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A PROSPECTIVE, RANDOMIZED TRIAL OF TACROLIMUS/PREDNISONE VERSUS TACROLIMUS/PREDNISONE/MYCOPHENOLATE MOFETIL IN RENAL TRANSPLANT RECIPIENTS*

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Background. **Between September 20, 1995 and September 20, 1997, 208 adult patients undergoing renal transplantation were randomized to receive tacrolimus/prednisone (n=106) or tacrolimus/prednisone/mycophenolate mofetil (n=102), with the goal of reducing the incidence of rejection.**

Methods. **The mean recipient age was 50.7±13.7 years. Sixty-three (30.3%) patients were 60 years of age or older at the time of transplantation. The mean donor age was 34.5±21.7 years. The mean cold ischemia time was 30.5±9.2 hr. The mean follow-up is 15±7 months.**

Results. **The overall 1-year actuarial patient survival was 94%; the overall 1-year actuarial graft survival was 87%. When the patient and graft survival data were stratified to recipients under the age of 60 who did not have delayed graft function, the overall 1-year actuarial patient survival was 97%, and the corresponding 1-year actuarial graft survival was 93%. There were no differences between the two groups. The overall incidence of rejection was 36%; in the double-therapy group, it was 44%, whereas in the triple therapy group, it was 27% (P=0.014). The mean serum creatinine was 1.6±0.8 mg/dl. A total of 36% of the successfully transplanted patients were taken off prednisone; 32% of the patients were taken off antihypertensive medications. The incidence of delayed graft function was 21%, the incidence of cytomegalovirus was 12.5%, and the initial and final incidences of posttransplant insulin-dependent diabetes mellitus**

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were 7.0% and 2.9%; again, there was no difference between the two groups.

***Conclusions.* This trial suggests that the combination of tacrolimus, steroids, and mycophenolate mofetil is associated with excellent patient and graft survival and a lower incidence of rejection than the combination of tacrolimus and steroids.**

With the increasing accumulation of data regarding its use in renal transplantation (*1–10*), tacrolimus has become accepted as an effective immunosuppressive agent. However, the optimal manner in which it should be used has not yet been established. One question has concerned the utility of an adjunctive third agent. In an earlier trial comparing two tacrolimus-based regimens, with and without azathioprine, triple therapy was associated with a not-quite-significant reduction in the incidence of acute rejection, 45% vs. 55%, but worse graft survival, 76% vs. 84% in the double-therapy group, at 3 years (*3*, *11*). Subsequent to the completion of that trial, mycophenolate mofetil (MMF*; CellCept) was approved by the Food and Drug Administration (*12–15*), and a new, prospective randomized trial was begun, comparing tacrolimus/prednisone with tacrolimus/prednisone/MMF. The first report of this trial suggested a lower incidence of rejection in the triple-therapy group, without differences in patient or graft survival (*16*). In this report, we present 1-year actuarial data, in a larger number of patients, which confirm these original observations.

PATIENTS AND METHODS (TABLE 1)

Between September 20, 1995, and September 20, 1997, 208 renal transplantations, in 206 patients, were performed in adult recipients of first or second cadaveric kidneys only, who consented to participate in the trial. One hundred six were randomized to receive tacrolimus and prednisone, and 102 were randomized to receive tacrolimus, prednisone, and MMF, without induction antilymphocyte antibody therapy. Living donor recipients, patients undergoing their third or greater transplant, patients receiving an additional organ (e.g., pancreas, islets, liver, and/or bone marrow), patients refusing to consent, and pediatric recipients were excluded from the trial. The mean recipient age was 50.7±13.7 years (range: 19–84). Thirty-one (14.9%) patients were undergoing retransplantation, and 11 (5.3%) had a panel-reactive antibody level over 40%. Sixty-three (30.3%) patients were 60 years of age or older at the time of transplantation. Sixteen (7.7%) patients had undergone previous liver (*13*) or heart (*3*) transplantation. The mean donor age was 34.5±21.7 years (range: 0.01–76.5). Twenty-five (12%) transplants were with pediatric en-bloc kidneys from donors less than 4 years of age, and 28 (13.5%) were with kidneys from donors 60 years of age or older. The mean cold ischemia time was 30.5±9.2 hr (range: 4.5–57.1). The mean number of matches and mismatches was 2.5±1.4 and 3.1±1.5; there were 17 (8.2%) 0 antigen mismatch cases. There were no significant differences between the two arms in any of these parameters, except for a slightly older mean recipient age in the double-therapy arm (52.5±13.3 years vs. 48.7±13.6 years, $P<0.05$) and a slightly longer mean cold ischemia time in the triple therapy group (32.2±9.5 hr vs. 28.8±8.7 hr, $P<0.02$).

