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Long-term maintenance of therapeutic cyclosporine levels leads to optimal graft survival without evidence of chronic nephrotoxicity

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Abstract Since the introduction of cylcosporine into clinical use, a major area of concern within the transplant community has been the fear of chronic nephrotoxicity. Although progressive renal damage does appear to occur in native kidneys of heart and liver transplant patients receiving cyclosporine, it has been our contention that its use is not a major cause of deterioration in renal allografts. We therefore undertook a study of 91 consecutive renal transplants performed over a three-year period with a minimum graft survival of 1 year and a follow-up of 7–9 years. Serial serum creatinine values, iothalamate clearances and cyclosporine levels were obtained at 3 months after transplantation and yearly thereafter. Biopsies were performed on all grafts that had failed as well as on the majority of patients with deteriorating renal function, and were interpreted by two nephropathologists. As measured by iothalamate clearances, 65 % of the patients in this series exhibited absolutely stable renal function despite the maintenance of cyclosporine levels of more than 200 ng/ml for 7–9 years. Since these stable patients did not reveal any decline in renal function, it therefore follows that they did not experience chronic cyclosporine nephrotoxicity. Furthermore, none of the patients with declining renal function or with failed grafts showed any evidence of nephrotoxicity on biopsy. Chronic cyclosporine nephrotoxicity may be a cause of declining function or graft loss with renal transplant recipients, but if so, it is exceedingly rare.

Key words Cyclosporine, nephrotoxicity, kidney transplantation, graft survival, immunosuppression

Introduction

With the introduction of cyclosporine (CyA) to clinical transplantation, marked improvement in early renal allograft survival occurred [9]. It was noted, however, that there appeared to be little change in the rate of allograft loss after the first post-transplant year compared to conventional immunosuppression with azathioprine (AZA) and steroids [6, 8]. Several possible explanations exist that address this observation. First, the beneficial effect of CyA could be limited to the early post-transplant period with respect to a decrease in the rate of allograft loss due to acute rejection. CyA may have no effect on the most common cause of allograft loss after the first year: chronic rejection. Alternatively, a decrease in overall, long-term allograft survival caused by a nonimmunologic, chronic CyA nephrotoxicity could overshadow the benefits of CyA on early allograft survival.

Yet another possibility is that, due to a fear of chronic CyA nephrotoxicity, many transplant centers progressively lowered the dose of CyA to subtherapeutic levels, thereby inviting chronic rejection. With such low levels of CyA, it is not surprising that the rate of allograft loss after 1 year was similar to that of the era of conventional immunosuppressives. In an attempt to shed some light on the actual cause of allograft loss after the first year, and to determine whether the entity of chronic CyA nephrotoxicity exists, the following study was undertaken.

Patients and methods

Patients

Ninety-one consecutive patients with renal transplants performed from 1989 through 1991 with a minimum graft survival of 1 year were entered into this study. All patients had agreed prospectively to participate and were maintained on CyA-based immunosuppression. Both living related graft and cadaveric graft recipients were included. In order to analyze the causes of allograft loss after the first post-transplant year, patients were prospectively divided into two groups based upon serial glomerular filtration rates (GFR) measured during the first year regardless of immunosuppressive protocol. Patients with deteriorating renal function, defined by a decline in GFR of more than 15% between 3 months and 1 year after transplantation, were placed in the *declining* group, whereas those showing no deterioration were included in the *stable* group.

