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Tacrolimus rescue therapy for cyclosporine-induced nephrotoxicity

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Abstract Following renal transplantation, the long-term use of cyclosporine can cause nephrotoxicity. This small study of ten patients looks at the effects of tacrolismus rescue therapy over a 6-month period. After conversion to tacrolismus, renal function improved in seven pateints, progressive graft dysfunction slowed and almost stabilized in two patients, and, in the remaining patient, deterioration continued and hemodialysis treatment was initiated at the end of the study period. A greater number of patients and a longer follow up are necessary to confirm these initially impressive results.

Key words Cyclosporine-induced nephrotoxicity · Tacrolismus rescue therapy · Arteriolopathy · Renal transplantation

Introduction

Nephrotoxicity is one of the most important side effects associated with long-term cyclosporine (CSA) treatment, and has become an important factor for long-term graft failure [1]. Until recently, the only available option was to withdraw the CSA or to reduce the daily dose. This approach has the potential to reverse the histological changes associated with CSA toxicity, but increases the risk of acute rejection [2]. The mechanism of CSA-induced arteriolopathy remains poorly defined. It has been suggested from experimental models that TGF-β production is enhanced by CSA [3]. In addition, increased renal tubular expression of this cytokine in human allografts correlates with CSA toxicity [4].

Tacrolimus (FK506), which has a mode of action very similar to CSA, has been shown to be an effective and well-tolerated immunosuppressant in solid organ transplantation. It has been reported that the change from CSA to tacrolismus can reverse the renal function deterioration secondary to acute CSA nephrotoxicity [5] as well as the CSA-associated hemolytic–uremic syndrome [6]. However, there are no data available on the outcome after conversion to tacrolimus in patients who have developed arteriolopathy and progressive graft function impairment due to long-term CSA treatment. The aim of the study was to investigate if the conversion from CSA to tacrolimus could improve the progressive renal dysfunction in patients with histological changes indicative of CSA-induced nephrotoxicity.

Patients and methods

Ten cadaveric kidney transplanted patients with progressive renal impairment were included in the study. At the start of the study, patients had been transplanted for more than 1 year and had been receiving CSA, prednisone, and azathioprine for the entire post-transplantation period. Due to progressive elevation in serum creatinine, a percutaneous graft biopsy was performed. According to the Banff criteria [7], patients were diagnosed with CSA-induced nephrotoxicity. The typical hyaline afferent arteriole thickening was observed in all of the cases. After the time of histological diagnosis, the CSA dose was reduced for 3 months with CSA levels lowered to a mean of 118 ± 24 ng/ml; however, renal function continued to decline in all patients. Conversion to oral tacrolimus therapy (initial dose: 0.15 mg/kg per day) was done the day after stopping CSA treatment. Tacrolimus doses were subsequently adjusted to maintain whole blood trough levels between 5 and 10 ng/ml. The doses of azathioprine and prednisone remained the same. Serum creatinine data during the 6 months before and after conversion to tacrolimus were used to calculate the 1/creatinine (1/Cr) versus

Table 1 Cyclosporine (CSA) nephrotoxicity criteria, according to Banff classification, observed on allograft biopsy

CSA-associated changes		Number of patients
Tubular	Isometric vacuolization	1
	Eosinophilic inclusions	–
	Microcalcification	3
Vascular	Nodular hyaline afferent arteriole thickening (mild/moderate)	6/4
	Thrombotic microangiopathy	–
	Occlusive arteriolar change	–
	Medial degeneration	–
Interstitial	Striped or patchy fibrosis	3
Glomerular	Sclerosis or ischemic collapse	3
	Juxtaglomerular apparatus hyperplasia	1

Table 2 Initial and final serum creatinine, creatinine clearances and results of 1/Creatinine vs time slopes obtained during the 6 months before and after conversion to tacrolimus (*HD* Hemodialysis)

Creatinine (mg/dl)		1/Creatinine slope		Creatinine clearance (ml/min)	
Pre	Post	Pre	Post	Pre	Post
8	5.2	–0.0229	+0.0095*	9.6	14.4
5.4	3.1	–0.0218	+0.0181*	18	32.4
3.1	2.3	–0.0032	+0.0154*	15	36.7
5	4.5	–0.0168	+0.0034*	18.6	20
2.7	2.8	–0.0540	–0.0014*	27	24.5
4.7	HD	–0.0070	–0.0083	17.9	HD
4.2	2.9	–0.0098	+0.0942*	10.4	27
2	1.5	–0.0249	+0.0089*	38.1	58.1
2.8	2.2	–0.0450	+0.0062*	29	44
2.8	2.9	–0.0712	–0.0067*	28.9	37

