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Preliminary Communication

Pilot trial of FK 506 in the management of steroid-resistant nephrotic syndrome

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Abstract. Seven patients with steroid-resistant nephrotic syndrome were treated with FK 506 monotherapy. Four patients were children with focal sclerosing glomerulonephritis (FSGS). Three of these had evidence for chronic progressive renal disease consisting of interstitial fibrosis and tubular atrophy on pretreatment renal biopsies. Two patients had also failed cyclosporin A (CsA), two cyclophosphamide, and one chlorambucil prior to treatment with FK 506. Three patients were adults with mesangial proliferative, membranoproliferative, and membranous glomerulonephritis. Three patterns of response were noted: (1) a reduction in proteinuria to normal levels; (2) partial response (50% reduction) or; (3) no improvement. All patients except one experienced at least a 50% reduction in protein excretion at some time during FK 506 therapy. Two of the children and one adult reduced protein excretion to essentially normal values. One patient had no sustained reduction in protein excretion and is considered to be a treatment failure, although her protein excretion was approximately 50% of pretreatment values intermittently. The drug was generally well tolerated. The most common side-effect was nephrotoxicity, which was reversible. These encouraging results suggest that FK 506 monotherapy may be effective in controlling the proteinuria of some patients with steroid-resistant nephrotic syndrome. The use of this drug may extend our understanding of the role of T lymphocytes and cytokines in the pathogenesis of glomerulonephritis. Further study of this agent in a larger population of patients is warranted.

Introduction

Steroid-resistant nephrotic syndrome (SRNS) is a group of disorders with diverse histological findings, which are by definition resistant to corticosteroids and to other therapy as well [1,2]. In most patients progression to end-stage renal disease is the ultimate outcome. Recently protocols using high-dose intravenous corticosteroids have shown some promise but continue to be limited by the complications of these agents and limited success in reversing proteinuria [3–5]. The use of other immunosuppressants such as cyclophosphamide and chlorambucil have resulted in remissions in some patients but were also met with limited success, particularly in adult patients, as one-third of childhood FSGS patients respond to either prednisone and/or cyclophosphamide/CsA [6].

Recently cyclosporin A has been used to treat patients with nephrotic syndrome [6–11]. Since many forms of idiopathic nephrotic syndrome may be immunologically mediated with derangements in T lymphocyte function and the abnormal production of cytokines, the use of a T-cell-specific inhibitor may have obvious advantages [12]. The rationale for using cyclosporin A in nephrotic syndrome has recently been summarized by Borel [13]. The most compelling argument for the use of this class of agents has been the ability of cyclosporin A to prevent experimental forms of glomerulonephritis. Unfortunately cyclosporin has been least effective in patients with steroid-resistant nephrotic syndrome [8,9]. FK 506, a new immunosuppressant agent is more potent than cyclosporin on a molar basis and may cause less drug-induced hypertension.

Cyclosporin A and FK 506 both bind to a similar class of cytosolic binding proteins (cis–trans peptidyl-prolyl isomerase, collectively termed immunophilins) [14]. Since FK 506 also selectively inhibits $CD4^+$ T helper lymphocyte activation and proliferation, we have begun a pilot trial of FK 506 in the management of steroid-resistant nephrotic syndrome. We have previously reported our encouraging experience with FK 506 in two patients with steroid-resistant nephrotic syndrome [15]. In this report we will update and expand our experiences and observations.

Subjects and methods

Seven patients with steroid-resistant nephrotic syndrome were treated with FK 506 monotherapy (Table 1). This study

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Table 1.