Immunosuppression

The immunosuppressive regimen given to each patient was determined by an assessment of the patient's immunologic risk and initial allograft function. Patients considered to be at low immunologic risk and exhibiting good initial allograft function received dual therapy consisting of 14 mg/kg per day CyA in divided doses and prednisone (PRED) according to our standard taper. Patients at low immunologic risk were defined as having: 1) panel-reactive antibodies (PRA) below 30%, 2) primary transplants, or 3) repeat transplants with the first allograft functioning for more than 6 months. Patients with an average urine output of more than 100 ml/hr and whose serum creatinine (SCr) decreased by more than 2 mg% within the first 24 hours after transplantation were regarded as showing good initial function. Patients judged to be at low immunologic risk but exhibiting a less than good initial function were maintained on triple therapy with 8 mg/kg per day CyA in divided doses, 1.5–2.0 mg/kg per day AZA, and the standard PRED taper. Patients considered to be at high immunologic risk and/or showing no initial allograft function received induction therapy consisting of 5 mg/day OKT3, 50 mg/day AZA, and the standard PRED taper. When the SCr fell below 3 mg%, or on post-transplant day 10, CyA was introduced at 8 mg/kg per day, and AZA was increased to 1.5–2.0 mg/kg per day. OKT3 was discontinued when adequate CyA levels were achieved. Additionally, three patients with failing primary allografts that had exhibited good function on triple therapy for more than 6 months underwent retransplantation prior to resuming dialysis. These patients were maintained on triple therapy without induction therapy.

After administering a 500 mg bolus of methylprednisolone at the time of transplantation, our standard PRED taper consisted of an oral dose of 2 mg/kg on the first postoperative day followed by a rapid taper to 20 mg/day by postoperative day 15. Patients remained on 20 mg/day for 30 days, after which the dosage was decreased by 2.5 mg every other week until a maintenance dose of 7.5 mg/day was achieved. CyA levels were assayed by employing monoclonal TDX methodology using whole blood 12-hour trough specimens. Target CyA levels were 300–400 ng/ml during the first month, 250–350 ng/ml during months 2–12, and 200–250 ng/ml thereafter. Rejection episodes were treated with 500 mg/day pulse methylprednisolone for 3 days followed by a recycling of PRED. Lack of response to steroids was treated with 5 mg/day OKT3 for 10–14 days. For patients with anti-OKT3-antibodies, 15 mg/kg per day ALG was given for 10–14 days.

Concomitant Therapy

Patients received Nefedapine starting immediately after operation unless previously on a different calcium channel blocker, which was then continued. Additionally, beginning with the first day after operation, all patients received misoprostol (Cytotec) at a dose of 200 mg four times a day as tolerated. Approximately 30% of the patients required a decrease to 100 mg q.i.d. or complete discontinuation of these medications due to side effects. Angiotensin-converting enzyme inhibitors were prohibited for these patients for the first post-transplant year, and were generally not used during the follow-up.

Determinations

Serial laboratory evaluations including SCr and CyA levels were obtained routinely, and a sodium iothalamate clearance was performed at 3 months after transplantation and yearly thereafter. Glofil (Isotex, Friendswood, Tex.) was mixed with 0.1 ml of 1:1000 epinephrine and given subcutaneously in the upper arm. Three urine collections were obtained through voluntary voiding, and blood samples were drawn before and after each time of collection. I 125 activity in the urine and serum was determined by counting 0.5-ml samples for 2 minutes using a Tracor analytic gamma counter, model 1197 (Tracor Analytical, Des Plaines, Ill.). The sodium iothalamate clearance was calculated using the UV/P formula, in which U and P are serum counts and V is the volume of urine per minute. The mean clearance was calculated from three consecutive values.

Renal allograft biopsies were performed percutaneously using a Trucut needle and ultrasound guidance. Indications for biopsy included: 1) allograft dysfunction, 2) declining iothalamate clearances, and 3) significant (> 500 mg/dl) or increasing levels of proteinuria. All renal biopsies were subjected to light, immunofluorescent, and electron microscopic evaluation, and were interpreted by two independent transplant nephropathologists.

It has been established that the pathologic features of chronic rejection are not specific, but consist of a number of changes that may be identified in the vessels, interstitium, and glomeruli [11, 15, 16].