$P > 0.05$ by break point analysis

time slope. In addition, creatinine clearance, serum urea, glucose, triglicerides, cholesterol, ALT, hemoglobin, and hematocrit were measured during the study period. Two patients consented to an additional kidney transplant biopsy which was performed at the end of the study period to observe histological changes.

Statistical analysis

Results are shown as mean ± SD. To determine in each patient if, after conversion to tacrolimus, there was a variation in progressive graft dysfunction, the 1/Cr versus time slope obtained during the 6 months before and after conversion was analyzed by the break point test [8]. In addition, both before and after conversion 1/Cr vs time slopes were obtained separately and their means compared by the paired Student's *t*-test.

Results

At the moment of histological diagnosis of CSA nephrotoxicity, patients had been transplanted for 50.8 ± 34.5 months (range 13–120). Different biopsy findings suggestive of CSA toxicity and severity score, according to Banff scheme, are shown in Table 1.

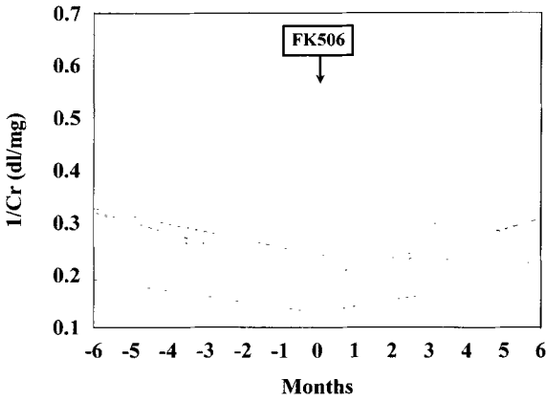

Fig. 1 1/creatinine (*1/Cr*) vs time slopes during the 6 months before and 6 months after the immunosuppressive change from cyclosporine (CSA) to tacrolimus (*FK506*) in ten patients diagnosed with CSA-induced nephrotoxicity

Tacrolimus rescue therapy improved the 1/Cr versus time slope in all but one of the ten patients. In seven of them, renal function improved throughout the study period and, in the other two, the progressive graft dysfunction while they were on CSA treatment became slower and almost stabilized after conversion. In the remaining patient, renal impairment continued and hemodialysis treatment was initiated at the end of the study period (Fig. 1). There were significant differences between means of both 6 months before and after tacrolimus 1/Cr versus time slopes: -0.0257 ± 0.024 versus $+0.0139 \pm 0.029$ ($P < 0.01$). The absolute values of slopes, initial and final serum creatinine, and creatinine clearances in each patient are shown in Table 2.

Histopathological examination of the second biopsy performed in two patients showed that CSA-induced arteriolopathy had disappeared in one patient and declined in severity from grade 2 to grade 1 in the other. However, other findings such as tubular atrophy, interstitial fibrosis and intimal thickening did not change or progressed. No acute rejection episodes were observed after immunosuppressive conversion. Tacrolimus was well tolerated and no side effects were observed.

Discussion

Nephrotoxicity is a recognized adverse effect in patients treated over long periods with CSA. In addition to kidney transplanted patients, elevated serum creatinine levels have been reported in heart, liver and bone marrow recipients and in patients receiving CSA for treatment of different autoinmmune diseases [9–12]. Acute

CSA nephrotoxicity usually responds to dosage reductions, but chronic CSA renal impairment does not respond to dose reductions. Resolution or improvement of biopsy-proven arteriolopathy can occur after discontinuation of CSA treatment; however, the risk of acute rejection increases [2]. A recent publication described improvement of renal function after conversion to tacrolimus in patients with acute CSA nephrotoxicity [5]. Until now, no conclusive data have been reported about the effectiveness of this immunosuppressive change in patients with nephrotoxicity arising from long-term CSA treatment.

