failed previous treatment with conventional immunosuppressive drugs such as prednisone with IVCY ($n=7$) or prednisone with azathioprine ($n=2$). At study entry, all patients had WHO type IV nephritis, four patients had elevated serum creatinine levels (>126 μmol/l). Sixteen out of 17 patients had nephrotic syndrome. All 17 patients responded to CSA initially, with improvement in laboratory parameters (Table 2 and Figure 1). Twelve patients (11 female, 1 male) completed 48 months of treatment with CSA. Three patients required the addition of azathioprine at 12, 38, and 47 months, respectively for disease flare with skin rashes refractory to hydroxychloroquine, and one patient was lost to follow-up at 40 months. The mean $\pm$ SD duration of treatment was 43.2 ± 10.1 months (range 15.7–48.0 months) and the mean $\pm$ SD dosage of prednisolone was 19.7 ± 13.5 mg/day (range 5–40). Of the 17 patients, three had a relapse with proteinuria of $\geqslant 3$ g/24 h at 6, 36, 47 months (patients 15, 10 and 9, respectively), while one other patient (patient 11) had an extra-renal flare with cutaneous vasculitis at 22 months, and all four required addition of azathioprine (Table 1). Two of the four patients with elevated serum creatinine levels at study entry had normalization of their serum creatinine at the end of the trial.

Clinical manifestations

Apart from the predominant renal manifestations, no patient had CNS manifestations, leucopenia, throm-

Table 1 Demographic data of patients at entry

Patient	Sex	Age (years)	Disease duration (months)	Treatment*	Pred (mg/day)	Cr (μmol/l)	CrCl (ml/min)	UP (g/day)	Alb (g/l)	AI	CI	Comments
1	F	33	84.4	None	25	111	66	10.3	17	19	5	
2	F	31	44.3	IVCY	50	86	82	3.5	25	11	5	
3	F	36	30.8	IVCY	25	91	77	5.1	28	11	7	
4	F	44	55.3	None	15	51	51	3.8	23	NA	NA	
5	F	30	80.8	None	40	130	58	3.8	27	6	5	Defaulted at 40 m
6	F	50	1.9	None	20	64	131	4.3	32	19	8	
7	F	41	24.1	Aza	5	84	76	6.1	31	5	6	
8	F	36	118.5	Aza	30	173	33	8.2	22	4	5	
9	F	37	51.4	IVCY	5	195	43	5.5	33	8	2	Increased proteinuria at 47 m
10	F	31	156.9	IVCY	5	92	56	3	34	5	5	Increased proteinuria at 36 m
11	F	35	16	None	15	56	148	1.7	36	9	4	Extra-renal flare at 22 m
12	F	35	206.5	IVCY	10	69	99	6.7	34	7	7	
13	F	37	27.1	IVCY	20	118	67	6.8	23	10	2	
14	F	52	98.5	None	5	91	68	3.8	30	13	4	
15	F	32	113.6	None	30	145	51	5.7	24	9	2	Increased proteinuria at 6 m
16	F	43	131.3	IVCY	5	95	76	6.4	18	13	4	
17	M	26	1.7	None	30	118	60	11	22	9	2	

* Previous drug treatment. Aza, azathioprine; IVCY, intravenous cyclophosphamide; Cr, serum creatinine; CrCl, creatinine clearance, UP, urine protein; Alb, serum albumin; AI, activity index; CI, chronicity index.

