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"SUBOPTIMAL" KIDNEY DONORS

THE EXPERIENCE WITH TACROLIMUS-BASED IMMUNOSUPPRESSION

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Female, pediatric, and older donors have been associated with inferior graft survival after renal transplantation. We analyzed these three subgroups in 397 patients receiving tacrolimus-based immunosuppression. There were no differences in recipient age, incidence of retransplantation, or percentage of sensitized patients. Female donors, compared with male donors, were associated with comparable 1- and 3-year patient survival rates (96% and 93% vs. 95% and 92%, respectively) and comparable 1- and 3-year graft survival rates (90% and 80% vs. 88% and 81%, respectively). Renal function was also similar. Recipients of pediatric en bloc kidneys, when compared with recipients of other cadaveric kidneys, also had comparable 1- and 3-year patient survival rates (94% and 94% vs. 95% and 91%, respectively) and comparable 1- and 3-year graft survival rates (84% and 84% vs. 89% and 79%, respectively). Renal function was better in recipients of en bloc kidneys, with a mean serum creatinine level of 1.4±1.8 mg/dl vs. 2.0±1.5 mg/dl (P=0.01). In contrast to the first two subgroups, donors over 60 years of age, when compared with donors under 60 years of age, were associated with worse 1- and 3-year patient survival rates (88% and 80% vs. 96% and 94%, respectively; P<0.03) and worse 1- and 3-year graft survival rates (74% and 62% vs. 91% and 83%, respectively; P<0.0001). Renal function was worse in the older donor group, with a serum creatinine level of 2.7±1.2 mg/ml vs. 1.9±1.5 mg/dl (P=0.01).

We conclude that, under tacrolimus-based immunosuppression, kidneys from female or very young pediatric donors are not associated with adverse outcomes, whereas kidneys from donors over 60 years of age are associated with inferior outcomes.

A potential conflict in renal transplantation relates to the interest in using "expanded criteria" donors to increase the stagnant organ supply, and the importance of the "quality" of a given kidney and its impact on long-term outcome. There have been many reports of inferior outcomes with kidneys from female donors, pediatric donors, and older donors (*1–15*), and many theories advanced to explain these findings (*16, 17*). In view of the improving results reported with tacrolimus-based immunosuppression in renal transplantation (*18–23*), we thought it would be useful to look at these three different subgroups in some detail, with a view toward perhaps modifying our notions of what constitutes a truly "suboptimal" donor. This analysis was performed on a well-studied group of patients who entered a prospective, randomized, open-label trial of tacrolimus/prednisone versus tacrolimus/azathioprine/prednisone, between August 1, 1991, and December 9, 1993 (*20*).

MATERIALS AND METHODS

A total of 397 kidney transplantations were performed during the course of the above-mentioned trial. The details of the donor and recipient population, immunosuppressive protocols, and overall outcomes have been reported previously (*18–20*). In this analysis, we compared outcomes with kidneys from female (n=166) versus male (n=231) donors, en bloc kidneys from pediatric donors 3 years of age or younger (n=50) versus kidneys from other, i.e., mostly adult cadaveric donors (n=308), and kidneys from donors over (n=43) versus donors under (n=354) the age of 60 years (Table 1). None of the subgroups differed significantly in terms of recipient age or percentage of recipients over 60, nor did they differ in terms of the percentage of recipients undergoing retransplantation or having a panel reactive antibody (PRA*) level over 40%. Parameters studied were 1-year actual and 3-year actuarial patient and graft survival rates, measures of renal function, and the incidence of delayed graft function and rejection. The two immunosuppressive groups were pooled for the purposes of the subgroup analyses, to allow for adequate sample size.

Statistical analysis. Continuous variables were described as the mean ± SD, and categorical variables were described as proportions.

The standard two-sample t test was used to test differences between means, and differences in proportions were tested using Pearson's chi-square test or Fisher's exact test if expected frequencies were less than 5. The Wilcoxon rank sum test, a nonparametric equivalent to the standard two-sample t test, was used for highly skewed data.

Patient survival rates were calculated from the date of kidney transplantation until death, and graft survival rates from the date of kidney transplantation until graft failure, retransplantation, or patient death. Survival curves were generated using the Kaplan-Meier (product-limit) method and compared using the log-rank (Mantel-Cox) test. Cox's proportional hazards model was used to compute the relative risk of graft failure and 95% confidence intervals. All tests

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* Abbreviations: BUN, blood urea nitrogen; PRA, panel reactive antibody.

TABLE 1. Donor and recipient characteristics[a]

Donor subgroup	Donor age (yr)	Recipient age (yr)	Retransplant n (%)	PRA ≥40% n (%)	Recipient >60 yr n (%)
Female (n=166)	35.9±21.9	44.3±14.2	34 (21)	19 (11)	28 (17)
Male (n=231)	32.7±19.4	44.9±14.0	66 (29)	34 (15)	44 (19)
En bloc (n=50)	1.4±1.1	43.4±15.0	8 (16)	5 (10)	12 (24)
Other cadaver (n=308)	38.3±18.1	45.6±14.0	88 (29)	47 (15)	59 (19)
>60 yr (n=43)	65.4±3.3	45.3±13.3	6 (14)	2 (5)	7 (16)
≤60 yr (n=354)	30.2±18.4	44.6±14.2	94 (27)	51 (14)	65 (18)

[a] P=NS for recipient age, retransplants, PRA ≥40%, and recipients >60 years old.

were two-tailed. A P-value of less than 0.05 was considered statistically significant.

This study was performed before tacrolimus received approval from the U.S. Food and Drug Administration. In view of the study's prospective, randomized design, local institutional review board approval, with yearly renewal, was routinely sought and granted.

RESULTS

The mean follow-up period was 33±10 months for all subgroup analyses.

