Rescue Immunosuppressive Therapies in Living-Related Renal Allotransplant: A Long-term Prospective Randomized Evaluation

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Abstract

Objectives: **The majority of our patients are maintained on prednisolone, cyclosporine, and azathioprine as primary immunosuppression. In the presence of repeated episodes of acute rejection, this maintenance immunosuppressive regimen is increased by replacing cyclosporine with tacrolimus or azathioprine with mycophenolate mofetil. To the best of our knowledge, there are no available data among living-related renal allotransplants that evaluate the long-term efficacy and safety of these rescue immunosuppressive therapies. Therefore, we sought to evaluate the long-term efficacy and safety of rescue immunosuppressive therapies among living-related renal allotransplant recipients.**

Materials and Methods: **We reviewed the long-term follow-up data of 212 renal transplant recipients at the Urology and Nephrology Center Mansoura University in Mansoura, Egypt, who had been maintained on a primary immunosuppressive protocol that included prednisolone, cyclosporine, and azathioprine. Patients were randomized at a ratio of 1:2 to receive more-intensive maintenance immunosuppression by replacing cyclosporine with tacrolimus in 65 patients (group TAC) and replacing azathioprine with mycophenolate mofetil in 147 patients (group MMF).**

Results: **We found no statistically significant difference between the 2 groups regarding rejection-free patients or those who experienced 1 or more episodes of acute rejection ($P > .5$). In group TAC and group MMF, graft survival rates were 87.3% and 96.3% at 2 years and 78.7% and 80% at 5 years, respectively ($P = .07$). The corresponding patient survival rates were 98.4% and 98.5% at 1 year, 98.4% and 97.7% at 2 years, and 94.4% and 94.4% at 5 years, respectively ($P = .65\%$). There were more patients with diabetes and serious bacterial infections in group TAC than there were in group MMF ($P = .001$ and .04, respectively).**

Conclusions: **Conversion from cyclosporine to tacrolimus or from azathioprine to mycophenolate mofetil is a safe, equipotent rescue especially with repeated acute rejections. However, mycophenolate mofetil rescue therapy was more beneficial regarding graft survival.**

Key words: *Renal transplant, Postconversion, MMF, Tacrolimus rescue*

The introduction of new and more-potent immunosuppressive agents since 1985 has resulted in the progressive improvement in 1-year graft survival rates after renal transplant (1); however, the number of functioning grafts continues to decline at an annual rate of 3% to 5% (2). In the majority of patients, late graft loss is attributed to chronic allograft nephropathy or death with a functioning graft (3). The leading cause of death is a cardiovascular event (4). The risk of posttransplant cardiovascular disease is increased by hypertension, hyperlipidemia, and diabetes, all of which can be exacerbated by the use of immunosuppressive agents (5, 6).

It is well known that mycophenolate mofetil is superior to azathioprine for immunosuppression after renal transplant. However, in developing countries, cost is a limiting factor. In 1 double-blind study (7), patients experiencing biopsy-proven rejection were randomized to receive mycophenolate mofetil or azathioprine plus pulse corticosteroids. At 6 months,

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there was a greater need for subsequent antilymphocyte therapy in the azathioprine group (42%) than there was in the mycophenolate mofetil group (17%) ($P < .05$). On the basis of these data, several centers have started to introduce mycophenolate mofetil at first rejection.

Switching from cyclosporine to tacrolimus can be an alternative strategy in kidney transplant patients with acute rejection episodes. In these patients, the persistently improving renal function over several months suggests that tacrolimus might be less nephrotoxic than cyclosporine and could prolong transplant function despite cyclosporine failure (8). To assure a successful rescue effect, if there is a tendency toward deterioration of renal function, tacrolimus should be given soon after transplant (9). Ferraresso and associates (10) reported that tacrolimus can play an important role in the salvage treatment of pediatric kidney transplants with deteriorating graft function because of acute rejection that is refractory to standard therapy, especially those associated with cyclosporine toxicity.

Jordan and associates (11) found after 5-year follow-up that tacrolimus has sustained efficacy as a rescue agent for ongoing renal allograft rejection. On the basis of these data, they recommend that tacrolimus be used as an alternative to conventional antirejection therapy in renal transplant recipients.