Patient	Age start FK 506 Age (disease onset)	Sex	Histology	Prior therapy	Response to prior therapy
1	2.5 (1.5)	Male	FSGS	Pred, Cyphos	No improvement
2	40 (39)	Male	Mes. Prolif. GN	Pred	No improvement
3	12 (9)	Female	FSGS	Pred, ChlorA, CsA	Partial response to CsA, later refractory
4	13 (12)	Male	FSGS	Pred, CsA	(same as no. 3)
5	2.5 (1.5)	Male	FSGS	Pred, Cyphos, CsA	(same as no. 3)
6	20 (17)	Male	MPGN	Pred	No improvement
7	32 (30)	Male	Membranous GN	Pred	No improvement

GN, glomerulonephritis; FSGS, focal sclerosing GN; MPGN, membranoproliferative GN; CsA, cyclosporin A; Cyphos, cyclophosphamide; ChlorA, chlorambucil; Pred, prednisone.

was approved by the institutional review boards of the Pittsburgh Children's and Presbyterian–University Hospitals. Appropriate informed consent was obtained from each patient or his or her guardian. All patients except patient nos 2 and 4 clearly had idiopathic nephrotic syndrome. Both of the latter patients had documented additional illnesses which might have been associated with glomerulonephritis. Four patients with FSGS were children with age range of 2.5–13 years. Three were adults with age range of 20–40 years. Six were male and one was female. Baseline renal biopsies were performed in all patient prior to initiating FK 506 therapy. Three of the four children with FSGS had interstitial fibrosis, and tubular atrophy on pretreatment biopsies, suggesting chronic renal insufficiency. The adults had more disparate histological findings.

All patients in this series had been treated with corticosteroids, primarily oral prednisone, prior to entry into this study. In addition to corticosteroids, two of the four patients with FSGS had been unsuccessfully treated with cyclophosphamide, one patient with chlorambucil and two with cyclosporin A. Patient no. 1 had been treated with cyclophosphamide (2 mg/kg/day) for only 2 days prior to starting FK 506. Corticosteroids were discontinued in all patients except patient no. 3 in whom 5 mg prednisone every other day was continued. In all cases prednisone was tapered before stopping the drug.

FK 506 was administered orally in all patients with an initial dose of 0.15 mg/kg/day given twice daily. The dosage of FK 506 was adjusted based upon drug level, renal function, and overall clinical state. Approximate desirable drug levels were values greater than 0.5 and less than 2.0 ng/ml. The minimal detectable level for this assay is 0.1 ng/ml.

Adequate 24-h collections were confirmed in adults by accepting only specimens with creatinine excretions of at least 15 mg/kg/day in females and 20 mg/kg/day in males. Foley catheters were placed in all children.

Results

FK 506 reduced 24-h protein excretion, reaching nearly 50% of pretreatment values in all patients (Table 2, Figures 1, 2). The maximal benefit occurred in most patients within the first 2 months. The treatment duration on FK 506 ranged from 5 to 14 months.

Twenty-four-hour protein excretion decreased to subnephrotic range in four patients (nos. 1, 2, 5, and 7) after 3 months of therapy (Table 2, Figure 2). In patient no. 6, after 6 months of FK 506, protein excretion decreased from 8.3 g to 1700 mg/day. FK 506 therapy was temporarily discontinued by two patients (nos 1, and 2), which resulted in prompt relapses of proteinuria to pretreatment levels (Figure 3). The proteinuria corrected within days after reinstituting therapy in patient no. 1. In patient no. 2 FK 506 was reinstituted at half the dose prior to stopping the drug at the patient's own request. Improvement in proteinuria was attained at this subtherapeutic dosage but he has again stopped the drug, with a full recurrence of nephrotic syndrome.

One patient (no. 3) with FSGS experienced no sustained reduction in protein excretion, although values reached approximately half of the pretreatment values on several occasions. FK 506 was discontinued after 5 months of therapy. Serum creatinine (SCr) which had increased during therapy, declined to its pretreatment levels. After FK 506 was stopped cyclophosphamide was begun but the protein excretion returned to pretreatment levels (approximately 9 g/day).

In another patient (no. 4), FK 506 concentrations only transiently increased within the therapeutic range. Concerns about compliance have prevented progressive dosage increases; however, this 13-year-old boy with sickle-cell anaemia experienced a decline in protein excretion from approximately 27 to 5.3 g.