Tacrolimus dosing (Table 2). All patients received tacrolimus (0.15 mg/kg orally) on call to the operating room. Postoperatively, intravenous tacrolimus (0.025–0.05 mg/kg/day as a continuous infusion) was begun in the recovery room. Patients were converted to oral tacrolimus (0.15 mg/kg twice daily) as soon as they were able to tolerate oral dosing, generally within 2–3 days. Target levels were 20–25 ng/ml whole blood by IMX for the first 2 weeks after transplantation, 15–20 ng/ml by 1 month, 10–15 ng/ml by 3 months, and 5–12 ng/ml chronically. The target levels were the same in both groups.

Steroid dosing. All patients received a 1000-mg bolus of intravenous methylprednisolone in the operating room, and a short steroid recycle, from 200 to 20 mg/day, of intravenous methylprednisolone or oral prednisone, during the first 6 days after transplantation. In the ideal scenario, the prednisone dose was decreased to 15 mg/day by 3–4 weeks after transplantation, and then by 2.5 mg/day decrements to 10 mg/day by 2–3 months. Further tapering was individualized, but generally followed the schedule of 1.25–2.5 mg/day decrements every 4–6 weeks, with the protocol-defined goal of discontinuing steroids in all patients. In practice, the development of early (<1 month) acute rejection slowed down the timetable for steroid tapering, but steroid withdrawal remained the routine goal. Patients who developed rejection at low doses of prednisone (5–7.5 mg/day) necessarily received an increase in their steroid dosage as part of the treatment for rejection, but here also the possibility of complete steroid withdrawal was not necessarily obviated. Generally, no more than two attempts were made to withdraw steroids.

Mycophenolate mofetil. Patients randomized to the triple-therapy group were given 1 g of MMF orally before transplantation, and 1 g orally twice daily postoperatively. The dose was cut in half if a patient developed symptoms of toxicity, e.g., diarrhea. If symptoms did not respond to a decrease in the dosage, MMF was discontinued. MMF and tacrolimus doses were separated by 2–4 hr within a few months of the initiation of the trial, to allow for greater tolerability of the combination of the two agents.

Rejection. Rejection was biopsy-proven in over 95% of cases and was treated initially with a 1000-mg bolus and recycle of steroids, and an increase in the tacrolimus dose. Steroid-resistant rejections were treated with antilymphocyte preparations, generally OKT3, but occasionally ATG. Patients randomized to double therapy could be crossed over to triple therapy if they developed steroid-resistant or mild-moderate (or greater) rejection, at the discretion of the treating physician. Occasionally, refractory rejection was treated with intravenous immunoglobulin (2 g/kg) in 7–10 divided doses, again at the discretion of the treating physician (*17*, *18*).

Although all of the agents utilized in this trial were approved by the Food and Drug Administration, because of its randomized nature, approval from the Institutional Review Board of the University of Pittsburgh was obtained, with yearly renewals.

Statistical analysis (*19*). Continuous variables are presented as mean ± standard deviation, and categorical variables as proportions.

Randomization was done by sequential draw of assignment using a variable block randomization scheme. The block sizes varied (4 or 6) and were selected with equal probability. The order of assignment within a block was determined by generating a random number between 0 and 1 and then rearranging the random numbers in ascending order.

Baseline characteristics of the patient population were compared using the standard two-sample t test for continuous data and Pearson's chi-square test for categorical data.

Patient survival was calculated from the date of kidney transplantation until death and graft survival from the date of kidney transplantation until graft failure, repeat transplantation, or patient death. Survival curves were generated using the Kaplan-Meier (product-limit) method (*20*) and compared by the log-rank (Mantel-Cox) test (*21*). All tests were two-tailed. A P-value less than 0.05 was considered statistically significant. All analyses were performed using SPSS for Windows software.

The data were analyzed by intention to treat for all patients in the trial. In addition, patient and graft survival data were calculated for recipients under 60 years of age who did not have delayed graft function. This subgroup analysis was performed to facilitate comparison with large multicenter trials, the entry criteria for which often

* Abbreviations: MMF, mycophenolate mofetil; PTDM, posttransplant diabetes mellitus.

TABLE 1. Recipient and donor demographics[a]

	Tacrolimus/Prednisone	Tacrolimus/Prednisone/MMF	Overall
N	106	102	208
Recipient age (yr)	52.5±13.3	48.7±13.6*	50.7±13.7
(Range)	(19.3–84.1)	(18.8–72.5)	(18.7–84.1)
Repeat transplantation	13 (12.2%)	18 (17.6%)	31 (14.9%)
PRA >40%	6 (5.7%)	5 (4.9%)	11 (5.3%)
>60 yr	36 (34.0%)	27 (26.5%)	63 (30.3%)
Previous liver or heart transplant	7 (6.6%)	9 (8.8%)	16 (7.7%)
Donor age (yr)	33.8±20.9	35.5±22.6	34.5±21.7
(Range)	(0.2–76.4)	(0.01–76.5)	(0.01–76.5)
≥60 yr	12 (11.3%)	16 (15.7%)	28 (13.5%)
<4 yr	14 (13.2%)	11 (10.8%)	25 (12.0%)
(En bloc)			
Cold ischemia time	28.8±8.7	32.2±9.5**	30.5±9.2
(Range)	(4.2–49.0)	(15.3–57.1)	(4.7–57.1)
Antigen match	2.4±1.4	2.6±1.4	2.5±1.4
Antigen mismatch	3.2±1.5	3.1±1.5	3.1±1.5
0 Antigen mismatch	6 (5.7%)	11 (10.8%)	17 (8.2%)

