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TACROLIMUS RESCUE THERAPY FOR RENAL ALLOGRAFT REJECTION—FIVE-YEAR EXPERIENCE[1]

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Over the 5 year period from 7/14/1989 until 5/24/1994, we have attempted graft salvage with tacrolimus conversion in a total of 169 patients (median age 33 years, range 2–75 years) with ongoing rejection on baseline CsA immunosuppression after failure of high dose corticosteroids and/or antilymphocyte preparations to reverse rejection. The indications for conversion to tacrolimus were ongoing, biopsy confirmed rejection in all patients. The median interval to tacrolimus conversion was 2 months (range 2 days to 55 months; mean 4.3±2.6 months) after transplantation. All patients had failed high dose corticosteroid therapy and 144 (85%) of the 169 patients had received at least one course of an antilymphocyte preparation plus high dose corticosteroid therapy prior to conversion. Twenty-eight patients (17%) were dialysis-dependent at the time of conversion owing to the severity of rejection. With a mean follow-up of 30.0±2.4 months (median 36.5 months, range 12–62 months), 125 of 169 patients (74%) have been successfully rescued and still have functioning grafts with a mean serum creatinine (SCR) of 2.3± 1.1 mg/dl. Of the 144 patients previously treated

with antilymphocyte preparations, 117 (81%) were salvaged. Of the 28 patients on dialysis at the time of conversion to tacrolimus, 13 (46%) continue to have functioning grafts (mean SCR 2.15±0.37 mg/dl) at a mean follow-up of 37.3± 16.7 months. In the 125 patients salvaged, prednisone doses have been lowered from 28.0±9.0 mg/d (median 32, range 4–60 mg/d) preconversion to 8.5±4.1 mg/d (median 12 mg/d, range 2.5–20 mg/d) postconversion. Twenty-eight patients (22.4%) are currently receiving no steroids. This 5 year experience demonstrates that tacrolimus has sustained efficacy as a rescue agent for ongoing renal allograft rejection. Based on these data, we recommend that tacrolimus be used as an alternative to the conventional drugs used for antirejection therapy in renal transplantation.

Tacrolimus is a new immunosuppressant that is currently undergoing clinical trials for efficacy in renal transplantation. It has been previously reported that this agent is safe and effective for primary renal transplantation, with apparent advantages that include steroid tapering and monotherapy in up to 60% of recipients (1–3). Perhaps even more striking is the utility of this drug as a salvage agent for refractory renal allograft rejection. We previously reported in a series of 77 patients with refractory acute rejection on baseline cyclosporine (CsA)* therapy that graft salvage with tacrolimus conversion could be achieved in 74% of cases (4). This group included 61 patients who had been unsuccessfully treated with antilymphocyte preparations in an attempt to reverse ongoing rejection, of whom 79% were salvaged. This early study provided relatively short term follow-up (mean 13.9 months). Since that initial report, we have entered an additional 92 patients for a total of 169 renal transplant recipients who have been converted to tacrolimus in order to attempt graft salvage. The overall period of the entire study was from July 14, 1989 until May 24, 1994, with a current mean follow-up of 30.0±2.4 months (range 12–62 months). The results of this expanded experience with tacrolimus conversion for recalcitrant renal allograft rejection are reported herein.

MATERIALS AND METHODS

Patients. Between July 14, 1989 and May 24, 1994, 169 patients (98 male, 71 female) with a mean age of 36.2±13.1 years (range 2–75 years) with ongoing allograft rejection under baseline CsA immunosuppression were converted to tacrolimus immunosuppression. The causes of end stage renal disease (ESRD) included insulin dependent diabetes mellitus (IDDM) in 48 patients, glomerulonephritis in 43, hypertension in 14, adult polycystic kidney disease in 12, systemic lupus erythematosus in 7 patients, reflux nephropathy in 6, renal hypoplasia or dysplasia in 5, focal segmental glomerulosclerosis (FSGS) in 4, and posterior urethral valves, Wegener's granulomatosis, calculous disease, and connective tissue disease in 2 patients each. In 22 patients the cause of ESRD was unknown. One hundred and thirty-eight patients (82%) were primary transplant recipients and 31 (18%) had been retransplanted (21 second, 7 third, 2 fourth, and 1 fifth transplant). One hundred and thirty-two patients (78%) were recipients of cadaver (CAD) grafts and 37 (22%) were from

* Abbreviations: ACR, acute cellular rejection; AZA, azathioprine; CsA, cyclosporine; CAD, cadaver; CMV, cytomegalovirus; ESRD, end stage renal disease; FSGS, focal segmental glomerulosclerosis; IDDM, insulin dependent diabetes mellitus; LD, living donor; PTLD, posttransplant lymphoproliferative disorder; SCR, serum creatinine.

living donors (LD). Nineteen patients had received combined kidney-pancreas allografts.