Consistent reductions in protein excretion to very low or undetectable values occurred in three patients (nos 1, 2, and 5): two children with FSGS and one adult with mesangial proliferative glomerulonephritis (Figure 1). Both patients with FSGS had interstitial nephritis and tubular atrophy on pretreatment renal biopsies, although serum creatinine did not reflect this. Patient no. 5 had failed to respond to corticosteroids, cyclophosphamide, and cyclosporin A. In the two children, the reduction in protein excretion was dramatic, falling to their nadir within 1 month after starting FK 506.

Control of oedema was improved in all patients when protein excretion declined. This clinical benefit was apparent even in patients without a significant increase in serum albumin. The most dramatic effects were seen in the three patients with near normal

Table 2.

	Patient Pre-treatment				After 3 months of PK 506			
	U-protein (mg/day)	Creat. (μmol/l)	Chol. (mM/l)	Albumin (g/l)	U-protein (mg/day)	Creat. (μmol/l)	Chol. (mM/l)	Albumin (g/l)
1	1400	35.4	16.3	27	10	26.5	4.4	39
2	8000	70.7	9.3	24	600	106	6.5	35
3	8300	150.3	10.6	13	4500	114.9	22.1	18
4	26950	44.2	11.7	23	5300	70.7	10.6	26
5	3352	26.5	11.4	16	398	17.7	4.7	33
6	8300	176.8	7.8	24	4195	247.5	5.4	35
7	6528	114.9	6.5	23	1500	194.5	3.9	39

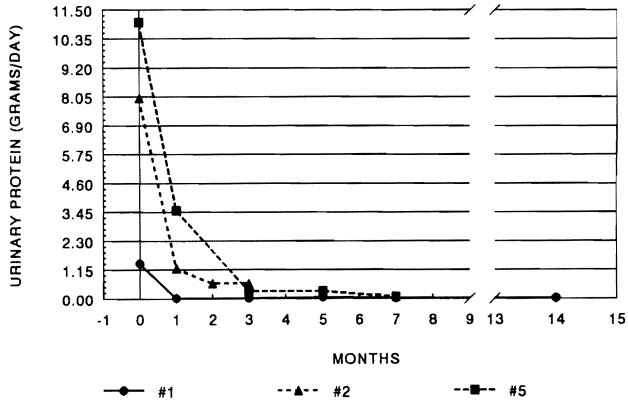

Fig. 1. Urinary protein excretion in three patients with complete remissions of nephrotic syndrome under FK 506. Values at time zero equal pretreatment determinations. Data on patients no. 1 and no. 2 represent only data while patients were taking the drug, values from the periods of drug withdrawal have been omitted.

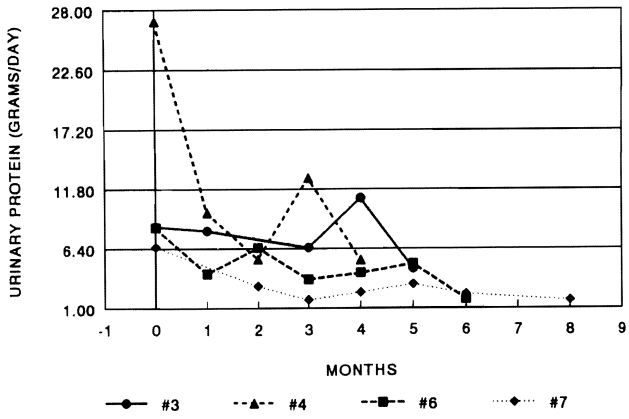

Fig. 2. Urinary protein excretions in four patients with partial responses to FK 506 therapy. Values at time zero equal pretreatment determinations. Therapeutic levels were seldom attained in patient no. 4.

treatment protein excretions, but a benefit was also apparent in those with less significant reductions in proteinuria. This clinical improvement was not due to increased diuretic dosage, since this had been reduced, not increased.