[a] *, $P < 0.05$; **, $P < 0.02$.

TABLE 2. Immunosuppression[a]

Tacrolimus	
Preoperative	0.15 mg/kg orally
Postoperative	0.025–0.05 mg/kg intravenously, continuous infusion, until tolerating orally, then 0.15 mg/kg orally twice a day
Target levels (ng/ml whole blood IMX)	
First 2 weeks	20–25
1 month	15–20
3 months	10–15
Chronically	5–12
Steroids (intravenous methylprednisolone or po prednisone)	
Intraoperative	1000 mg
POD 1–6	200 → 20 mg/day
3–4 weeks	15 mg/day, then 2.5 mg/d decrement to
2–3 months	10 mg/day, then
Every 4–6 weeks	1.25–2.5 mg/day decrement, to 0 mg/day, if possible
Mycophenolate mofetil	
Preoperative	1000 mg orally
Postoperative	1000 mg orally twice a day

[a] IMX, POD, postoperative day.

have been restricted to patients under 60 years of age who have functioning allografts.

RESULTS (TABLE 3)

The mean follow-up was 15±7 months. The overall 1-year actuarial patient survival was 94%; in the stratified group, it was 97%. There was no difference between the double- and triple-therapy arms in either the overall or the stratified group.

The overall 1-year actuarial graft survival was 87%; in the stratified group, it was 93%. Again, there was no difference between the two arms in either the overall or the stratified group.

The overall incidence of rejection and steroid-resistant rejection was 36% and 5.3%; in the double-therapy arm, it was 44% and 7.5%, and in the triple-therapy arm, it was 27% (P=0.014) and 2.9% (P=NS). Rejections were histologically somewhat more severe in the double-therapy group, although the differences were not statistically different (Table 4; the pathologists were blinded as to the randomization status of each patient). In the triple-therapy patients who never discontinued MMF, the incidence of rejection and steroid-resistant rejection was 16% and 1.5%, whereas in those who discontinued MMF at any time, it was 49% and 5.7%. Most (80%) rejection episodes occurred within the first month after transplantation, in either group, and within the triple-therapy group, in either subgroup (i.e. those remaining on MMF or those discontinuing MMF).

At most recent follow-up, the mean serum creatinine was 1.6±0.8 mg/dl and did not differ between the two arms. The mean tacrolimus dose was 8.7±6.6 mg/day, 8.4±6.0 mg/day in the double-therapy arm, and 9.0±7.1 mg/day in the triple-therapy arm (P=NS). The mean tacrolimus level was 10.0±4.4 ng/ml, again without differences between the two arms. The lack of difference between the two groups was not surprising, as the protocol dosing and target levels were designed to be similar. The mean MMF dose was 1142±493 mg/day in the MMF arm.

A total of 36% of successfully transplanted patients were withdrawn from steroids, and 32% were withdrawn from antihypertensive medications. The mean serum cholesterol was 196±55 mg/dl. There were no differences between the two arms for any of these parameters.

The incidence of delayed graft function was 21%, and the incidence of cytomegalovirus, including asymptomatic infection, was 12.5%. The incidence of posttransplant lymphoproliferative disorder was 0.5%. The initial and final incidences of insulin-dependent posttransplant diabetes mellitus (PTDM) was 7.0% and 2.9%. Again, there were no differences between the double- and triple-therapy arms with regard to these adverse events.

Cross-over occurred in 31% of cases, 28% from double to triple therapy, and 34% from triple to double therapy. In the second year of the trial, the incidence of cross-over from triple to double therapy was 12%.

