Acta Derm Venereol (Stockh) 1990; 70: 361–365

LETTERS TO THE EDITOR

Changes in Renal Biopsies during Low Dosage Cyclosporin Treatment

Sir,

The efficacy of cyclosporin (Sandimmun®) in treatment of psoriasis (1) has been thoroughly documented and cyclosporin has also been shown to be useful in cases of severe progressive systemic sclerosis (2). But because cyclosporin is a known nephrotoxic drug (3) there is legitimate concern about both short- and long-term toxicity. Due to our concern about potential long-term renal toxicity in spite of a low-dosage regime, we studied pre- and post-treatment renal biopsies in 8 cases (5 psoriatics, and 3 patients with systemic sclerosis). The patients were treated from 6 to 18 months with between 2.5 and 5 mg cyclosporin/kg/day; one patient, however, received 7 mg/kg/day for a period of 2 weeks in order to control her severe psoriasis. The dosages are shown in Table I.

All patients had normal serum creatinine and normal serum creatinine clearances prior to treatment. Five patients (4 psoriatics and 1 scleroderma patient) had increases in serum creatinine to pathological values, which led to dosage reductions. The average increases in serum creatinine are shown in Table I. These increases were all reversible, as were several non-significant increases in blood pressure which did not require treatment. Two patients had moderate changes in their prekidney biopsy; one of these (no. 6) had previously suffered an acute renal failure necessitating dialysis during the course of a severe infectious hepatitis. All 3 scleroderma patients – and possibly 3 patients with psoriasis – showed changes in their renal biopsies which were conceivably related to therapy. The findings developing between the two biopsies were slight to moderate hyalinosis and sclerosis of arterioles, slight to moderate tubular atrophy, and slight focal fibrosis.

One of us (T.S.O.) performed a blind morphometric evaluation of the biopsies using a point count method (4). This investigation showed an increase in the average amount of interstitial connective tissue, from 34 to 44% ($p = 0.03$) using a blind, semiquantitative scoring, a non-significant increase in hyaline arteriolosclerosis (average score increase from 0.9 to 1.9), and in numbers of sclerotic glomeruli (from 3 to 9%).

The findings in the renal biopsies follow the pattern known from the literature from investigations in patients treated with higher dosages of cyclosporin (5–6). None of our biopsies from scleroderma patients had acute arterial or arteriolar lesions characteristic of systemic sclerosis, such as mucoid intimal proliferation or arteriolar fibrinoid necrosis, and no severe intimal fibrosis was found in the arteries.

Table I. *Serum creatinine and kidney biopsies in low-dose Sandimmun treatment*

Pat. no.	Sex/Age	Diagnosis[a]	Dosage (mg/kg)	Serum creatinine			Prebiopsy[b]	Postbiopsy[b]
				Before (mmol/l)	Average during treatment (mmol/l)	Average increase (%)		
1	F/44	S	3	63	78	23	+F	+F +AH
2	M/47	S	3.5	65	77	18	+F	++F++AH
3	F/27	S	2.5–4	78	90	15	++F +AH	++F++AH
4	F/39	P	3.5–5(7)	78	76	0	N	+F
5	F/21	P	2.5–5	76	101	32	N	++F
6	F/42	P	2–3	94	108	14	++F++AH	++F +AH
7	M/37	P	2.5–5	87	127	45	N	++F
8	M/43	P	2–2.5	102	110	7	N	++F +AH

[a]S = Systemic sclerosis. P = Psoriasis.
[b]Blind, semiquantitative evaluation. N = Normal biopsy; F = Fibrosis and tubular atrophy; AH = Arteriolar hyalinosis. + = slight. ++ = moderate.

Tubular atrophy and interstitial fibrosis may occur in systemic sclerosis, but tend to depend on the severity of sclerosis-associated vascular changes. Although we cannot entirely rule out that an increase in interstitial connective tissue in the scleroderma patients could be disease-related rather than treatment-related, this does not appear to be the case for the psoriasis patients. Kidney biopsies in uncomplicated psoriasis have been found normal (7).

The present preliminary study gives no information concerning the clinical relevance of the minor changes we have found hitherto, and does not exclude the use of cyclosporin A in severe psoriasis or severe systemic sclerosis when necessary. But we feel it important that long-term renal toxicity should also be taken into consideration in so-called low-dose cyclosporin therapy of these diseases.

REFERENCES

1. Ellis C, Gorsulowsky D, Hamilton T, et al. Cyclosporin improves psoriasis in a double-blind study. JAMA 1986; 256: 3110–3116.
2. Zachariae H, Zachariae E. Cyclosporin A in systemic sclerosis. Br J Dermatol 1987; 114: 741–742.
3. Mihatsch M, Thiel G, Ryffel B. Cyclosporin-associated nephropathy. In: Schindler R, et al. Cyclosporin in autoimmune diseases. Berlin: Springer Verlag, 1985: 50–58.
4. Gundersen H, Bendtsen T, Korbo L, et al. Some new simple, and efficient stereological methods and their use in pathological research and diagnosis. APMIS 1988; 96: 379–394.
5. Myers BD, Ross J, Newton L, et al. Cyclosporin-associated chronic nephropathy. N Engl J Med 1984; 311: 699–705.
6. Svenson K, Bohman S-O, Hällgren R. Renal interstitial fibrosis and vascular change. Occurrence in patients with auto-immune diseases treated with cyclosporin. Arch Int Med 1986; 146: 2007–2010.
7. Zachariae H, Grunnet E, Søgaard H. Accidental kidney biopsies in psoriasis. Br J Dermatol 1976; 94: 655–657.

Received March 19, 1990.

Hugh Zachariae,[1] Knud Kragballe,[1] H. E. Hansen[2] and T. Steen Olsen[3]
[1]Department of Dermatology, Marselisborg Hospital, University of Aarhus, [2]Department of Nephrology and Internal Medicine C, and [3]University Institute of Pathology, Aarhus Kommunehospital, University of Aarhus, Aarhus, Denmark.