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## Tacrolimus for Rescue of Refractory Renal Allograft Rejection

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**S**IGNIFICANT improvements in the results of renal transplantation in the 1980s were largely due to the development of cyclosporine (CyA) and the use of antilymphocyte agents for induction protocols and/or treatment of rejection. However, rejection refractory to treatment with corticosteroids and/or antilymphocyte agents has remained a major obstacle to long-term success and account for a significant proportion of short- and long-term graft losses.<sup>1,2</sup> Tacrolimus is a new immunosuppressant that has undergone extensive clinical testing for efficacy in renal transplantation. In both U.S. and European multicenter trials,<sup>3,4</sup> tacrolimus has been found to be associated with a significant reduction in acute rejection episodes.

An additional proven advantage of tacrolimus includes steroid tapering and monotherapy in up to 60% of recipients.<sup>5</sup> Perhaps even more striking is the utility of this drug as a salvage agent for refractory renal allograft rejection.<sup>6-9</sup> We reported that of 77 patients with refractory acute rejection on baseline cyclosporine (CyA) therapy, graft salvage with tacrolimus conversion could be achieved in 74%.<sup>8</sup> An additional 92 patients were subsequently converted to tacrolimus to attempt graft salvage, bringing the total to 169 patients.<sup>9</sup>

We report here the results of this expanded experience with tacrolimus conversion for recalcitrant renal allograft rejection. Other reports from both single-center and multicenter studies have confirmed that tacrolimus provides an excellent alternative to corticosteroids and antilymphocyte preparations for the treatment of refractory renal allograft rejection and they form the basis of this discussion.

### MATERIALS AND METHODS

A total of 169 patients (98 male, 71 female) with a mean age of  $36.2 \pm 13.1$  years (range 2 to 75 years) with ongoing allograft rejection under baseline CyA immunosuppression were converted to tacrolimus immunosuppression between July 14, 1989, and May 24, 1994. One hundred and thirty-two patients (78%) were recipients of cadaver (CAD) grafts and 37 (22%) were from living donors (LD). There were 138 (82%) primary transplant recipients and 31 (18%) had been retransplanted (21 second, 7 third, 2 fourth, and 1 fifth transplants). Nineteen patients received combined kidney-pancreas allografts. All patients had uncontrolled rejection on primary immunosuppressive therapy, which had consisted of CyA and prednisone either with ( $n = 117$ , 69%) or without ( $n = 52$ , 31%) azathioprine (AZA). Two patients had previously been given mycophenolate mofetil (MMF) 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 U.S. centers where they were deemed to be losing their grafts owing to the severity of their rejection. All patients had been maintained on maximized but safe and tolerable CyA dosing. Previous antirejection therapy had been administered to all 169 patients in the form of bolus high-dose corticosteroids with additional monoclonal (OKT3) and/or polyclonal (ATG or ATGAM) antilymphocyte preparations in 144 (85%) of the 169 patients.

Prior to conversion to tacrolimus, allograft dysfunction secondary to technical causes was ruled out by Doppler ultrasound and radionuclide flow study of the allograft. Biopsy material was 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 rejections (ACR) was present on biopsy 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) and 16 patients (9.5%) who were dialysis-dependent from the time of transplantation (primary non-function with ongoing ACR).

As previously described,<sup>4</sup> all patients underwent a simple switch ("clean conversion") from CyA to tacrolimus. Tacrolimus was given at a standard daily oral dose of 0.2 to 0.3 mg/kg per day in divided doses every 12 hours starting 12 to 24 hours after the last CyA dose had been administered. Dosage adjustments were based upon monitoring of trough serum tacrolimus levels by ELISA in the early (1989 to early 1994) portion of the study to achieve 12-hour trough levels of 1.0 to 2.0 ng/mL, and in the latter part of the study (mid-1994 to present) by whole-blood MEIA-IMx assay to achieve initial 12-hour trough levels of 20 to 25 ng/mL within the first week, and also according to clinical and biochemical parameters. Additional treatment at the time of tacrolimus conversion in the form of bolus high-dose corticosteroids or antilymphocyte preparations was not given. Data were analyzed for statistical significance by two-tailed Student's *t*-test or chi-square analysis when appropriate.

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## RESULTS

The criteria for successful graft salvage with tacrolimus included a return to or improvement in baseline serum creatinine (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. With a mean follow-up of  $30.0 \pm 2.4$  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. All 169 patients converted to tacrolimus displayed ongoing cellular rejection on preconversion allograft biopsy. 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 pre-conversion biopsy, 47 (75%) were salvaged ( $P = \text{NS}$  vs ACR alone). Of the 16 patients with primary graft nonfunction and rejection, 8 (50%) were salvaged by conversion to tacrolimus ( $P = .1$ , 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 CyA therapy. Thus, of 169 patients, a total of 28 patients (17%) were dialysis-dependent at the time of tacrolimus conversion, and 13 (46%) were successfully salvaged and came off dialysis. With a mean follow-up of  $37.3 \pm 16.7$  months (range 18 to 62 months) following conversion, these 13 patients have respective 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  $2.15 \pm 0.37$ ). Excluding the 28 patients who were on dialysis at the time of tacrolimus conversion, the mean SCR prior to and after conversion in the successful conversions was  $3.1 \pm 1.7$  mg/dL and  $2.3 \pm 1.1$  mg/dL ( $P = .0002$  vs preconversion).