The vascular changes resulting from chronic rejection may be the most helpful in diagnosis, although they can be difficult to distinguish from those caused by chronic cyclosporine nephrotoxicity, donor-transmitted nephrosclerosis, and thrombotic microangiopathy. The concentric intimal thickening of arterioles and larger arteries without hyalinosis constitutes a change most characteristic of chronic rejection. In its advanced state, this change is termed

Table 1 Demographics[a]

	Stable (%)	Declining (%)
n	65 (71)	26 (29)
Male/female	36/29 (55/45)	14/12 (54/46)
Diabetic	20 (31)	11 (42)
Black*	4 (6)	10 (38)
Tx > 1	13 (20)	3 (12)
Living related	13 (20)	7 (27)
2 Haplotype	5 (8)	3 (12)
1 Haplotype	8 (12)	4 (15)
Cadaveric	52 (80)	19 (73)
AB mismatch	2.6	2.5
DR mismatch	1.1	1.2

* $P < 0.05$ for stable vs declining patients
[a] Tx > 1 means patients having their second or third treatment, AB mismatches refers to the number of mismatches at HLAA, and HLAB locus and DR mismatch refers to the HLA DR locus

obliterative transplant arteriolopathy. In contrast, circumferential hyalinosis of arterioles with a relative sparing of larger arteries represents a change most characteristic of chronic cyclosporine nephrotoxicity. In addition, hyalinosis caused by chronic cyclosporine toxicity may occur in a nodular pattern within the vessel wall, helping to distinguish it from changes resulting from donor-transmitted nephrosclerosis. Aside from fibrosis or hyalinosis, a subendothelial mucoid change may be recognized in arterioles. This change is most characteristic of thrombotic microangiopathy and may occur occasionally in connection with cyclosporine toxicity, but is not commonly encountered in chronic rejection. Smooth muscle cell necrosis of arterioles, related to the subendothelial mucoid change, is not characteristic of chronic rejection, but may be seen in cases of chronic cyclosporine toxicity or thrombotic microangiopathy.

Interstitial changes, although nonspecific, are met with commonly in chronic rejection. Most frequently, interstitial fibrosis occurs, which may be patchy in distribution. Although chronic cyclosporine toxicity may result in an interstitial fibrosis described as "striped," its pattern is generally not a reliable discriminator.

Similarly, interstitial inflammation is commonly seen in chronic rejection and is likewise nonspecific. The interstitial infiltrate is typically composed of lymphocytes with admixed monocytes and plasma cells, and may be associated with areas of fibrosis. Although chronic interstitial inflammation may be helpful in excluding an acute process such as thrombotic microangiopathy, it does not generally help in distinguishing chronic rejection from chronic cyclosporine toxicity or nephrosclerosis.

Lastly, glomerular changes may be helpful in diagnosing chronic rejection. Glomeruli frequently reveal nonspecific ischemic changes such as an increased mesangial matrix with a thickening and wrinkling of basement membranes. In some cases, however, glomeruli show changes that are similar to those resulting from thrombotic microangiopathy and membranoproliferative glomerulonephritis, and called chronic transplant glomerulopathy.

Statistics

Statistical analysis was accomplished by means of the True Epistat Program (Epistat Services, Richardson, Tex.) using one-tailed Student's *t* tests and chi-square where appropriate.

Results

Patient demographics are compiled in Table 1. The proportion of black patients was higher in the declining group than in the stable group (38% vs 6%; $P < 0.05$). This accounted for the only significant difference between the two groups.

Iothalamate clearances, SCr and CyA levels are compared in Table 2. Stable patients had mean iothalamate clearances between 60 and 64 ml/min throughout the study. Declining patients started with mean clearances of 62 ml/min, which were identical to the initial clearances of the stable group. Their clearances declined steadily over the ensuing 8 years to a mean value of 21 ml/min ($P < 0.001$ for stable vs declining).