The majority of our patients are maintained on prednisolone, cyclosporine, and azathioprine as primary immunosuppression. In the presence of repeated episodes of acute rejection, this maintenance immunosuppressive regimen is increased by adding tacrolimus or mycophenolate mofetil. To the best of our knowledge, there are no available studies that evaluate the long-term efficacy and safety of these rescue immunosuppressive therapies among living-related renal allotransplant recipients. Therefore, we sought to evaluate the long-term efficacy and safety of rescue immunosuppressive therapies among living-related renal allotransplant recipients.

Patients and Methods

Study population

We reviewed the long-term follow-up data of 212 renal transplant recipients at the Urology and Nephrology Center Mansoura University in Mansoura, Egypt, who had been maintained on a primary immunosuppressive protocol that included prednisolone, cyclosporine, and azathioprine. Only adult primary renal transplant recipients between 18 and 60 years with 1 haplotype HLA mismatch were included. Patients with biopsy-proven chronic rejection were excluded. Because of repeated acute rejections, patients were randomized at a ratio of 1:2 to receive more-intensive maintenance immunosuppression by replacing cyclosporine with tacrolimus in 65 patients (group TAC) and replacing azathioprine with mycophenolate mofetil in 147 patients (group MMF). All patients received kidneys from living-related donors with previous donor nonspecific blood transfusions. We compared the 2 groups using several analyses to investigate clinically relevant endpoints indicative of long-term survival that could be affected by the immunosuppressive regimen. Preconversion clinical data of all the kidney transplant patients were reviewed. Demographic data included recipient age and sex; donor age and sex; causes of end-stage renal disease; human leukocyte antigens (HLA)-A, B, and DR mismatching; and medical complications such as hypertension, diabetes mellitus, and infections.

Methods

The protocols used in this study were approved by the local ethics committee before the study's initiation and conform to the ethical guidelines of the 1975 Helsinki Declaration. Written informed consent was obtained from all patients.

For all patients in both groups, primary immunosuppression was begun with prednisolone the day before transplant at a dose of 8.5 mg/kg/day and tapered gradually until the smallest maintenance dose of 0.15 mg/kg/day was reached by the end of the ninth month. Azathioprine was given in a dose of 2 mg/kg/day beginning the third day after surgery, and thereafter; while cyclosporine was introduced at a dose of 8.5 mg/kg/day and was adjusted to maintain trough levels between 200 and 400 ng/mL for the first 2 months and between 125 and 175 ng/mL thereafter. Cyclosporine trough levels were measured at first using Radio-immune Assay Kits (Sandoz, Basel, Switzerland) and then with monoclonal specific antibody (Abbott Laboratories, Abbott Park, IL, USA). At the time of conversion (the second episode of rejection), azathioprine was replaced with mycophenolate mofetil in small, gradually increasing dosages until 2 g/day was achieved. When cyclosporine was replaced with tacrolimus, we stopped the cyclosporine for 24 hours

before starting tacrolimus at a dosage of 0.075 mg/kg/day with a target trough level between 5 and 8 ng/mL.

Postconversion acute rejection episodes were biopsy proven and treated with pulse-steroid therapy (500 mg methyl prednisolone for 5 days). Steroid-resistant rejection was treated with antithymocyte globulin. Plasmapheresis was added to the treatment plan as an adjuvant therapy in cases of vascular rejections.

Statistical analyses

The statistical analyses were done with SPSS software (Statistical Product and Services Solutions, version 11.5, SPSS Inc, Chicago, IL, USA). All values are expressed as means ± standard deviation for continuous parametric data, medians for continuous nonparametric data, and frequencies for categorical data. Kaplan-Meier actuarial curves were constructed for patient and graft survival rates. Patients who lost their grafts were excluded at the time of graft loss; and when evaluating graft survival, patients who died with a functioning graft were excluded at the date of death. Values for *P* less than .05 were considered statistically significant.