Table 2 Change in proteinuria and serum albumin during CSA treatment

Duration (months)	0	1	6	12	24	36	48
Urine protein (mean ± SD) (g/24 h)	5.6 ± 2.5	4.4 ± 2.5***	2.4 ± 2.4***	1.7 ± 1.5***	1.1 ± 1.1***	0.9 ± 0.9***	0.7 ± 0.6***
Serum albumin (mean ± SD) (g/l)	27.0 ± 5.8	30.7 ± 4.2***	35.0 ± 4.3***	37.1 ± 3.7***	33.6 ± 4.5**	31.9 ± 5.6*	33.7 ± 3.0***

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

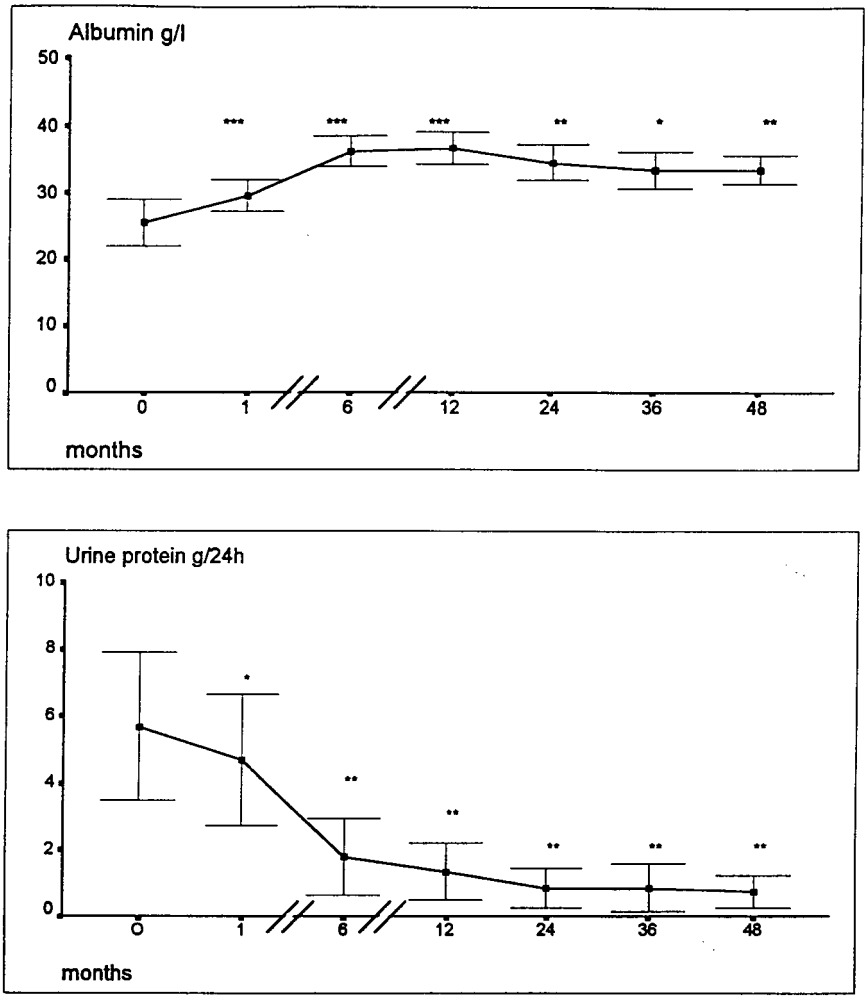

Figure 1. Normalization of serum albumin and 24-h urine protein during CSA therapy. *$p<0.05$; **$p<0.01$; ***$p<0.001$.

bocytopenia, fever, serositis, cutaneous features, vasculitis or arthritis on entry into the study. During treatment with CSA, there were no symptoms elicited that were related to any of the aforementioned organ systems, with the exception of one patient who developed cutaneous vasculitis at 22 months.

Proteinuria

Proteinuria decreased significantly in 16/17 patients from 5.6 ± 2.5 to 0.7 ± 0.6 g/24 h throughout CSA administration (Table 2, Figure 1).