Initial mean SCr values were 1.6 mg% and 1.8 mg% in the stable and declining groups, respectively (P = NS). The stable patients continued to show a mean SCr of 1.5 ± 0.1 mg% during years 1 through 8, compared to a steadily increasing mean SCr (3.3 mg% at 8 years) for the declining group ($P < 0.01$ for stable

Table 2 Serial iothalamate clearances *(IoCl)*, serum creatinine *(SCr)* values and cyclosporine *(CyA)* levels in stable and declining patients

Renal function		3 months	1 year	2 years	3 years	4 years	5 years	6 years	7 years	8 years
Stable	Number of patients	65	65	65	65	65	65	63	62	58
	IoCl (ml/min)*	60.7	63.7*	61.9*	62.5*	61.1*	61.2*	63.7*	60.3*	59*
	SCr (mg%)**	1.6	1.5**	1.5**	1.5**	1.5**	1.5**	1.4**	1.6**	1.6**
	CyA level (ng/ml)***	422	342	223	215	212	211	226	220	203
Declining	Number of patients	26	26	22	17	14	9	7	6	4
	IoCl (ml/min)*	62.3	50.6*	41.6*	43.1*	29.1*	43.6*	36.0*	21.0	35*
	SCr (mg%)**	1.8	2.2**	2.3**	2.6**	2.7**	2.7**	2.7**	2.7**	3.3**
	CyA level (ng/ml)***	416	342	222	229	190	180	230	173	176

* $P < 0.001$ for stable vs declining patients
** $P < 0.01$ for stable vs declining patients
*** P = NS

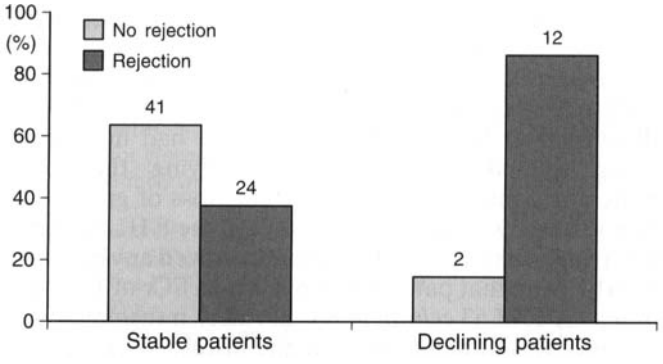

Fig. 1 Percentage of stable and declining patients who experienced acute rejection episodes

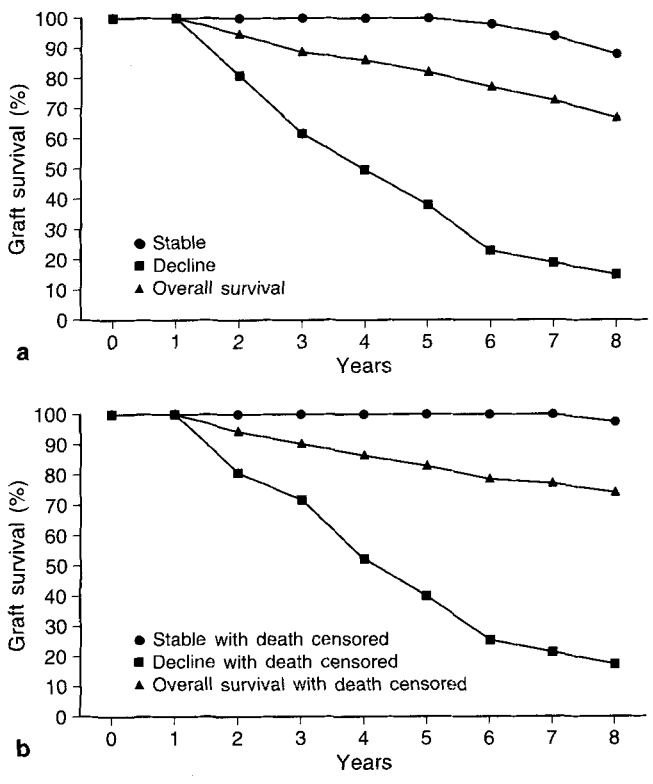

Fig. 2 Graft survival in stable and declining patients without (**a**) and with (**b**) death censored