All 169 patients converted to tacrolimus had uncontrolled rejection on primary CsA-based immunosuppressive therapy. Maintenance immunosuppression had consisted of CsA and prednisone in all patients, either with (n=117, 69%) or without (n=52, 31%) azathioprine (AZA). Two patients had previously been placed on mycophenolate mofetil in unsuccessful attempts to reverse rejection. The majority of the patients in this series (156 of 169, 92%) were referred to our institution from 32 other centers where they were deemed to be losing their grafts owing to the severity of their rejection. The participating centers included Akron City Hospital, Allegheny General Hospital, Beaumont Hospital, Borgess Medical Center, New York Hospital, Duke University Medical Center, Geisenger Medical Center, Hartford Hospital, Henry Ford Hospital, Hospital of the University of Pennsylvania, Lehigh Valley Hospital, Medical College of Virginia, Montefiore Medical Center, Pritzker Medical Center, St. Elizabeth Hospital, Stanford University Medical Center, SUNY Medical Center, Sutter Memorial Medical Center, Thomas Jefferson University Hospital, UCLA Medical Center, University of Arkansas, University of Illinois, University of Kansas, University of Maryland, University of Massachussetts, University of Miami, University of Michigan, University of Minnesota, University of North Carolina, University of Southern California, University of Tennessee, and Washington Hospital Center. In all cases, careful consideration was given to ensure that all patients had been maintained on maximized but safe and tolerable CsA dosing. Previous antirejection therapy had been administered to all 169 patients in the form of bolus high dose corticosteroids. A total of 144 of the 169 patients (85%) had also received at least one course of a monoclonal (OKT3) and/or polyclonal (ATG or ATGAM) antilymphocyte preparation. Forty-seven patients (28%) had received 2 or more courses of OKT3 prior to tacrolimus conversion and 51 patients (30%) received both OKT3 and a polyclonal antilymphocyte preparation prior to tacrolimus.

Tacrolimus conversion protocol. In all cases prior to conversion to tacrolimus, allograft dysfunction secondary to technical causes was ruled out by doppler ultrasound and radionuclide flow study of the allograft. Pathologic specimens of biopsy material were reviewed from the referring center and core biopsies of the allograft were repeated at our own institution in all patients to verify the continuing presence of ongoing rejection prior to conversion to tacrolimus. Acute cellular rejection (ACR) was present in biopsy specimens of all 169 patients prior to conversion, including 62 patients (37%) whose biopsies also revealed a vascular component of rejection (lymphocytic infiltration in arterial walls, intraglomerular hemorrhage, and/or infarction). In addition, 16 patients demonstrated ACR on biopsy of kidneys that remained dialysis-dependent from the time of transplantation. As previously described (4), all patients underwent a simple switch ("clean conversion") from CsA to tacrolimus. Tacrolimus was given at a standard daily oral dose of 0.2–0.3 mg/kg/day in divided doses every 12 hr starting 12–24 hr after the last CsA dose had been administered. Dosage adjustments were based upon monitoring of trough serum tacrolimus levels by ELISA (5) in the early (1989–early 1994) portion of the study to achieve 12-hr trough levels of 1.0 to 2.0 ng/ml, and in the latter part of the study (mid 1994–present) by whole blood MEIA - IMx assay (6, 7) to achieve 12-hr trough levels of 15–20 ng/ml, and also according to clinical and biochemical parameters. Data were analyzed for statistical significance by two tailed Student's *t* test or chi square analysis when appropriate.