The average preconversion prednisone dose of  $28.0 \pm 9.0$  mg/d has been lowered to  $6.6 \pm 5.1$  mg/d, and 28 patients (22%) of the 125 with functioning grafts are on tacrolimus monotherapy. The mean tacrolimus dose has decreased from  $19.3 \pm 9.1$  mg/d at conversion to  $11.3 \pm 6.8$  mg/d at last follow-up ( $P < .01$ ). Tacrolimus conversion was successful in 96 of 133 (72%) CAD and in 29 of 36 (80%) LD recipients ( $P = \text{NS}$ ). Successful rescue was also obtained in 107 of 138 (78%) primary transplants, 13 of 21 (62%) second transplants, 3 of 7 (43%) third transplants, 1 of 2 (50%) fourth transplants, and in the 1 fifth-transplant patient ( $P = .14$ ). Of the 19 recipients of combined kidney-pancreas allografts, 18 (95%) were successfully rescued. There was no difference in success rates if conversion occurred  $<2$  months' (67/86, 78%) or  $>2$  months' (61/83, 73%) posttransplant or  $< (92/120, 77\%)$  or  $> (32/49, 65\%)$  3 months' posttransplant ( $P = .5$  and  $.13$ , respectively). However, conversion was more successful if performed within 6 months of transplantation (77% success) compared with  $> 6$  months' posttransplant (50%,  $P = .006$ ).

Immunosuppression with either triple-therapy (CyA-steroid-AZA) or double-therapy (CyA-steroids) did not influ-

ence the likelihood of a graft salvage after tacrolimus conversion (triple therapy: 90 of 117, 77%; double therapy: 35 of 52, 67%;  $P = .26$ ). Both patients unsuccessfully treated with MMF for rescue prior to referral were successfully salvaged with tacrolimus. Of the 144 patients treated with antilymphocyte antibody prior to conversion, 117 (81%) were salvaged with tacrolimus conversion.

Since this series was initiated in 1989, there have been a total of 10 deaths, 7 of which occurred in patients who had an unsuccessful attempt at graft salvage with tacrolimus conversion. Overall, 4 of the 10 deaths (PTLD in 2, sepsis in 1, and TB in 1) were likely related to over immunosuppression prior to conversion, although an additive effect of tacrolimus to the immunosuppressive risk in these patients should be considered. Tacrolimus conversion in these 4 patients (all of whom failed conversion) was in retrospect probably 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 for tacrolimus conversion had prior complications including cytomegalovirus (CMV) in 12, renal artery stenosis (RAS) in 6, lymphocele in 5, urine leak in 4, ureteral obstruction in 4, perforated duodenal ulcer 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 meningitis secondary to OKT3 in 1, and myocardial infarction in 1. These early complications were treated prior to conversion. 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 medication), urinary tract infection in 6, CMV disease in 6, deep vein thrombosis in 2, line sepsis in 2, RAS requiring angioplasty in 2, bacterial pneumonia in 2, cecal perforation in 1, disease recurrence (membranoproliferative glomerulonephritis) in 1, proteinuria in 1, gout 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 (26%) of tacrolimus conversion in this group of 169 patients. Eleven patients had repeat rejection episodes after initial successful rescue and lost their grafts. Twenty-two patients had ongoing renal allograft rejection, which was refractory to tacrolimus conversion. Eight patients with primary allograft nonfunction with superimposed rejection were not salvaged, 2 patients lost their graft due to noncompliance, and 1 patient died with a functioning graft.

## DISCUSSION

The value of an agent that provides salvage of ongoing rejection must be proven in the long term and should demonstrate ongoing efficacy in sufficient numbers of patients. In this large long-term experience with tacrolimus

rescue therapy, the majority (144/169, 85%) of patients had failed prior treatment with antilymphocyte preparations, and a subset of 28/169 (17%) of the patients had rejections severe enough to require ongoing dialysis therapy prior to conversion.

Overall, graft salvage was obtained in 125 of 169 patients (74%), an outcome identical to that observed in an initial reported series of 77 patients.<sup>8</sup> The mean follow-up of 30 months reflects the longevity of the salvage effect. In fact, in the subgroup of successful rescues from the original series of 77 patients, there have been only 9 late graft losses with an additional 28 months' follow-up such that 48 of the 57 patients (84%) originally salvaged continue to have functioning grafts, now with 42 months' follow-up.<sup>10</sup>

In an additional subset of 92 patients who were converted to tacrolimus since the original report, the success rate is higher than in the earlier study in that 77 patients (84%) have been successfully rescued, with a mean follow-up of 19 months (range 12 to 29 months).<sup>9</sup> The reasons for this improvement likely reflect a learning curve with the use of this drug, earlier conversion before elements of chronic rejection are present in the graft, and better patient selection. We have previously found that grafts with chronic rejection without any acute component are unlikely to benefit from tacrolimus conversion.<sup>6</sup> Patients with ACR alone experienced a 77% salvage rate; vascular rejection, 75%; ACR superimposed on primary allograft nonfunction, 50% ( $P = .1$ ). Therefore, histologic severity of rejection may not necessarily be a predictor of outcome.