Notably, in as early as 1 month after commencement of CSA, all except five patients responded to treatment with reduction of proteinuria by 20–82% (mean 23%) as compared to their initial base-line level (patients 1, 5, 10, 14, 16). By 6 months, all but two patients (5 and 14) had reduction of proteinuria by 20% (mean 58%) as compared to their initial baseline level. Three patients relapsed with recurrence of proteinuria of $\geqslant 3$ g/24 h: one (patient 15) had an initial response, until proteinuria recurred at 6 months, which persisted until 12 months, when azathioprine was added. The second (patient 9) relapsed at 38 months, while the third (patient 10) at 47 months. One patient (patient 5) was lost to follow-up at 40 months. In those patients with relapse, it was noted that their baseline serum creatinine levels were higher and creatinine clearances were lower than those who showed continuous improvement.

There were no significant differences in the reduction of proteinuria between those who had previously been treated with IVCY or azathioprine, and those who had not.

Serum albumin levels

There were significant increases in serum albumin during CSA therapy detected as early as the first month, with improvement seen throughout CSA therapy (Table 2) (Figure 1).

Renal histology

All 17 patients had renal involvement had diffuse proliferative glomerular lesions, categorized as type

IV in the WHO classification, and all reverted to WHO type II at 12 months. The activity indexes (maximum 24), mean $\pm$1SD at baseline decreased from 10.1 $\pm$4.7 at baseline to 4.9 $\pm$1.8 ($p<0.001$) at 12 months. The chronicity indexes (maximum 12), mean $\pm$1SD at baseline was 5.1 $\pm$0.5 and 5.7 $\pm$0.6 ($p>0.05$) at 12 months. None of the biopsies revealed any features of CSA nephrotoxicity.

Haematology

The mean haemoglobin level did not show improvement in the group overall, except at the 6-months time point. However, in patients with baseline haemoglobin $<$12 g/dl ($n=9$), there were significant improvements after treatment at 6, 12 and 48 months, respectively (Table 3).

Only one patient had leucopenia at entry and their white blood cell count (WBC) normalized by 6 months. No patient had thrombocytopenia at the onset of the study. WBC and platelet count did not show significant changes throughout the treatment period.

Renal function

There were no significant changes in serum creatinine level or creatinine clearance as a group throughout CSA therapy (Table 3).

C3 and C4 levels

There was no change in C3 or C4 levels, except for a marginally higher C3 level noted at 6 months after treatment was started (Table 3).

Steroid-sparing effect and CSA dosage

The dosage of prednisolone and CSA dosage were both decreased during CSA therapy (Table 3).

Side-effects

The most significant side-effect during the study was hypertension, which occurred in all patients, many of whom required two to three anti-hypertensive agents for blood-pressure control. The elevated blood pressure was reversible when dosages of CSA were reduced. Other side-effects included gingival hyperplasia in four patients, nausea in one patient, that did not require discontinuing the drug, and mild hirsuitism in one patient. Paraesthesia or tremors were not reported. No patients had nephrotoxicity which required discontinuation of the drug. In addition, no patients had increase in liver enzymes or episodes of sepsis attributable to treatment with CSA.

Discussion

There are very few reports in the literature on the efficacy of long-term treatment with CSA in SLE.[7–14] Available information suggests a favourable response to CSA in the treatment of SLE.[7–14,18] This includes reduction of disease activity score,[7,8,10,13,14,19] improvement in clinical manifestations such as fever, fatigue, arthralgia, skin lesions, serositis, anaemia, cell count elevations from low to normal, as well as CNS manifestations.[13,14] Improvement in immunological parameters and corticosteroid-sparing effects have also been observed.[14,19] In addition, most reports have shown a marked response, with reduction of proteinuria.[7,9,10,13,14,19,20] However, interpretation of responses to CSA should take into account the problems arising in many of the studies in which combination immunosuppressive therapies were used. In most trials, only small numbers of patients have actually completed the study due to inefficacy, non-compliance or flare of the disease.[7–11,13]

In this study, we were able to observe the effects of CSA on a group of lupus patients with predominant renal disease, as all our patients have WHO type IV nephritis. Unlike most patients in other studies who have multi-organ involvement, our patients lacked most of the extra-renal features, and as such they are a much more homogenous group than those described elsewhere.