RESULTS

The criteria for successful graft salvage with tacrolimus included a return to or improvement in baseline SCR, and/or improvement on follow up renal biopsy, and/or freedom from dialysis if the patient was dialysis dependent at the time of conversion to tacrolimus. One hundred sixty-nine patients

failing primary CsA based immunosuppression with ongoing rejection were converted to tacrolimus at an average of 4.3 ± 2.6 months (range 2 days to 55 months) following transplantation. With a mean follow-up of 30.0 ± 2.4 months (median 36.5 months, range 12 to 62 months), 159 of 169 patients (94%) remain alive and 125 of 169 patients (74%) have achieved graft salvage according to the aforementioned criteria. Kaplan-Meier patient and graft survivals from the time of tacrolimus conversion are shown in Figure 1. All 169 patients converted to tacrolimus displayed ongoing cellular rejection on preconversion allograft biopsy (Table 1). Of these, 62 patients (37%) also had evidence of a vascular component of rejection and 16 patients (9%) had never achieved initial graft function. Ninety-one of the 169 patients (54%) had elements of acute cellular rejection (ACR) only. The outcome of tacrolimus conversion according to the preconversion biopsy diagnosis is shown in Table 1. Of the 91 patients with ACR only on preconversion biopsy, 70 (77%) achieved graft salvage after tacrolimus conversion. Of the 62 patients with elements of both ACR plus vascular rejection on preconversion biopsy, 47 (75%) also achieved graft salvage (P=NS vs. ACR alone). Of the 16 patients with primary graft nonfunction who remained on dialysis from the time of transplantation until conversion, 8 (50%) were salvaged by conversion to tacrolimus (P=0.1, ACR vs. ACR + vascular rejection vs ACR + primary nonfunction). An additional 12 patients with primary graft function prior to conversion became dialysis dependent as a result of severe ongoing rejection during initial CsA therapy. Thus, of 169 patients, a total of 28 patients (17%) were dialysis dependent at the time of tacrolimus conversion. Thirteen of these patient (46%) currently have functioning grafts, with a mean serum creatinine of 2.15 ± 0.37 mg/dl at a mean follow-up of 37.3 ± 16 months (range 18 to 62 months) postconversion.

Tacrolimus conversion was successful in 96 of 133 (72%) CAD and in 29 of 36 (80%) LD recipients (P=NS). Successful rescue was also obtained in 107 of 138 (78%) primary transplants, 13 of 21 (62%) second transplants, 3 of 7 (43%) third

TABLE 1. Outcome of tacrolimus conversion in 169 renal transplant recipients failing primary CsA therapy

Preconversion biopsy	Number of Pts. (%)	Success	(%)[a]
Acute cellular rejection	91 (54%)	70	(77%)
Vascular rejection	62 (37%)	47	(75%)
Acute cellular rejection with primary nonfunction	16 (9%)	8	(50%)
Total	169	125	(74%)

[a] P=0.1

transplants, 1 of 2 (50%) fourth transplants, and in the one fifth transplant patient (P=0.14). Of the 19 recipients of combined kidney-pancreas allografts, 18 (95%) were successfully rescued. Table 2 shows the influence of time elapsed between transplantation and tacrolimus conversion on the likelihood of successful conversion. If conversion took place earlier than 2 or 3 months posttransplantation, there was no significant difference in success rates compared to conversion >2 months or >3 months posttransplantation (P=0.5 and 0.13, respectively). However, conversion was more likely to be successful if undertaken within 6 months of transplantation (77% success) as compared with >6 months after transplantation (50%, P=0.006).

Preconversion immunosuppression and tacrolimus conversion. All 169 patients in the study were receiving CsA-steroid based immunosuppression either in combination with azathioprine (n=117) or without azathioprine (n=52). Immunosuppression with either triple therapy (CsA-steroid-AZA) or double therapy (CsA-steroids) did not influence the likelihood of graft salvage after tacrolimus conversion (triple therapy: 90 of 117, 77%; double therapy: 35 of 52, 67%; P=0.26). Both patients treated with mycophenolate mofetil prior to referral were successfully salvaged with tacrolimus. In addition to receiving high dose corticosteroid therapy to treat ongoing rejection, 144 of 169 patients (85%) also received at least one course of an antilymphocyte preparation (OKT3, ATG, and/or ALG, average length of treatment 14.2 ± 5.8 days). Forty-seven patients received two or more courses of OKT3 prior to conversion. Eighty-nine patients had received OKT3 only, 4 patients either ALG or ATG only and 51 patients received a course of OKT3 and a course of ALG or ATG. Of the 144 patients treated with antilymphocyte antibody prior to conversion, 117 (81%) were salvaged with tacrolimus conversion.