vs declining). However, it should be noted that, although the mean SCr and iothalamate clearance remained stable in this group overall, there were a number of patients who either died, experienced graft loss, or did show some deterioration of their renal function over the 9 years of the study. Seven grafts were lost due to patient death; five patients died of cardiac causes, one of lymphoma and one of pancreatic cancer. There were two graft losses at 8 and 9 years with admittedly noncompliant patients with biopsy-proven chronic rejection. Additionally, there were four other grafts in this group that exhibited deterioration of their renal function over the 9 years of the study. Two of these patients showed biopsy-proven chronic rejection, one of whom was admittedly noncompliant. One diabetic patient suffering from cardiac disease with a severe cardiomyopathy remains with a SCr of 1.9 mg% at 8 years. This patient's GFR has deteriorated over the course of the study, mainly in the last 2 years, during which time her cardiac disease has worsened significantly. The last patient refused renal biopsy and remains with a SCr of 2.0 mg% at 8 years. All other patients within the stable group remain with absolutely stable SCr values and iothalamate clearances at years 7–9 of the follow-up.

Mean CyA levels were 422 and 416 ng/ml at 3 months and 342 and 342 ng/ml at 1 year in the stable and declining groups, respectively (P = NS). Levels were maintained at approximately 200–250 ng/ml for all patients during years 2 through 8 and did not differ significantly between the two groups (P = NS).

Long-term allograft survival in this study was not affected by immunosuppressive protocol. Patients treated initially with dual therapy, triple therapy, or induction therapy showed similar rates of allograft loss and declining function. Additionally, within the stable and declining groups, chronic therapy with a two or three drug regimen did not affect long-term allograft survival or function.

As shown in Fig. 1, the rates of acute rejection differed significantly between the two groups. Only 37% of the stable patients experienced a rejection episode, whereas 86% of the declining patients experienced at least one episode of rejection ($P < 0.05$).

Of the 26 patients with declining function, 22 (84%) lost their allografts during the 9 years of the follow-up (Fig. 2). Histologic material was available for all but 2 of these patients. The etiology of graft loss in this group was as follows: there were 2 patients with IgA nephropathy, 2 with focal and segmental glomerulosclerosis, 1 with fibrillar glomerulonephritis, 1 with membrano-proliferative glomerulonephritis Type I, 2 patients with cholesterol emboli, and 12 patients with chronic rejection. Of the 12 patients whose graft loss was secondary to chronic rejection, 11 had experienced one to four acute rejection episodes during the first post-transplant year. It should also be noted that 9 of these 12 patients were black, which constitutes a significant over-representation in the group with chronic rejection. The 2 patients for whom no histology was available both died of severe cardiomyopathy with functioning grafts. Their decline in function was attributed to prerenal causes. Neither of these patients ever experienced a rejection episode.

Results of the biopsies and the most recent SCr values for the 4 remaining patients exhibiting declining function are as follows: 1 patient remains with IgA nephropathy and a SCr of 1.9 mg% at 8 years, 1 patient

with focal segmental glomerulosclerosis and a SCr of 2.4 mg% at 8 years, and 2 patients with chronic rejection and SCr values of 1.5 mg% and 3.5 mg%, respectively, at 8 years. It should be noted that none of the 26 patients with declining function revealed a biopsy diagnostic of chronic cyclosporine nephrotoxicity.

Discussion

Since the introduction of CyA as the primary immunosuppressant in transplantation, fear of its nephrotoxicity has led to attempts to lower its dosage over the long term. While there is little doubt that CyA can result in acute nephrotoxicity [4, 7], its ability to cause a chronic progressive loss of renal function remains questionable [5, 8, 10, 14, 17]. The classic studies of Myers et al. [12, 13] resulted in the widely accepted view that CyA causes a chronic and progressive loss of renal function with heart transplant patients. The generalization of this finding to kidney transplant patients may not be appropriate for several reasons. First, the heart transplant population is affected by multiple factors that may result in diminished renal function at the time of transplantation. Advanced age, atherosclerotic vascular disease, hypertension and congestive heart failure can all contribute to decreased renal reserve and might sensitize the kidneys to CyA. Secondly, heart transplant recipients in Myers' studies received significantly higher doses of cyclosporine than are commonly used in renal transplantation. Lastly, native kidneys are innervated and may react to CyA differently than the denervated renal allograft.