We observed significant improvement in Hgb during treatment in those with baseline Hgb $<$12, even though Hgb did not improve in the group overall. Other reports have also shown an improvement in Hgb.[14] While improvements in other blood cell counts, especially neutrophils and platelets, have been observed by some investigators during CSA treatment,[13,14,19] we did not find significant changes in WBCs and platelets during the treatment period. This can be explained by the lack of patients with leucopenia or thrombocytopenia at study entry (except one with WBC 3000).

With regard to the effect of CSA on the kidney, Favre *et al*. observed striking effects with significant reduction of proteinuria (exact values not stated) in only 4/26 patients with membranous glomerulonephritis and nephrotic syndrome.[10] Caccavo *et al*. observed reduction in proteinuria in three patients with membranous glomerulonephritis and one with membranoproliferative glomerulonephritis out of a total of 27.[14] Additionally, in 9/16 patients in the study of Manger, there was a 68% reduction of proteinuria, though the renal histology was not specified,[13] and 1/10 patients with WHO type IV nephritis in study by Tokuda *et al*. showed reduction of proteinuria.[19] In our study a significant reduction of proteinuria occurred as early as 1 month after starting CSA in the majority of our patients, of whom

Table 3 Changes in haemoglobin in all 17 patients as a group, and in anaemic patients (Hgb <12 g/dl), serum creatinine, creatinine clearance, C3, C4, prednisone and CSA dosages

Duration (months)	0	6	12	24	36	48
Haemoglobin (mean $\pm$ SD) g/dl ($n=17$)	11.8 $\pm$ 1.8	12.7 $\pm$ 1.3*	12.5 $\pm$ 1.3	12.5 $\pm$ 2.1	12.3 $\pm$ 2.0	12.3 $\pm$ 2.3
Hgb <12 g/dl (mean $\pm$ SD) ($n=9$)	10.7 $\pm$ 0.6	12.6 $\pm$ 1.4***	11.9 $\pm$ 1.2**	12.0 $\pm$ 1.9	11.5 $\pm$ 2.4	12.4 $\pm$ 1.2**
Serum creatinine (mean $\pm$ SD) µmol/l	104.0 $\pm$ 39.6	109.5 $\pm$ 27.0	108 $\pm$ 19.5	103.5 $\pm$ 38	103.3 $\pm$ 40.6	102.6 $\pm$ 38.0
Creatinine clearance (mean $\pm$ SD) ml/min	73.1 $\pm$ 29.6	65.5 $\pm$ 19.1	69.3 $\pm$ 18.7	75.5 $\pm$ 27.0	74.3 $\pm$ 31.5	74.3 $\pm$ 31.5
C3 (mean $\pm$ SD) mg/l	733 $\pm$ 305	877 $\pm$ 247*	831 $\pm$ 190	841 $\pm$ 223	677 $\pm$ 181	807 $\pm$ 178
C4 (mean $\pm$ SD) mg/l	178 $\pm$ 80	193 $\pm$ 58	182 $\pm$ 58	189 $\pm$ 70	139 $\pm$ 48	180 $\pm$ 77
Prednisolone dose (mean $\pm$ SD) mg/day	19.7 $\pm$ 13.5***	6.1 $\pm$ 2.1***	4.7 $\pm$ 2.3***	4.3 $\pm$ 1.5***	5.3 $\pm$ 4.3***	4.8 $\pm$ 2.6***
CSA dose (mean $\pm$ SD) mg/kg/day	4.8 $\pm$ 0.7	4.0 $\pm$ 0.7	3.1 $\pm$ 0.9	2.0 $\pm$ 0.9	1.6 $\pm$ 0.7	1.9 $\pm$ 0.7

* $p<0.05$; ** $p<0.02$; *** $p<0.005$.