Kaplan-Meier Patient and Graft Survival

— Patient Survival (n=169)

- - - Graft Survival (n=169)

Time (Years)

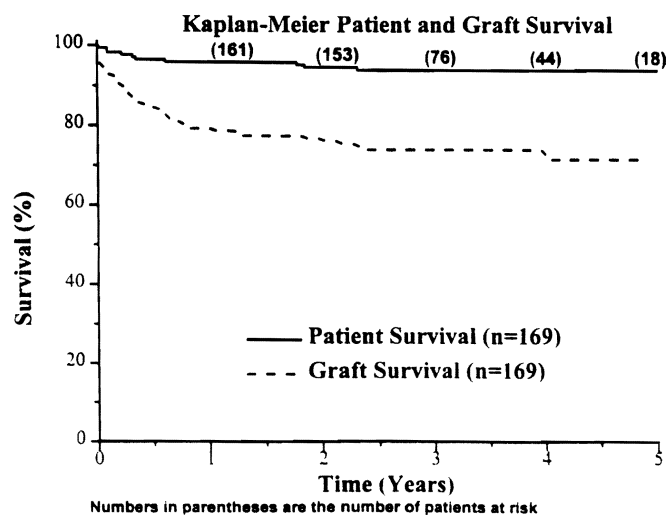Numbers in parentheses are the number of patients at risk

FIGURE 1. Kaplan Meier patient and graft survival of 169 patients converted from CsA to tacrolimus therapy for refractory renal allograft rejection. Calculations are based on events from the time of conversion to tacrolimus. Numbers in parentheses indicate patients at risk at each time point.

TABLE 2. Effect of interval to tacrolimus conversion following renal transplantation[a]

Conversion after KTX (mo)	Success	(%)	P
<2	67/86	(78%)	
			0.5
>2	61/83	(73%)	
<3	92/120	(77%)	
			0.13
>3	32/49	(65%)	
<6	114/147	(77%)	
			0.006
>6	11/22	(50%)	

[a] Mean interval to conversion: 4.3 ± 2.6 mo post-Tx; median interval: 2 mo (range: 2 days–55 mo)

Renal function before and after tacrolimus conversion. Twenty-eight patients were dialysis dependent at the time of referral for tacrolimus conversion owing to the severity of the ongoing rejection; of these, 13 (46%) were successfully salvaged and came off dialysis. With a mean follow up of 37.3±16.7 months (range 18 to 62 months) following conversion, these 13 patients have SCR levels of 1.6, 1.6, 1.7, 1.8, 1.8, 1.9, 2.2, 2.4, 2.5, 2.5, 2.6, 2.6, and 2.8 mg/dl (mean SCR 2.15±0.37). Excluding the 28 patients who were on dialysis at the time of tacrolimus conversion, the mean SCR prior to conversion in the successful switches was 3.1±1.7 mg/dl. The mean SCR after tacrolimus conversion was 2.3±1.1 mg/dl ($P=0.0002$ vs. preconversion) for patients not on dialysis at conversion. Of the 125 successful conversions, 112 patients were not on dialysis prior to conversion. Table 3 shows the sequence of improvement in renal function following tacrolimus conversion in these patients. Excluding the 28 patients on dialysis prior to conversion, there were a total of 81 patients with initial SCR ≤3 mg/dl, of whom 68 (84%) were successfully rescued, compared with 44 of 60 patients (73%) with an initial SCR >3 mg/dl. Although the quality of initial renal function trended toward a higher likelihood of successful conversion, this did not reach statistical significance ($P=0.18$).