Lack of reliability of clinical response based on histologic criteria prior to conversion has also been observed in two recent single-center studies.<sup>11,12</sup> More important may be the timing of tacrolimus conversion after transplantation. There appears to be a slight but statistically significant advantage to conversion < 6 months after transplantation in that 114/147 (77%) patients experienced graft salvage compared with 11/22 (50%) success if conversion was attempted >6 months after transplantation ( $P = .006$ ).

Another important feature that appears to be unique to tacrolimus as a salvage agent when compared to other agents<sup>8,9,12</sup> 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 long-term ( $37.3 \pm 16.7$  months' follow-up) stable allograft function (mean SCR of 2.15 mg/dL). In those patients not on dialysis preconversion, the degree of renal functional impairment did not statistically influence the likelihood of successful conversion in that those patients with a SCR of < 3 experienced a salvage rate of 84% compared with 73% in those patients initially presenting with a SCR > 3 (excluding the 28 patients on dialysis at the time of conversion) ( $P = .18$ ).

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.<sup>9</sup> That trend was maintained in this expanded experience, and currently 28/125 (22%)

patients with functioning grafts are on tacrolimus monotherapy.

Since 1993, a total of 23 papers have described successful salvage of refractory renal allograft rejection with tacrolimus, with success rates ranging from 52%<sup>13</sup> to 100%<sup>14</sup> in both single-center and multicenter North American and European studies. The largest multicenter study to date with 73 patients from 14 institutions reported a 78% salvage rate,<sup>7</sup> confirming our original<sup>8</sup> and subsequent<sup>9</sup> observations. A total of 382 cases of tacrolimus rescue therapy for refractory renal allograft rejection have now been reported in the literature, with a mean salvage rate of 75%.

In addition to the now well-established graft salvage effects of tacrolimus, several other agents have shown promise as rescue agents, including mycophenolate mofetil (MMF)<sup>15,16</sup> and perhaps sirolimus.<sup>17</sup> MMF has been studied in a large randomized multicenter trial in which patients received either corticosteroids or MMF therapy for refractory rejection. However, unlike the trials with tacrolimus, the MMF study excluded patients on dialysis, pediatric patients, third or greater transplants, and patients with serum creatinine (SCR) > 5.0 mg/dL.

In comparing the results of the MMF study to the tacrolimus multicenter and Pittsburgh experience by performing a meta-analysis, Woodle has reported similar patient and graft survival rates in the MMF and tacrolimus studies, but significantly less recurrent rejection, incidence of CMV, and requirement for antilymphocyte antibody to treat recurrent rejection in the tacrolimus studies when compared to the MMF study.<sup>18</sup> If the same criteria that were used to exclude patients from the MMF study are applied to the 169 patients studied at the University of Pittsburgh, 70 patients (41%) would fulfill the entry criteria and could be considered a "low-risk" rescue group. The remaining 99 patients (59%) would include those on dialysis, greater than third transplant, children, or those with initial SCR > 5.0 mg/dL; these could be considered a "high-risk" group for rescue. The incidence of CMV in the low-risk group was 2% compared with 5% in the high-risk group; however, there were 6 retransplants (9%) in the low-risk group compared with 25 (25%) in the high-risk group. Low-risk patients experienced 6- and 12-month patient and graft survival rates (96% and 87%, 96% and 84%, respectively), which are virtually identical to the overall 6-month patient and graft survival reported by the MMF arm of the MMF multicenter study (97% and 88%, respectively) and are superior to the steroid arm of that study (98% and 78%). However, even the "high-risk" tacrolimus rescue group had very acceptable outcomes, with patient and graft survival of 95% and 76% at 6 months and 94% and 70% at 12 months.

Further experience with both MMF and tacrolimus in both primary and rescue therapy is necessary to learn how best to use these new valuable additions to the pharmacologic armamentarium for transplantation. Clearly, these agents need not be mutually exclusive, and can be used in a complementary fashion, both for primary therapy<sup>19</sup> and

perhaps even for rescue. Optimizing rescue therapy for refractory rejection should be individualized for each patient. Both MMF and tacrolimus are effective in this regard; however, tacrolimus appears to have the added advantages of providing graft salvage in patients with greatly diminished renal function ( $SCR > 5.0$ ), or even in those on dialysis, in pediatric patients, those with multiple ( $>2$ ) transplants, while also permitting steroid tapering. It is also the only rescue agent thus far to have proven long-term efficacy in providing graft salvage.

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