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TACROLIMUS RESCUE THERAPY FOR RENAL TRANSPLANT REJECTION

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Introduction

Despite the improved results seen in renal transplantation observed with the introduction of cyclosporine (CyA) immunosuppression in the 1980's, a finite number of grafts are still lost due to irreversible and ongoing rejection (1-3). Although the use of sequential induction therapy with antilymphocyte preparations followed by CyA mitigates the incidence of initial first rejection episodes to a certain extent, even retreatment with high dose steroids and/or further anti-lymphocyte therapy may be unsuccessful (4-6). These observations in clinical renal transplantation have stimulated interest in the development of novel drugs that may be useful in "rescuing" renal allografts failing these standard protocols. Tacrolimus is a novel macrolide immunosuppressant which has been used with encouraging results in primary renal transplantation (7, 8). This drug appears to have the additional advantage of permitting the tapering, and in some cases, cessation of steroid therapy allowing for tacrolimus monotherapy in up to 40% of patients (8). The efficacy of tacrolimus in primary renal transplantation led us to evaluate this agent for "rescue" of renal allografts undergoing intractable acute rejection which could not be reversed by the standard therapies available, including high dose steroids and antilymphocyte preparations (9, 10). This report summarizes our experience with tacrolimus for salvage therapy of rejecting renal allografts under primary CyA immunosuppression.

Materials and Methods

Seventy-seven patients (mean age 33.3 $\pm$ 12.4 years) under primary CyA immunosuppression with ongoing biopsy-proven acute cellular rejection were converted to tacrolimus immunosuppression. The characteristics of the 77 patients are shown in Table 1. The majority of the patients (59) were primary transplant recipients; however, a significant number

(23%) had been re-transplanted. Fifty-two patients (68%) received cadaveric grafts and 25 (32%) living donor grafts. Four of the 77 patients received kidney-pancreas transplants and 1 kidney and pancreatic islet transplant. All of the patients had ongoing, biopsy-confirmed acute cellular rejection either with (n=20, 26%) or without (n=47, 61%) a vascular component of rejection at the time of conversion to tacrolimus. In addition, 10 patients (13%) had rejection in grafts that had never functioned from the time of the transplant. The majority of the patients (n=64, 78%) were referred with their failing grafts from other institutions; the remainder (n=13, 22%) were entered into this study early in this series from our own center (prior to our exclusive use of tacrolimus as a primary immunosuppressive agent in 1990). Baseline immunosuppression included CyA and prednisone in all patients, either with (n=22, 29%) or without (n=55, 71%) azathioprine as a third agent. Anti-rejection therapy administered to all patients included high dose bolus corticosteroids, and 61 patients (79%) also received at least 1 course of a monoclonal (OKT3) or polyclonal (ATG or ATGAM) antilymphocyte preparation. Tacrolimus was started only after the most recent biopsy (<1 week) confirmed the presence of ongoing acute rejection and Doppler ultrasound and/or radionuclide study of the allograft had confirmed the absence of a technical cause for allograft dysfunction. Tacrolimus conversion was carried out as a simple switch ("clean conversion") from CyA with no overlapping doses starting 12 hours following the last dose of CyA, as previously described (10). Tacrolimus was given at 0.3 mg/kg/day orally in divided doses every 12 hours. Parenteral doses of 0.025 to 0.1 mg/kg/day overlapping with the first 1 to 4 days of oral therapy were also given to 16 patients. Monitoring of trough serum tacrolimus levels by ELISA (10) to achieve a 12 hour trough level of 1.0 to 2.0 ng/ml was used for dosage adjustments.