In our study neither acute rejection episodes nor side effects were observed after the discontinuation of CSA therapy and immediate conversion to tacrolimus. An adequate response in progressive graft dysfunction was achieved in nine of the ten patients included in the study. In addition, arteriolar damage due to CSA improved or disappeared in two kidney transplant biopsies performed 6 months after conversion.

The mechanism of the improvement in graft function which accompanies the switch from CSA to tacrolimus is not clear. In spite of their chemical dissimilarities, both drugs have a very similar mode of action and side-effect profile [13]. Their immunosuppressive potency depends on the ability to bind competitively to an intracytoplasmic specific protein (cyclophilin for CSA and FKBP for tacrolimus) and thereby block the action of calcineurin. This blockage inhibits T cell function by impairing the gene transcription of interleukin-2 and other cytokines [14]. Both drugs are nephrotoxic and may produce dose-dependent deterioration in renal function which is reversible during the early posttransplantation phase. The pattern of nephrotoxicity is essentially indistinguishable both clinically and pathologically [13]. On the other hand, chronic nephrotoxicity is not clearly dose-dependent and may be related to individual susceptibility.

Our preliminary results are very impressive. They reflect that conversion from CSA to tacrolimus, in kidney-transplanted patients with long-term CSA-induced nephrotoxicity, leads to an improvement of progressive graft dysfunction in the majority of cases. However, a greater number of patients and a longer follow-up period are necessary to confirm the therapeutic advantage.

References

1. Remuzzi G, Perico N (1995) Cyclosporine-induced renal dysfunction in experimental animals and Human. Kidney Int Suppl 52: 70–74
2. Morozumi K, Thiel G, Albert FW, Banfi G, Gudat F, Mihatsch MJ (1992) Studies on morphological outcome of cyclosporine-associated arteriolopathy after discontinuation of cyclosporine in renal allografts. Clin Nephrol 38: 1–8
3. Wolf G, Thaiss F, Stahl RA (1995) Cyclosporine stimulates expression of transforming growth factor-beta in renal cells. Possible mechanism of cyclosporine antiproliferative effects. Transplantation 60: 237–241
4. Pankewycz OG, Miao L, Isaac R, Guan J, Pruett T, Haussmann G Sturgil BC (1996) Increased renal tubular expression of transforming growth factor-beta in human allografts correlates with cyclosporine toxicity. Kidney Int 50: 1634–1640
5. Hariharan S, Munda R, Cavallo T, Demny AM, Schroeder TJ, Alexander JW, Firt MR (1996) Rescue therapy with tacrolimus after combined kidney/pancreas and isolated pancreas transplantation in patients with severe cyclosporine nephrotoxicity. Transplantation 61: 1161–1165
6. Abdalla AH, al-Sulain MH, al-Khader AA (1994) FK506 as an alternative in cyclosporine-induced hemolytic-uremic syndrome in a kidney transplant recipient. Transpl Int 7: 382–384
7. Solez K, Axelsen RA, Benediktsson H, et al (1993) International standardization of criteria for the histologic diagnosis of renal allograft rejection. The Banff working classification of kidney transplant pathology. Kidney Int 44: 411–422
8. Jones RH, Molitoris BA (1984) A statistical method for determining the breakpoint of two lines. Anal Biochem 141: 287–289
9. Myers BD, Newton L, Oyer P (1992) The case against the indefinite use of cyclosprine. Transplant Proc 23: 41–42
10. McCanley J, Van Thiel DH, Starzl TE, Puschett JB (1990) Acute and chronic renal failure in liver transplantation. Nephron 55: 121
11. Hows JM, Chipping PM, Fairhead S, Smith J, Baughan A, Gordon-Smith EC (1983) Nephrotoxicity in bone marrow transplant recipients treated with cyclosporine. Br J Haematol 54: 69–78
12. Dieterle A, Abewyckrama K, Graffenried B von (1988) Nephrotoxicity and hypertension in patients with autoimmune diseases treated with cyclosporine. Transplant Proc 20: 349
13. McCauley J (1993) The nephrotoxicity of FK506 as compared with cyclosporine. Curr Opin Nephrol Hypertens 2: 662–669
14. Brauman G, Zenke G, Wenger R, Hiestand P, Quesmianx U, Andersen E, Scherier MH (1992) Molecular mechanism of immunosuppression. J Autoimmun 5(suppl A):67–72