16/17 patients had nephrotic syndrome. The reduction of proteinuria at the end of the trial was 87%, which is far greater than in any of the previous reported studies.[13,14,19] Furthermore, there was a corresponding increase in serum albumin. Serum creatinine and creatinine clearance did not change significantly in our group of patients, which is consistent with the findings of previous investigators.[10,13,14,19] In addition, both the quantitative and qualitative improvement in the second renal biopsy in our patients 1 year after treatment with CSA attests to the efficacy of CSA as a disease-modifying, immunosuppressive agent. Despite the impressive effect on renal biopsy activity scores, the non-significant change in serum creatinine and creatinine clearance in the group overall can best be explained by the presence of established changes in the kidneys, reflected by the chronicity indices which remained unchanged, and additionally, the renal disease being relatively mild, as indicated by the serum creatinine and creatinine clearances at study entry. While Favre *et al.*[10] also noted a significant reduction in activity indexes of renal morphology in 12/26 of their patients after CSA treatment, it is worth noting that their renal histology at study entry was much less homogenous as a group as well as less aggressive compared to ours.[10] Consistent with the findings of others,[8–10,12,13,19,20] we did not observe any CSA nephrotoxicity.

We are unable to comment on changes in immunological parameters such as ANA titres, levels of anti-DNA antibodies and immunoglobulin levels, which were not measured. Discrepancies in results in these parameters have previously been noted in different studies.[7,14,19] Nonetheless, we found some elevation of C3 levels (at 6 months), consistent with the findings of Manger and Tokuda.[13,19] Others have also noted improvement in disease activity[7,13,14,16,19] indicated by SLE scoring devices such as systemic lupus activity measure (SLAM), ECLAM or others.[13,14] It would have been useful had we included such disease activity measurements in our study. Nevertheless, we doubt if there would actually be significant improvement in activity scores, because most of our patients had renal disease without other clinical manifestations of lupus, unlike those described in previous studies.

The observation that significant reduction of corticosteroid dosage was possible during this study is also consistent with those noted in some of the previous studies, even though none of our patients had features of hypercortisolism.[10,14] Hence, CSA may have a significant steroid-sparing effect.

Our study, with 13/17 patients followed up for 4 years, (16 patients for over 3 years), is the longest reported follow-up for patients on CSA that we are aware of, demonstrating the efficacy and safety of CSA in the treatment of SLE. Significant improvement in haemoglobin levels, striking reduction of proteinuria with corresponding elevation in serum albumin, improvement in renal histology without CSA nephrotoxicity, preservation of renal function and absence of infections in all patients during this period of follow-up would suggest CSA is a valid and a less toxic alternative drug for lupus nephritis. The drug would be especially useful in patients in whom other immunosuppressants had been ineffective, or in those who are young and would contemplate childbearing. CSA is also safe when used during pregnancy. The side-effects are quite minor as compared with agents such as cyclophosphamide in terms of risk of infections, tetratogenic potential, infertility, and bladder toxicity.[21–24] Our study was an uncontrolled open trial, and as such, prospective randomized controlled multicentred trials are needed to elucidate the usefulness of this agent more clearly.