Immunosuppression after tacrolimus rescue therapy. All 169 patients were receiving steroid therapy prior to conversion from CsA to tacrolimus. Table 4 shows the preconversion and postconversion prednisone doses. In the 125 patients successfully rescued, the average preconversion prednisone dose of 28.0±9.0 mg/day has been lowered to 6.6±5.1 mg/day, and 28 patients (22%) of the 125 with functioning grafts are on tacrolimus monotherapy. Of the 97 patients still taking prednisone, 87 have had their prednisone doses lowered from the preconversion dose and 10 patients remain on the same preconversion dose. Eighty-seven of the 125 patients (70%) were also on AZA at the time of conversion. Of these, 6 (7%) have had an increase in the AZA, 24 (28%) have had a decrease, 18 (20%) remain on the same AZA dose, and 39 (45%) have stopped AZA. One patient initially on mycophenolate mofetil required its discontinuation because of leukopenia; the other patient initially taking mycophenolate mofetil continues on it, and both patients still have functioning grafts. In the 125 patients with functioning grafts, the mean tacrolimus dose has decreased from 19.3±9.1 mg/d at conversion to 11.3±6.8 mg/d at last follow-up ($P<0.01$). Pre- and postconversion tacrolimus levels were not compared for the purpose of statistical analysis because of the variability in the method of detection during the 5 years of the study.

Morbidity and mortality. Since this series was initiated in 1989, there have been a total of 10 deaths, 7 of which oc-

TABLE 4. Prednisone dose before and after tacrolimus conversion

Pred (Mg/D)	No. patients (%)	
	Preconversion (n=125)	Postconversion (n=125)
0	0 (0%)	28 (22%)
2.5	0 (0%)	9 (7%)
5	0 (0%)	24 (19%)
7.5	0 (0%)	19 (15%)
10	12 (10%)	23 (18.5%)
12.5	5 (4%)	12 (10%)
15	6 (5%)	7 (6%)
20	33 (26%)	3 (2.5%)
>20	69 (55%)	0 (0%)
Mean Dose	28.0±9.0	6.6±5.1

curred in patients who had an unsuccessful attempt at graft salvage with tacrolimus conversion. In the initial series reported in 1994, there were a total of 6 deaths due to posttransplant lymphoproliferative disorder (PTLD) in 2 patients (one of whom was found to have had unsuspected PTLD at the time of conversion), sepsis in 1, tuberculosis in 1 (patient exposed to TB at referring center prior to transfer), and intracranial hemorrhage in 1 (4). The sixth patient died after returning to dialysis 8 months after failing tacrolimus conversion. In this expanded report of 169 patients, there have been an additional 4 deaths. Three of these deaths occurred in patients from the original series who were initially successfully salvaged. One of these 3 patients died of overwhelming sepsis with a functioning graft 27 months following successful conversion. A second patient died of a myocardial infarction 16 months after successful conversion. A third patient returned to dialysis 3 months after initial successful conversion and died on dialysis (etiology unknown). A fourth patient who was not successfully rescued died of a myocardial infarction one week after conversion. This patient was the only mortality of the 92 additional patients converted to tacrolimus since the original series ended in February 1993. Overall, 4 of the 10 deaths (PTLD in 2, sepsis in 1, and TB in 1) were likely related to overimmunosuppression prior to conversion, although an additive effect of tacrolimus to the immunosuppressive risk in these patients must certainly be considered. In retrospect, tacrolimus conversion in these 4 patients (all of whom failed conversion) was likely ill-advised. None of the remaining 6 deaths could be temporally or causally related to tacrolimus conversion. Excluding the patients who died, 39 patients referred to us for tacrolimus conversion had prior complications including cytomegalovirus (CMV) disease requiring antiviral therapy (ganciclovir and/or CMV hyperimmune globulin) in 12, renal artery stenosis requiring angioplasty in 6, lymphocele requiring drainage in 5, urine leak requiring surgical correction in 4, ureteral obstruction in 4, perforated duodenal ulcer following high dose steroid therapy for rejection in 1, cardiac arrest in 1, cutaneous herpes virus infection in 1, *Candida* esophagitis in 1, segmental renal infarction with no sequelae in 1, *Clostridium difficile* colitis in 1, aseptic menigitis secondary to OKT3 in 1, and myocardial infarction in 1. Thirty of these 39 patients (77%) were subsequently rescued. There were 35 complications following tacrolimus conversion, including new onset diabetes mellitus in 9 patients (5 requiring insulin therapy, 4 controlled by oral med-

TABLE 3. Renal function after conversion from CsA to tacrolimus[a]