Results

Table 1 shows the characteristics of the donors and the recipients. The majority of recipients were men in their 20s, while more than half of the donors were women in their 30s. The 2 groups were homogenous in terms of the donor and recipient age and sex, causes of renal failure, prior blood transfusion, pretransplant hypertension, and acute rejection episodes. In addition, no preformed antibodies against donor antigens were detected in the pretransplant crossmatch of any of the patients. The techniques used to re-establish urinary continuity were also essentially similar. There were no statistically significant differences in the graft survival between the 2 groups (95.3% in group TAC vs 97.8% in group MMF) until the end of the first year (the time of conversion in most of cases) (Figure 1).

Rejection episodes

The frequencies of rejection episodes, after conversion are shown in Table 2. We found no statistically significant differences between the 2 groups regarding rejection-free cases or those who experienced 1 or more rejection episodes ($P > .5$). The percentage of patients with 2 or more rejections was lower in the rescue group using mycophenolate mofetil, but the difference was not statistically significant ($P = .09$). Table 3 shows the 2 groups as comparable regarding

Table 1. Preconversion characteristics of donors and recipients in the 2 groups.

	Group TAC (n=65) steroid/ tacrolimus/ azathioprine		Group MMF (n=147) steroid/ mycophenolate mofetil/ cyclosporine		*P* value
Mean age of donors (y)	35.8 ± 10		35.9 ± 10		.35
Donor sex (male/female)	22/43		64/83		.75
Mean age of recipients (y)	27.4 ± 12		29.6 ± 10		.23
Recipient sex (male/female)	49/16		108/39		.19
Original kidney disease:					
Glomerulonephritis, n	36		59		.056
Chronic pyelonephritis, n	1		2		.59
Nephrosclerosis, n	3		1		.16
Pretransplant hypertension, n	39		81		.50
HLA matching ≥ 50%	44		110		.47
DR matching 50%	61	94.1%	134	91.6%	.66
Acute cellular rejection episodes	59	83%	110	83%	.92
Acute vascular rejection episodes	9	75%	19	73%	.76

Abbreviations: DR, loci of DR; HLA, human leucocyte antigen

Table 2. Rejection episodes in the 2 groups after conversion.

	Group TAC (n=65) steroid/ tacrolimus/ azathioprine		Group MMF (n=147) steroid/ mycophenolate mofetil/cyclosporine		*P* value
	No. of patients (%)		No. of patients (%)		
No rejection	35	(53.9)	76	(51.7)	.88
1 rejection	19	(29.2)	59	(40.1)	.17
> 2 rejections	11	(16.9)	12	(8.2)	.09

Table 3. Types of rejection episodes in the 2 groups before and after conversion.

	Group TAC (n=65) steroid/ tacrolimus/ azathioprine		Group MMF (n=147) steroid/ mycophenolate mofetil/cyclosporine		*P* value
Acute cellular rejections:	**Total (n=71)**	**(%)**	**Total (n=133)**	**(%)**	
Preconversion	59	(83)	110	(83)	.92
Postconversion	12	(17)	23	(17)	.90
Acute vascular rejections:	**Total (n=12)**	**(%)**	**Total (n=26)**	**(%)**	
Preconversion	9	(75)	19	(73)	.76
Postconversion	3	(25)	7	(27)	.78
Chronic rejection	3	(30)	12	(28.1)	.88

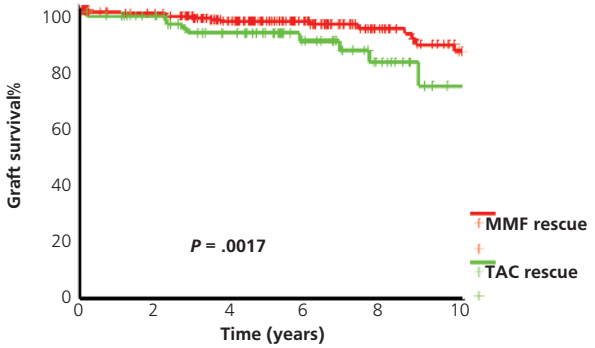

Figure 1. Patient survival in the 2 groups of patients.

the frequency of acute rejections (cellular or vascular) after conversion. Also, postconversion chronic rejection was comparable in both groups ($P = .88$).