Creatinine clearance decreased in all patients after

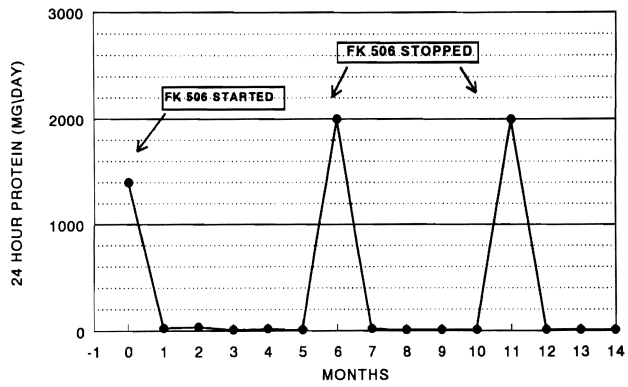

Fig. 3. Urinary protein excretion in patient no. 1. FK 506 was discontinued twice resulting in recurrence of the nephrotic syndrome. The proteinuria resolved within days of reinstituting the drug.

instituting FK 506. Renal function returned toward pretreatment values when the dosage was reduced or the drug was stopped (Figure 4). A renal biopsy was repeated in patient no. 1 after 7 months of therapy. This patient, with FSGS, had interstitial nephritis and tubular atrophy on the pretreatment biopsy. Repeat biopsy revealed no worsening of interstitial nephritis or glomerulosclerosis; however, there was no improvement in glomerular pathology. Areas of foot process fusion persisted on electron-microscopy.

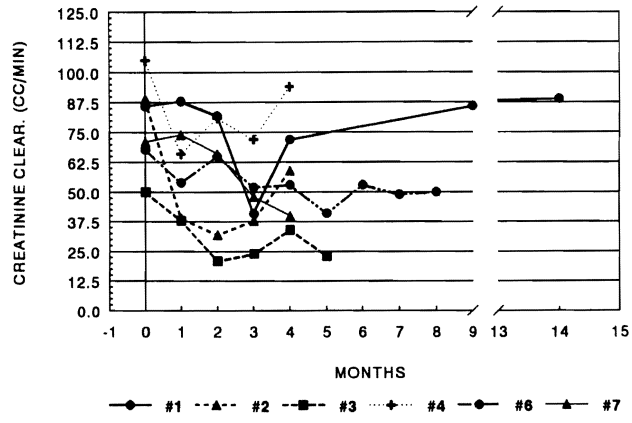

Fig. 4. Creatinine clearance for all patients. In children values are expressed as cc/min./1.73 m^2.

FK 506 was generally well tolerated. The most common side-effect was tremor, which occurred in the three adults but not in the children. The tremor resolved after reduction in FK 506 dosage and was considered to be evidence of overdosage. Vivid dreams were noted in two adult patients and diarrhoea was reported in one child and one adult. Hyperkalaemia responsive to fludrocortisone (0.1 mg twice per day) developed in two patients. Hypertension developed in one patient and worsened in a second after fludrocortisone was started. None of the patients developed hyperuricaemia, but one developed hypomagnesaemia. Hyperglycaemia was not apparent in any patient. Two patients have permanently discontinued therapy: patient no. 3, who was termed a failure, and patient no. 2. The latter patient, who had stopped the drug earlier, moved to another country, and changed his primary physician who substituted a non-steroidal anti-inflammatory agent for FK 506. No therapeutic improvement was apparent after 1 month of this new therapy.

Discussion

This pilot trial demonstrate that FK 506 can be effective in reducing proteinuria in some patients with steroid-resistant nephrotic syndrome. Three patterns of response seemed apparent: (1) rapid decline in proteinuria to near normal values; (2) approximately 50% reduction in proteinuria; (3) no improvement.