Time after conversion	Scr (mg/dl)	Range	n	P vs. time 0
0	3.09±1.7	0.9–11.4	112	
1 wk	3.12±1.8	0.5–9.5	112	0.8
12 mo	2.13±0.8	0.9–5.2	95	<0.01
24 mo	2.20±1.0	1.0–6.0	51	<0.01
36 mo	2.13±0.9	1.2–5.6	28	0.005
48 mo	2.05±0.6	1.3–3.5	16	0.02

[a] Excluding patients on dialysis at the time of conversion.

ication), urinary tract infection in 6, CMV disease requiring antiviral (ganciclovir) therapy in 6, deep vein thrombosis in 2, line sepsis in 2, renal artery stenosis requiring angioplasty in 2, bacterial pneumonia in 2, cecal perforation in 1, disease recurrence (membranoproliferative glomerulonephritis) in 1, proteinuria in 1, gout requiring colchicine and allopurinol therapy in 1, epistaxis in 1, and a cerebrovascular accident in 1. None of these postconversion complications resulted in patient death.

Causes of graft loss after tacrolimus conversion. There were 44 failures of tacrolimus conversion in this group of 169 patients. Twenty-two patients had ongoing renal allograft rejection that was refractory to tacrolimus conversion. Eleven patients had repeat rejection episodes after initial successful rescue and lost their grafts. Five of these 11 were late immunologic graft losses due to chronic rejection at 8, 24, 26, 28, and 48 months, respectively, following initial successful conversion in patients from the original series of 77 previously reported (4). Three of these five patients had elements of chronic rejection on preconversion biopsy. Six of 11 were among the 92 additional patients converted to tacrolimus since our original series, and they have experienced late immunologic graft loss, one each at 5, 6, 6, 9, 10, and 20 months following initial successful conversion. Eight patients with primary allograft nonfunction with superimposed rejection were not salvaged, two patients lost their graft due to noncompliance, and one patient died with a functioning graft.

DISCUSSION

One of the most exciting developments of the new age of immunosuppressive therapy in the 1990s is the emergence of novel agents that have the ability to reverse ongoing rejection episodes in renal allograft recipients receiving traditional baseline immunotherapy with CsA (4, 8–12). Tacrolimus (formerly known as FK506) has previously been shown to provide salvage of refractory allograft rejection in 74% of patients on baseline CsA therapy who have failed either high dose corticosteroid therapy and/or antilymphocyte therapy in short term follow-up (4). Clearly, the utility of an agent which provides salvage of ongoing rejection must be proven in the long term and should have sustained efficacy in sufficient numbers of patients. Since our initial report in 1994, we have experience with an additional 92 patients referred to our center for tacrolimus conversion. The profiles of patients in this expanded study are very similiar to those in our earlier study, in that the majority (144/169, 85%) of the patients had failed prior treatment with antilymphocyte preparations and a subset of 28/169 (17%) of the patients had rejections so severe as to necessitate ongoing dialysis therapy prior to conversion. Overall, graft salvage was obtained in 125 of 169 patients (74%), which is identical to the salvage rate obtained in our earlier reported series of 77 patients (4). Significantly, this was with a mean follow-up of 30 months, reflecting the longevity of the salvage effect. The subset of 92 patients who were converted to tacrolimus since our original report were all referred from outside institutions where the patients were deemed to be losing their grafts owing to ongoing rejection. In this subgroup of 92 patients (mean follow-up 19 months, range 12 to 29 months), 77 patients (84%) have been successfully rescued. In attempting to identify patients who would not benefit from conversion to tacrolimus, we stratified the patients according to initial biopsy findings. We have previously found that grafts with chronic rejection without any acute component are unlikely to benefit from tacrolimus conversion (13). Although in our earlier series we found that the presence of vascular rejection conferred an approximate 20% disadvantage to the likelihood of salvage with tacrolimus, this was not statistically significant in our expanded experience. The patients with ACR alone experienced a 77% salvage rate, whereas those with components of vascular rejection experienced a 75% salvage rate (P=NS). In the group of patients with ACR superimposed on primary allograft nonfunction, the salvage rate of 50% was comparable to the rate of 40% previously reported (4). Overall, however, the difference in salvage rates with respect to the findings on preconversion biopsy did not reach statistical significance (P=0.1).