Outcome

After conversion, graft survival rates were 87.3% in group TAC versus 96.3% in group MMF at 2 years and 78.7% versus 80% at 5 years, respectively ($P = .07$). The corresponding patient survival rates were 98.4% in group TAC versus 98.5% in group MMF at 1 year, 98.4% versus 97.7% at 2 years, and 94.4% versus 94.4% at 5 years, respectively (Figure 2) ($P = .65$). There were significantly more survivors with a functioning graft in group MMF ($P = .04$), while there were significantly more survivors undergoing dialysis in the TAC group ($P = .04$) (Table 4). We found no statistically significant difference between group TAC and group MMF regarding those who died with or without a functioning graft ($P = .69$ and $P = .16$, respectively).

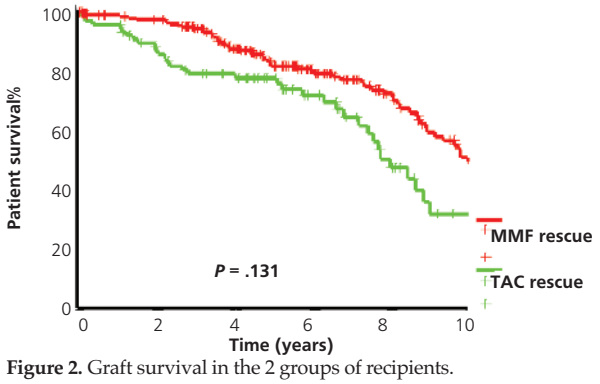

Figure 2. Graft survival in the 2 groups of recipients.

Table 4. Condition at last follow-up in the 2 groups.

	Group TAC (n=65) steroid/ tacrolimus/ azathioprine		Group MMF (n=147) steroid/ mycophenolate mofetil/cyclosporine		*P* value
	No.	(%)	No.	(%)	
Living with function graft	43	(66.2)	118	(80.3)	.04
Living on dialysis	17	(26.2)	20	(13.6)	.04
Died with function graft	2	(3.1)	8	(5.4)	.69
Died with failed graft	3	(4.6)	1	(0.7)	.16

Graft function

The number of patients with grades 1 and 2 graft function was comparable in both groups at 1 year and at the last follow-up (Table 5). The percentage of patients with grade-3 graft dysfunction was significantly higher in group1 at 1 year ($P = .001$). On the other hand, the percentage of these patients at the last follow-up was higher in group MMF, but this difference was not statistically significant ($P = .09$).

Complications

We found no significant differences between the 2 groups regarding posttransplant malignancies, hepatic impairment, or hypertension ($P > .05$). However, diabetic patients and those with serious bacterial infections were significantly more prevalent in group TAC than they were in group MMF ($P = .001$ and $P = .04$) (Table 6).

Table 5. Clinical grading of patients in the 2 groups at 1 year post-conversion and at last follow-up.

	Group TAC (n=65) steroid/ tacrolimus/ azathioprine		Group MMF (n=147) steroid/ mycophenolate mofetil/cyclosporine		*P* value
	No.	(%)	No.	(%)	
1 year postconversion					
Grade 1 (Cr < 1.5 mg/dL)	38	(58.4)	106	(72.1)	.07
Grade 2 (Cr 1.5-3 mg/dL)	20	(30.7)	40	(27.2)	.71
Grade 3 (Cr > 3-5 mg/dL)	7	(10.9)	1	(0.68)	.001
5 years postconversion					
Grade 1 (Cr < 1.5 mg/dL)	19	(29.2)	53	(36)	.41
Grade 2 (Cr 1.5-3 mg/dL)	24	(36.9)	62	(42.1)	.57
Grade 3 (Cr > 3-5 mg/dL)	22	(33.9)	32	(21.7)	.09

Cr = serum creatinine

Table 6. Types of serious complications encountered among the 2 groups.