The mechanism of the antiproteinuric effect of FK 506 is probably multifactorial and may even vary according to histological classification. Potential modes of action of FK 506 include inhibition of T-cell-mediated lymphokine production, improvement in glomerular basement membrane charge permselectivity independent of lymphokine production, correction of a fundamental immunological defect, or a reduction in GFR. The amelioration of proteinuria, however, is probably due to reversible changes in the permselectivity of the basement membrane rather than a fundamental correction of an immunological defect. Evidence for this includes the prompt return of proteinuria upon discontinuation of the drug and the lack of demonstrable improvement on follow-up renal biopsies. A reduction in GFR seen in most patients may play a role. However, in some patients the reduction in proteinuria appears greater than that expected for the degree GFR decline. This is most apparent in patients with the best results. The proteinuria remained very low even when FK 506 dosage had been tapered and creatinine clearance was very close to pretreatment levels. In trials with cyclosporin A similar to this series, the histological abnormalities persisted or worsened and proteinuria rapidly returned when the drug was stopped [8–10].

Recent reviews of cyclosporin A therapy for nephrotic syndrome suggests that steroid-resistant nephrotic syndrome is most refractory to this agent [8,9]. The response in patients with FSGS and interstitial fibrosis has prompted Meyrier to conclude recently that cyclosporin A is not indicated in FSGS with interstitial fibrosis [16]. In his study only 22% of patients with FSGS improved, and in patients with pre-existing interstitial nephritis this lesion progressed rapidly under cyclosporin therapy. In our series three of the four patients with FSGS had interstitial nephritis on pretreatment biopsies. Given our small sample size and the preliminary nature of this report, we cannot determine whether FK 506 will be more beneficial in patients with histological evidence of chronic renal disease than cyclosporin A. The complications of FK 506 therapy were, in general, not serious and easily reversed. The spectrum of side-effects with FK 506 has been previously reported by our group [17–20]. Acute nephrotoxicity represented by a reversible reduction in glomerular filtration (GFR) was the most frequent and serious. These studies in liver, kidney and heart transplant patients treated with FK 506 suggest that reversible elevations in serum creatinine are common and related to drug dosage and route of administration.

Hyperkalaemia is a common complication of FK 506. The pathogenesis is unknown but it has generally responded to fludrocortisone in the setting of transplantation. Likely mechanisms include resistance to aldosterone in renal epithelial cells or aldosterone deficiency, which may appear similar to type IV renal tubular acidosis.

The starting dose of FK 506 is now considered to be excessive. We have now reduced the initial dose to approximately 0.1 mg/kg/day in an attempt to minimize the nephrotoxicity while maintaining the drug's usefulness. The minimal effective dose has not been determined in most patients to date, so we cannot determine whether the persistent depression in renal function is a result of reversible FK 506 nephrotoxicity or the natural progression of renal failure. Since all of the histological lesions treated in this study tend to progress, future studies will require larger patient populations and extensive follow-up to answer this complex question.

FK 506, like cyclosporin A, has not been universally effective in controlling proteinuria. This study is a pilot study and not structured to determine the relative efficacy of FK 506 compared to cyclosporin A. This study does suggest that some patients are highly responsive to this T-cell-directed (cytokine) therapy, which may support the role of these factors in the pathogenesis of glomerulonephritis. It further uncovers patients with partial or no improvement from this therapy. In these patients other factors such as B lymphocytes, cytokines not directly affected by immunophilin-directed therapy, adhesion molecules, or eicosanoids, may play more important roles in sustaining the proteinuria and structural abnormalities. In Heymann nephritis different pathogenetic mechanisms dominate the induction and maintenance phases of this disease. Similar differences may occur in various forms of human glomerulonephritis. Future studies using anti-B-cell agents or monoclonal antibodies to adhesion molecules in combination with immunophil-

in-directed therapy may be more efficacious in these refractory patients.

In conclusion, FK 506 appears to be effective in controlling the proteinuria of steroid-resistant nephrotic syndrome in this pilot trial. The major important side-effect of FK 506 is nephrotoxicity, which appears to be reversible. Further work is needed to determine the minimal effective dose, the drug level required to induce and maintain a remission, and which histological groups are most likely to benefit. The potential benefit of combination therapy using drugs with different modes of action should be considered.