Results

Conversion from CyA to tacrolimus was deemed successful based on a return to baseline serum creatinine (SCR), and/or improvement on postconversion renal allograft biopsy, and/or freedom from dialysis if the patient was dialysis-dependent upon conversion. Of the 77 patients, successful rescue according to these criteria was achieved in 57 cases (74%) with a mean follow-up of 16 months. Of 18 patients who were dialysis-dependent at the time of conversion to tacrolimus, 9 (50%) were successfully salvaged and have a mean SCR of 2.3 mg/dl. Of the subset of 61 patients who received pre-conversion antilymphocyte preparations in an attempt to treat the ongoing rejection, success was achieved in 48 (79%). Successful conversion occurred in 37 of 52 (73%) cadaveric graft recipients and in 20 of 25 (80%) living donor recipients. Three of the four patients with combined kidney-pancreas grafts and the 1 kidney-pancreatic islet graft were rescued. The degree of success was influenced to a certain extent by the type of initial baseline immunosuppressive. Forty-five out of 55 (82%) of those patients initially receiving CyA-based triple therapy with azathioprine were salvaged compared with only 12/22 (55%) initially on CyA-prednisone double therapy ($p=0.03$). In those patients successfully rescued, prednisone tapering was possible: the average pre-conversion prednisone dose of 22.2 ± 7.2 mg/day was tapered to 7.5 ± 5.6 mg/day, and 12 patients (21%) of the 57 with functioning grafts are currently on tacrolimus monotherapy. No patient is receiving more steroid post-conversion than pre-conversion. Two patients had re-rejection episodes subsequent to initial successful rescue with tacrolimus. In one case, the SCR increased from 2.8 to 3.4 mg/dl 19 months following rescue and was treated successfully with an increased prednisone dose (7.5 to 15 mg/day) with a return to baseline SCR. Another patient required a 1 gm bolus of methylprednisone 3 weeks after

tacrolimus conversion for a rejection episode (SCR increased from 2.2 to 2.7 mg/dl) and continues to do well on 17.5 mg prednisone daily with a SCR of 2.3 mg/dl.

At long term followup following rescue (median = 42 months), 48 patients (62%) continue to have a functioning graft. There have been 9 late graft losses after initial successful rescue; 5 due to chronic rejection, 1 to noncompliance, and 3 to patient death.

Discussion

Even with triple and quadruple drug CyA immunosuppression the incidence of graft loss due to intractable rejection continues to be a vexing problem for transplant physicians. The development of novel immunosuppressive drugs in the last 5 years has resulted in several of these agents entering into clinical trials in an attempt to improve the results of renal transplantation witnessed in the 1980's under CyA-based regimens. One of the most promising of these agents, tacrolimus, is currently in phase III clinical trials, has been shown to be safe and efficacious in trials of renal, hepatic, and thoracic transplantation. Several potential advantages of tacrolimus suggested by these studies include steroid-sparing effects while lacking some of the more undesirable side effects of CyA (7-10). We have now demonstrated that an additional property of tacrolimus that is distinct from CyA is its ability to reverse ongoing rejection in renal allografts, even when agents as potent as antilymphocyte preparations have not been effective. The advantage of such an agent in the clinical armamentarium for renal transplantation is clear: the risks of excessive treatment with steroids and/or antilymphocyte preparations can be reduced or avoided. The specific cellular mechanisms by which tacrolimus acts in this regard are not clear, but are currently being investigated in our laboratory (11). Nevertheless, it is evident that trials comparing tacrolimus to the other more traditional agents used for rejection episodes (steroids,

OKT3, ATGAM) should be initiated to further elucidate the specific indications for the use of this promising drug for rescue of renal allograft rejection.

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Table 1

Characteristics of 77 Patients Converted to Tacrolimus for Ongoing Rejection

	No. Patients	(%)
Males	44	57%
Females	33	43%
Primary Transplants	59	77%
Repeat Transplants	18	23%
Cadaveric donor	52	68%
Living donor	25	32%
Maintenance Immunosuppression:		
CyA + prednisone	55	71%
CyA + azathioprine + prednisone	22	29%
Rejection Immunosuppression:		
High dose steroids alone	16	21%
High dose steroids + OKT3/ATG/ATGAM	61	79%
Biopsy at conversion to tacrolimus:		
Acute cellular rejection	47	61%
Acute cellular + vascular rejection	20	26%
Acute cellular rejection + primary nonfunction	10	13%