In our study, recipients were maintained on whole blood CyA levels of approximately 200–250 ng/ml following the first year. Sixty-five percent of the patients showed absolutely stable allograft function, as defined by serial SCr levels and iothalamate clearances, over 8 years. Clearly, these patients did not experience chronic nephrotoxicity clinically or functionally secondary to their therapeutic levels of CyA. One cannot rule out morphologic changes consistent with CyA toxicity with these patients since biopsies were not available for the vast majority of them; however, their clinical significance would certainly be in question given the excellent long-term allograft function.

If chronic loss of graft function were related to the administration of CyA, then donor type and antigen matching would not have any effect on the incidence of toxicity. In fact, both well-matched and poorly-matched grafts as well as patients without rejection and with acute rejection episodes would then all be at an equal risk of incurring nephrotoxicity. This was not the case in our study (Table 1).

Twelve of the 14 patients (86%) with chronic rejection, compared to 24/66 stable patients (37%), had one or more acute rejection episodes during the first year after transplantation ($P < 0.05$; Fig. 1). Basadonna [2] and Almond [1] reported that the most important predictor of long-term renal allograft function was the absence of early acute rejection episodes. Only 2 of the 14 patients diagnosed as having chronic rejection had undergone living related transplantation, implying that poor matching contributed to the chronic loss of graft function (Table 1). Additionally, only 1 of the 8 HLA identical living related donor transplants showed any decrease in GFR, and that patient remains with a SCr of 1.5 mg% and a GFR of 63 cc/min at 8 years after transplantation.

Since it is difficult to define the histologic criteria for chronic CyA nephrotoxicity versus chronic rejection [15, 16], it is possible that some of the patients diagnosed as having chronic rejection actually had nephrotoxicity as the etiology of declining glomerular filtration rate in this study. Even if that were the case, the incidence of chronic nephrotoxicity could at the very most be 18% (16/91 patients), but this would imply that there was not a single patient in this study with chronic rejection. Alternatively, considering all patients as truly having chronic rejection, an incidence of 18% is extremely low [3]. If we eliminate those patients who lost their grafts due to recurrent disease, cholesterol emboli, or heart disease, the overall excellent long-term stability of the allografts in this study argues for an indefinite maintenance of therapeutic CyA levels. Attempts to avoid chronic nephrotoxicity with a small percentage of patients would be far offset by the loss of grafts due to chronic rejection induced by decreasing the CyA dose for the majority of patients. We cannot, however, exclude the formal possibility that, had we lowered the dose of cyclosporine in the declining function group, improved survival for a small number of grafts might have been achieved. It is our belief that an indefinite maintenance of therapeutic CyA levels leads to optimal graft survival and stability. The lowering of the CyA dose to subtherapeutic levels should be avoided if optimal long-term renal allograft survival is to be attained for the majority of recipients.

Another important finding of this study was the possibility to divide the patients into a stable and declining group at 1 year post-transplant based upon serial iothalamate clearances. At this particular point, those patients who were at risk of progressive graft deterioration and loss still had a GFR of more than 50 cc/min. If studies aimed at preventing or delaying graft loss due to chronic rejection or chronic allograft nephropathy are to be undertaken, they must start while the allografts still exhibit a significant residual function. Otherwise, nonimmunologic factors will predominate and lead inevitably to graft loss due to hyperfiltration or other causes, which would not be amenable to treatment. Using the methods presented in this paper, one could define the group of patients for study at an early point (at 1 year), and design studies for treating the group at high risk of graft loss.

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