References

1. Brodehl J. Conventional therapy for idiopathic nephrotic syndrome in children. *Clin Nephrol* 1991; 35: s8–15
2. Ponticelli C, Passerini P. Conventional treatment of idiopathic nephrotic syndrome and membranous nephropathy in adults. *Clin Nephrol* 1991; 35: s16–s21
3. Meyrier A, Simon P. Treatment of corticoresistant idopathic nephrotic syndrome in adult: minimal change disease and focal segmental glomerulosclerosis. *Advances in Nephrology*. Yearbook Medical Publishers, Chicago, 1988, 127–150
4. Korbet SM, Schwartz MM, Lewis EJ. The prognosis of focal segmental glomerular sclerosis of adulthood. *Medicine* 1986: 65: 304–311
5. Pei Y, Cattran D, Delmore T, Katz A, Lang A, Range P. Evidence suggesting under-treatment in adults with idiopathic focal segmental glomerulosclerosis. Regional glomerulonephritis registry study. *Am J Med* 1987; 82: 938–944
6. Meyrier A. Collaborative group of the Societe de Nephrologie. Ciclosporin in steroid resistant nephrosis. *Am J Nephrol* 1989; 9 [Suppl]: 65–71
7. Rao TKS, Friedman EA. Prospective trial of cyclosporine in refractory nephrotic syndrome in adults: preliminary findings. *Kidney Int* 1987; 31: 214
8. Meyrier A. Treatment of glomerular disease with cyclosporin A. *Nephrol Dial Transplant* 1989; 4: 923–931
9. Ponticelli C, Rivolta E. Ciclosporin in minimal change glomerulopathy and focal segmental glomerulosclerosis. *Am J Nephrol* 1990; 10 [Suppl]: 105–109
10. Tejani A, Butt K, Trachtman H, Suthanthiran M, Rosenthal C, Khawar MR. Cyclosporine A induced remission of relapsing nephrotic syndrome in children. *Kidney Int* 1988; 33: 729–734
11. Niaudet P, Broyer M, Habib R. Treatment of idiopathic nephrotic syndrome with cyclosporin A in children. *Clin Nephrol* 1991; 35: s31–s36
12. Wardle EN. Cytokine growth factors and glomerulonephritis. *Nephron* 1991; 57: 257–261
13. Borel JF. Mechanism of action of cyclosporin A and rationale for use in nephrotic syndrome. *Clin Nephrol* 1991; 35: s23–s30
14. Schrieber SL, Lui J, Albers MW, Karmacharya R *et al.* Immunophilin–ligand complexes as probes of intracellular signaling pathways. *Transplant Proc* 1991; 23(6): 2839–2844
15. McCauley J, Tzakis AG, Fung JJ, Todo S, Starzl TE. FK 506 in steroid resistant focal sclerosing glomerulonephritis of childhood. *Lancet* 1990; 335: 674
16. Meyrier A. Adult steroid resistant nephrotic FSGS is not an indication for CsA treatment. *J Am Soc Nephrol* 1990; 1: 311
17. Shapiro R, Fung FF, Jain AB, Parks P, Todo S, Starzl TE. The side effects of FK 506 in humans. *Transplant Proc* 1990; 22 [Suppl]: 35–36
18. McCauley J, Fung J, Jain A, Todo S, Starzl TE. The effects of FK 506 on renal function after liver transplantation. *Transplant Proc* 1990; 22[Suppl]: 17–20
19. McCauley J, Takaya S, Fung F *et al.* The question of FK 506 nephrotoxicity after liver transplantation. *Transplant Proc* 1991; 23: 1444–1447
20. Starzl TE, Adu-Elmagd A, Tzakis A, Fung JJ, Porter KA, Todo S. Selected topics on FK 506 with special references to rescue of extrahepatic whole organ grafts, transplantation of forbidden organs, side effects, mechanisms and practical pharmacokinetics. *Transplant Proc* 1991; 23: 914–919

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