	Group TAC (n=65) steroid/ tacrolimus/ azathioprine		Group MMF (n=147) steroid/ mycophenolate mofetil/cyclosporine		*P* value
	No.	(%)	No.	(%)	
Malignancies	1	(1.5)	1	(0.7)	.86
Hepatic impairment	5	(7.7)	13	(8.8)	.99
Posttransplant hypertension	46	(70.8)	101	(68.7)	.88
Posttransplant diabetes mellitus	17	(26.2)	15	(10.2)	.001
Bacterial infections	14	(21.5)	15	(10.2)	.04

Discussion

The number of functioning grafts continues to decline at an annual rate of 3% to 5% (2). In most patients, late graft loss is attributed to chronic allograft nephropathy or death with a functioning graft (2, 3). Death with a functioning graft is a leading cause of late renal allograft loss, with cardiovascular events being the most common causes in most patients (4). The risk of posttransplant cardiovascular disease is increased by the presence of hypertension, hyperlipidemia, and diabetes, all of which can be exacerbated by the use of immunosuppressive agents (5, 6).

Most of our patients were maintained on prednisolone, cyclosporine, and azathioprine as a primary immunosuppressive protocol. The prevalence of acute rejection during the first 3 months was relatively high among our patients (possibly due to

ethnic or genetic factors (12) and had a negative impact on graft survival (13). By the second acute rejection episode, our policy was to strengthen the immunosuppressive regimen by using either tacrolimus or mycophenolate mofetil. Therefore, we evaluated the long-term efficacy and safety of rescue immunosuppressive therapies among living-related renal allotransplants.

Our patients were homogenous in terms of donors' and recipients' age and sex, causes of renal failure, number of prior blood transfusion, presence of pretransplant hypertension, and number of preconversion acute rejection episodes. In addition, no preformed antibodies against donor antigens were detected in the pretransplant crossmatch of any of the patients in this study. The techniques used to re-establish urinary continuity also were essentially similar.

After conversion, we found no significant difference between both groups regarding the overall acute rejection episodes. The percentage of patients with 1 episode of acute rejection was higher in group MMF ($P = .17$), while the percentage of patients with 2 or more rejection episodes was higher in group TAC ($P = .09$); this difference was not statistically significant. The Mycophenolate Mofetil Acute Renal Rejection Study Group (14) found a much higher requirement for subsequent antilymphocyte therapy in their patients given azathioprine (42%) than in their patients given mycophenolate mofetil (17%) at 6 months after transplant.

Even without frank nephrotoxicity, it has been shown that it is safe to reduce the dosage of cyclosporine after converting from azathioprine to mycophenolate mofetil. Burke and associates (15) reduced the cyclosporine dosage to achieve a target trough level of 50 ng/mL in 38 patients with impaired renal function, and noted a significant improvement in serum creatinine at 6 months. Similarly, Weir and associates (16) studied 28 patients with declining renal function. Their dosage of cyclosporine was halved, and mycophenolate mofetil was substituted for azathioprine. Renal function improved in 21 of these patients (75%). There were no episodes of acute rejection in that study. Because mycophenolate mofetil is superior to azathioprine in renal transplant, several centers have started to introduce mycophenolate mofetil at first rejection (7).

In our study, the number of patients with chronic rejection was similar in both groups at the last follow-up ($P = .88$), which might be because there was a higher incidence of gastric upset in patients given mycophenolate mofetil rescue therapy, which required dosage modification leading to possible underimmunosuppression and subclinical rejection (17, 18). The percentage of patients with 2 or more rejection episodes was higher in group MMF. Also, the presence of a member of calcineurin inhibitors in each immunosuppressive rescue protocol might be an important additional factor.

There were more survivors with functioning grafts in group MMF compared with group TAC (80.3% vs 66.2%, $P = .04$). On the other hand, there were more survivors undergoing dialysis in group TAC (26.2%, $P = .04$). This could be attributed to the higher prevalence of serious bacterial infections and diabetes among patients in group TAC. Patient survival was comparable in both groups ($P = .131$) (Figure 1); however, better graft survival was seen in the mycophenolate mofetil rescue protocol compared with the tacrolimus rescue protocol at both 1 and 5 years ($P = .017$) (Figure 2).