DISCUSSION

This report presents 1-year actuarial outcomes from the first randomized evaluation of MMF with tacrolimus-based therapy in renal transplant recipients. It confirms data reported with cyclosporine-based regimens, that MMF is associated with a significant reduction in the incidence of rejection, without any

TABLE 3. Results

	Follow-up at 15±7 months		
	Tacrolimus/prednisone	Tacrolimus/prednisone/MMF	Overall
1-year actuarial patient survival (whole group)	93%	96%	94%
1-year actuarial patient survival (stratified group)	95%	98%	97%
1-year actuarial graft survival (whole group)	85%	89%	87%
1-year actuarial graft survival (stratified group)	92%	93%	93%
Rejection	44%	27%[a]	36%
Steroid-resistant rejection	7.5%	2.9%	5.3%
Serum creatinine (mg/dl)	1.6±0.9	1.7±0.7	1.6±0.8
Tacrolimus dose (mg/day)	8.4±6.0	9.0±7.1	8.7±6.6
Tacrolimus level (ng/ml)	10.2±4.5	10.1±4.2	10.1±4.4
Off steroids	34%	39%	36%
Off antihypertensive medications	25%	39%	32%
Cholesterol (mg/dl)	200±62	192±46	196±55
Cytomegalovirus	8.5%	16.7%	12.5%
Posttransplant lymphoproliferative disorder	0.9%	0%	0.5%
Delayed graft function	21%	21%	21%
PTDM			
Initial	9.3%	4.7%	7.0%
Final	4.7%	1.2%	2.9%
Cross-over	2 → 3	3 → 2	
	28%	34% (2nd year; 12%)	31%

[a] $P = 0.014$.

TABLE 4. Severity of rejection[a]

	Tacrolimus/prednisone	Tacrolimus/prednisone/MMF
Borderline	5 (11%)	5 (19%)
Banff		
1A	16 (36%)	11 (41%)
1B	4 (9%)	4 (15%)
Banff 2	19 (43%)	7 (26%)
No biopsy	3	1

[a] Percentages are calculated within groups.

early difference in patient or graft survival (*12–15*). Although there was an increase in the incidence of cytomegalovirus in the triple-therapy group, this did not reach statistical significance.

Patient and graft survival were analyzed for both the entire group and a stratified group that excluded recipients over 60 years of age or who had delayed graft function. The stratification was made to allow for a comparison of primary outcomes with those from large multicenter trials, whose entry criteria generally exclude patients over 60 years of age or who have delayed graft function (*8, 9, 13, 14*). A substantial number of the patients entered into this trial were over 60 years of age, and, although this age group has been associated with acceptable outcomes, there has been a slightly higher mortality when compared with recipients under the age of 60 (*22–25*). Similarly, patients with delayed graft function are known to have worse graft survival than patients without delayed graft function (*26, 27*). When the stratified group was analyzed, 1-year actuarial patient and graft survivals of 97% and 93% were observed, comparable to those seen in the large multicenter trials (*8, 9, 13, 14*).

It is worth noting that there was no difference in tacrolimus dosing between the two arms. To some extent, this was driven by protocol, but it is still interesting that the use of MMF was not associated with any sparing of the nephrotoxic agent, in this case, tacrolimus.

Two other points bear mentioning. The first concerns the incidence of PTDM, which is lower than in previous reports. In the azathioprine trial, the initial and final incidence of PTDM was 18% and 9% (*28*), whereas in the American multicenter trial, it was 20% and 12% (*29*); in this trial, it was 7% and just under 3%. This suggests that, with more experience, it is possible to avoid this (largely reversible) complication. The second point concerns the incidence of cross-over. In the initial 6 months of this trial, some 48% of patients randomized to the triple-therapy arm had to discontinue MMF at one time or another, either because of gastrointestinal complications, principally diarrhea or gastritis, or hematologic problems, principally neutropenia or thrombocytopenia. In general, once MMF was discontinued, it was not resumed, although in a small number of patients (perhaps 10%), it was reintroduced at a low dose (250 mg once or twice daily). With separation of the MMF and tacrolimus dosages by 2–4 hr and early reduction of the MMF dosage at the first sign of toxicity, the rate of cross-over declined to 12% during the second year of the trial. The higher levels and the greater area under the concentration curve of MMF with tacrolimus (*30*) certainly explain the need for lower dosages of MMF, and in fact the average MMF dose at most recent follow-up was 57% of the starting dose. Not surprisingly, given the higher rate of rejection and increased severity of rejections in the double-therapy arm, cross-over to triple therapy was required in some 28% of patients originally randomized to double therapy. Cross-over to triple therapy was initiated in patients with a mild-moderate (Banff 1B) or greater rejection episode, or in patients with multiple episodes of mild acute rejection.

The data from this randomized trial confirm those recently reported in a nonrandomized experience (*31*), and suggest that the combination of tacrolimus and MMF is effective in patients undergoing renal transplantation, and that it is associated with a lower incidence of rejection than that seen in patients not receiving MMF. Short-term patient and graft survival are acceptable, although not different between the two groups. With increasing experience, cross-over from triple to double therapy has become less of a problem, and the

incidence of insulin-dependent PTDM has decreased. Future trials will look at the role of other agents, including induction with an anti-interleukin 2 monoclonal antibody (*32–35*), in combination with tacrolimus-based therapy, and will be compared with a tacrolimus/MMF-based regimen.

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