References

1. Steinberg AD, Steinberg SC. Long –term preservation of renal function in patients with lupus nephritis receiving treatment that includes cyclophosphamide versus those treated with prednisone only. *Arthritis Rheum* 1991; **34**:945–50.
2. Li EK, Lui SF, Ng PY, Cohen MG. Intravenous cyclophosphamide (IVCY) in diffuse proliferative lupus nephritis (DPLN). *Lupus* 1992 (suppl) **1**:111.
3. Krone M, Leonard WJ, Depper JM, *et al*. Green WC. Cyclosporin A inhibits T cell growth factor gene expression at the level of mRNA transcription. *Proc Natl Acad Sci USA* 1984; **81**:5214–18.
4. Reem GH, Cook LA, Vilcek J. Gamma interferon synthesis by human thymocytes and T lymphocytes inhibited by cyclosporin A. *Science* 1983; **221**:63–5.
5. Palacios R. Cyclosporin A inhibits antigen- and lectin-induced but not constitutive production of interleukin 3. *Eur J Immunol* 1985; **15**:204–6.
6. Berenbaum MC, Brown IN. Dose response relationships for agents inhibiting the immune response. *Immunology* 1964; **7**:65–71.
7. Miescher PA, Miescher A. Combined cylosporin-steroid treatment of system lupus erythematosus. In: Schindler R, ed. *Cyclosporin in autoimmune disease*. Berlin: Springer, 1985:337–45.
8. Miescher PA, Favre H, Chatelanat F, Mihatsch MJ. Combined steroid-cyclosporin treatment of chronic autoimmune disease. *Klin Wochenschr* 1987; **65**:727–36.
9. Miescher PA, Favre H, Mihatsch MJ. The place of CsA in the treatment of connective tissue diseases. *Transplant Proc* 1988 (suppl 4); **20**:224–37.
10. Favre H, Miescher PA, Huang YP, Chatelanat F, Mihatsch MJ. Cyclosporin in the treatment of lupus nephritis. *Am J Nephrol* 1989; **9**:57–60.
11. Bambauer R, Reinelt B, Pees H, *et al*. Therapeutic plasma exchange and cyclosporin A in severe systemic lupus erythematosus. *Transfus Sci* 1989; **10**:147–54.

12. Hussein MM, Mooij JMV, Roujouleh H. Cyclosporin in the treatment of lupus nephritis including two patients treated during pregnancy. *Clin Nephrol* 1993; **40**:160–3.
13. Manger K, Kalden JR, Manger B. Cyclosporin A in the treatment of systemic lupus erythematosus: Results of an open clinical study. *Br J Rheumatol* 1996; **35**:669–75.
14. Caccavo D, Lagana B, Mitterhofer AP *et al*. Long-term treatment of systemic lupus erythematosus with cyclosporin A. *Arthritis Rheum* 1997; **40:**27–35.
15. Tan EM, Cohen AS, Fries JF *et al*. The 1982 revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 1982; **25**:1271–7.
16. Churg J,Bernstein J, Glassock RJ. *Renal Disease. Classification and Atlas of Glomerular Disease*. New York, Igaku-Shoin, 1995; 151–77.
17. Schwartz MM, Lan SP, Bernstein J, Hill GS, Hoolet K, Lewis EJ, and the Lupus Nephritis Collaborative Study Group. Role of pathology indices in the management of severe lupus glomerulonephritis. *Kidney Int* 1992; **42**:743–8.
18. Feutren G, Querin S, Noel LH, *et al*. Effects of cyclosporin in severe systemic lupus erythematosus. *J Pediatr* 1987; **111**:1063–8.
19. Tokuda M, Kurata N, Mizoguchi A, *et al*. Effect of low-dose cyclosporin A on systemic lupus erythematosus disease activity. *Arthritis Rheum* 1994; **37**:551–8.
20. Gerkely P. Cyclosporin therapy of patients with systemic lupus erythematosus. *Orv Hetil* 1994; **135**:2591–5.
21. Drath DB, Kahan BD. Phagocytic cell function in response to immunosuppressive therapy. *Arch Surg* 1984; **119**:156–60.
22. Kahan BD. Cyclosporine. *N Engl J Med* 1989; **321**:1725–34.
23. Austin HA, Klippel JH, Balow JE, *et al*. Therapy of lupus nephritis: controlled trial of prednisone and cytotoxic drugs. *N Engl J Med* 1986; **314**:614–19.
24. Elliot RW, Essenhigh DM, Morley AR. Cyclophosphamide treatment of systemic lupus erythematosus: risk of bladder cancer exceeds benefit. *Br Med J* 1982; **284**:1160–1.