Conclusions

Conversion either from cyclosporine to tacrolimus or from azathioprine to mycophenolate mofetil is a safe and equipotent rescue immunosuppression, especially in the presence of repeated acute rejections. However, mycophenolate mofetil rescue therapy was more beneficial to graft survival.

References

1. Hariharan S, Johnson CP, Bresnahan BA, Taranto SE, McIntosh MJ, Stablein D. Improved graft survival after renal transplantation in the United States, 1988 to 1996. N Engl J Med. 2000;342(9):605-612.
2. Pascual M, Theruvath T, Kawai T, Tolkoff-Rubin N, Cosimi AB. Strategies to improve long-term outcomes after renal transplantation. N Engl J Med. 2002;346(8):580-590.
3. Ponticelli C, Villa M, Cesana B, Montagnino G, Tarantino A. Risk factors for late kidney allograft failure. Kidney Int. 2002;62(5):1848-1854.
4. Evenepoel P, Vanrenterghem Y. Death with functioning graft--a preventable cause of graft loss. Ann Transplant. 2001;6(4):17-20.
5. Silkensen JR. Long-term complications in renal transplantation. J Am Soc Nephrol. 2000;11(3):582-588.
6. Kasiske BL. Epidemiology of cardiovascular disease after renal transplantation. Transplantation. 2001;72(suppl 6):S5-S8.
7. Ojo AO, Meier-Kriesche HU, Hanson JA, et al. Mycophenolate mofetil reduces late renal allograft loss independent of acute rejection. Transplantation. 2000;69(11):2405-2409.
8. Cantarovich D, Renou M, Megnigbeto A, et al. Switching from cyclosporine to tacrolimus in patients with chronic transplant dysfunction or cyclosporine-induced adverse events. Transplantation. 2005;79(1):72-78.

9. Hu RH, Lee CY, Tsai MK, Lee PH. Effects of and predictors for tacrolimus rescue therapy among renal transplant patients under cyclosporine-based immunosuppression. Transplant Proc. 2004;36(7):2092-2095.
10. Ferraresso M, Ghio L, Edefonti A, Garavaglia R, Berardinelli L. Conversion from cyclosporine to tacrolimus in pediatric kidney transplant recipients. Pediatr Nephrol. 2002;17(8):664-667.
11. Jordan ML, Naraghi R, Shapiro R, et al. Tacrolimus rescue therapy for renal allograft rejection–five-year experience. Transplantation. 1997;63(2):223-228.
12. Sheashaa HA, Bakr MA, Ismail AM, et al. Long-term evaluation of basiliximab induction therapy in live donor kidney transplantation: a five-year prospective randomized study. Am J Nephrol. 2005;25(3):221-225.
13. Ghoneim MA, Bakr MA, Hassan N, et al. Live donor renal transplantation at Urology and Nephrology center of Mansoura: 1976-1998. In Terasaki P, Cecka J, eds. *Clinical Transplants*. 17th ed. Los Angeles, CA: UCLA tissue typing laboratory; 2001:167-178.
14. [No authors listed] Mycophenolate mofetil for the treatment of a first acute renal allograft rejection: The Mycophenolate Mofetil Acute Renal Rejection Study Group. Transplantation. 1998;65(2):235-241. Erratum in: Transplantation 1998;65(7).
15. Burke J, Islam M, Francos G, Dunn S. Introduction of mycophenolate mofetil (MMF) and reduction in cyclosporine (CyA) dosage is effective in the treatment of chronic renal allograft dysfunction. Nephrology 1997;3(S1):S329.
16. Weir MR, Anderson L, Fink JC, et al. A novel approach to the treatment of chronic allograft nephropathy. Transplantation. 1997;64(12):1706-1710
17. Pelletier RP, Akin B, Henry ML, et al. The impact of mycophenolate mofetil dosing patterns on clinical outcome after renal transplantation. Clin Transplant. 2003;17(3):200-205.
18. Hardinger KL, Brennan DC, Lowell J, Schnitzler MA. Long-term outcome of gastrointestinal complications in renal transplant patients treated with mycophenolate mofetil. Transpl Int. 2004;17(10):609-616.