Another important feature that appears to be unique to tacrolimus as a salvage agent when compared with other agents (8, 9, 12) is its ability to provide graft salvage in patients who have been on dialysis owing to the severity of rejection. Long-term graft salvage was obtained in 13 of 28 such patients (46%) resulting in stable allograft function (mean SCR of 2.15 mg/dl) with a mean follow-up of 37.3±16.7 months. Overall postconversion renal function in all of the 125 patients salvaged in this series was 2.3±1.1 mg/dl. Furthermore, with follow-up up to 48 months, the SCR has continued to improve in patients successfully salvaged, perhaps indicating a beneficial effect of tacrolimus in preventing the onset of chronic rejection in some patients. The degree of initial renal function impairment did not statistically influence the likelihood of successful conversion in that patients with an SCR of <3 experienced a salvage rate of 84% compared with 73% in patients initially having an SCR >3 (excluding the 28 patients on dialysis at the time of conversion) (P=0.18). Another potential factor that may have influenced the likelihood of successful rescue was the interval between the time of transplantation and tacrolimus conversion. In our earlier series we found no differences in the success rates whether tacrolimus conversion was performed before or after 2, 3, or 6 months following transplantation. In that earlier series, only 11 patients had been switched to tacrolimus >6 months posttransplantation. In the current series, there appears to be a slight but statistically significant advantage to conversion <6 months after transplantation in that 114/147 (77%) experienced graft salvage compared with 11/22 (50%) success if conversion was attempted >6 months after transplantation (P=0.006). Conversion performed before or after 2 or 3 months following transplantation did not appear to influence the outcome. Probably more important than the timing of conversion are the findings on preconversion biopsy, in which the presence of chronic rejection or ACR with primary allograft nonfunction portends a worse prognosis (4, 13). One of the most striking observations in our early experience with tacrolimus rescue was the ability to taper and even stop prednisone therapy in approximately 20% of patients successfully salvaged (4). This trend was maintained in this expanded experience, and currently 28/125 (22%) patients with functioning grafts are on tacrolimus monotherapy.

As a result of our expanded experience, we have learned that tacrolimus can provide effective salvage of ongoing renal allograft rejection for patients on conventional CsA-based immunotherapy. The utility of CsA as a primary immuno-

suppressive agent has stood the test of time for its efficacy in renal transplantation (*14–17*). However, there is a group of patients who experience refractory allograft rejection in whom CsA is no longer effective even when combined with antilymphocytic therapy to attempt rejection reversal (*16, 17*). In addition to the now well-established graft salvage effects of tacrolimus, several other agents have shown initial promise as rescue agents, including mycophenolate mofetil (*8, 9*), 15-deoxyspuergualin (*12*), and perhaps sirolimus (*10*). In the latter case report, sirolimus was effective in ameliorating rejection in a patient who was requiring dialysis therapy (*10*). Further experience with this agent in primary and rescue therapy is anticipated. Whether these agents will provide long-lived salvage rates and afford the opportunity to wean steroids after rescue (such as is possible with tacrolimus) remains to be determined.

The reasons for the salutary effects of tacrolimus on established renal allograft rejection remain speculative but may include additional or distinct immunosuppressive activities of tacrolimus that have not yet been identified at the molecular level (*18*). One such hypothesis may be that lymphocytes that have been previously inhibited by CsA now escape inhibition, permitting certain cell subsets to undergo clonal proliferation and perhaps become "tolerant" to the effects of CsA. It is hoped that further investigation will elucidate the mechanisms by which tacrolimus appears to be unique in its ability to provide effective long-term reversal of renal allograft rejection with what appears to be minimal attrition in the long term due to immunologic causes. We currently recommend that tacrolimus conversion be considered an alternative to antilymphocycte preparations for steroid resistant rejection in CsA based regimens. Tacrolimus is clearly also effective in salvaging rejecting grafts that have failed antilymphocyte therapy. With mandated reduction in costs and hospital lengths of stay upon us, minimizing the use of antilymphocyte preparations, both in terms of their expense and potential complications, would be most desirable, as long as equivalent graft survival rates can be achieved. Agents such as tacrolimus may provide a unique opportunity to address some of these concerns and may prove to be more cost effective than the traditional methods by which steroid resistant episodes have been treated in the past. The addition of tacrolimus to the immunosuppressive armamentarium has provided transplant physicians with a much needed alternative to the conventional drugs used for renal allograft rejection therapy.

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