Female donors versus male donors. There were no differences in outcomes between recipients of female or male kidneys (Fig. 1). One-year actual and 3-year actuarial patient survival rates were 96% and 93% with female donors and 95% and 92% with male donors, respectively. The corresponding graft survival rates were 90% and 80% for female donors and 88% and 81% for male donors, respectively. The mean serum creatinine level, blood urea nitrogen (BUN) level, and calculated creatinine clearance were 1.9±1.7 mg/dl, 29±15 mg/dl, and 58±27 ml/min, for female donors, and 1.9±1.2 mg/dl, 31±15 mg/dl, and 54±23 ml/min, respectively, for male donors (Table 2). The incidences of delayed graft function and rejection were also not different.

Pediatric en bloc donors versus other cadaveric donors. In this subgroup analysis, 1-year actual and 3-year actuarial patient survival rates were similar and were 94% and 94% for en bloc recipients, and 95% and 91% for recipients of all other cadaveric kidneys (Fig. 2). Graft survival rates were also similar overall, and were 84% at 1 year and 3 years for en bloc recipients, and 89% and 79% for other cadaveric recipients. The measures of renal function were significantly better in the en bloc recipients (Table 2), with a lower mean serum creatinine level and BUN level and higher calculated creatinine clearance (1.4±1.8 mg/dl, 23±9 mg/dl, and 69±24 ml/min, vs. 2.0±1.5 mg/dl, 32±16 mg/dl, and 52±23 ml/min, respectively), than in the other cadaveric recipients (P=0.01 for serum creatinine, P<0.0001 for BUN, and P<0.0001 for calculated creatinine clearance). In addition, while the incidence of delayed graft function was not different (30% vs. 39%), the incidence of rejection was significantly lower in the en bloc recipients (30% vs. 55%; P<0.001).

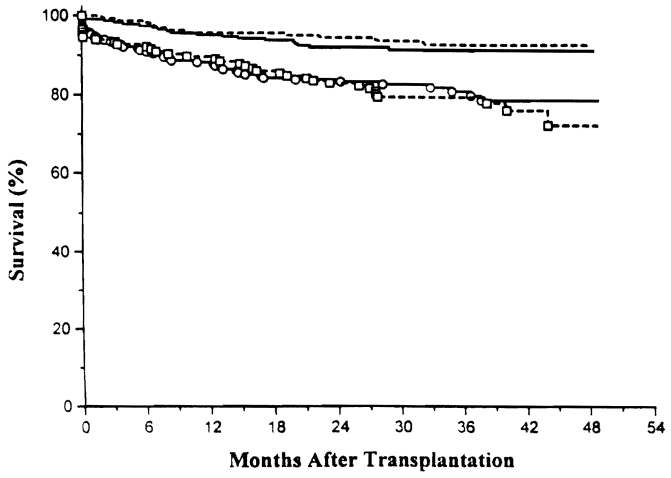

FIGURE 1. Patient and graft survival rates in recipients of kidneys from female versus male donors. For patient survival: ——— = male donors (n=230), - - - - - = female donors (n=165), P=0.516 (log rank). For graft survival: ○—○ = male donors (n=231), □- - -□ = female donors (n=166), P=0.559 (log rank).

Donors over versus donors under 60 years of age. There were marked differences in outcomes between recipients of kidneys from donors over and donors under 60 years of age (Fig. 3). Patient survival rates at 1 year and 3 years in the over-60 group were significantly worse (88% and 80%) than in the under-60 group (96% and 94%; P<0.03). There was no discernible pattern regarding the causes of death: cardiac disease, infectious problems, intracranial hemorrhage, and malignancy were all observed. Graft survival was also worse, with 74% and 62%, versus 91% and 83%, 1- and 3-year outcomes (P=0.001), in the over-60 and under-60 groups, respectively. While donor disease was noted in several patients losing their allografts, chronic allograft nephropathy was the most common cause of graft failure. Renal function was worse (Table 2), with a higher mean serum creatinine level and BUN level and lower calculated creatinine clearance in the over-60 group. Delayed graft function was seen in 54% of the over-60 group, significantly more than in the under-60 group (33%; P=0.006). In addition, the incidence of rejection was significantly higher in the over-60 group (67%) than in the under-60 group (48%; P<0.02).

DISCUSSION

In the United States, over 30,000 individuals are on the waiting list for renal transplantation, and this number increases at a rate at over 2000 patients/year (*24*, *25*). Thus, there is an active interest in expanding the donor pool. However, an important question with these expanded-criteria donor organs is whether they are of sufficient quality to justify their use. Our data with three different groups of "suboptimal" donors in patients treated with tacrolimus are reassuring for two of these categories and are troubling for the third.

The lack of effect of donor sex on any parameter of outcome or function is at variance with many published reports in the transplant literature (*1–9*, *26*). Explanations for worse outcomes have included factors such as the nephrotoxicity of

TABLE 2. Outcomes

	Serum creatinine (mg/dl)	BUN (mg/dl)	Creatinine clearance (ml/min)	Delayed graft function (%)	Rejection (%)
Female	1.9±1.7	29±15	58±27	31	48
Male	1.9±1.2	31±15	54±23	38	51
En bloc	1.4±1.8[a]	23±9[b]	69±24[b]	30	30[c]
Other cadaver	2.0±1.5[a]	32±16[b]	52±23[b]	39	55[c]
>60 years	2.7±1.2[a]	37±16[d]	43±17[e]	54[e]	67[f]
≤60 years	1.9±1.5[a]	30±15[d]	57±25[e]	33[e]	48[f]

[a] $P=0.01$.
[b] $P=0.0001$.
[c] $P=0.001$.
[d] $P<0.03$.
[e] $P=0.006$.
[f] $P<0.02$.

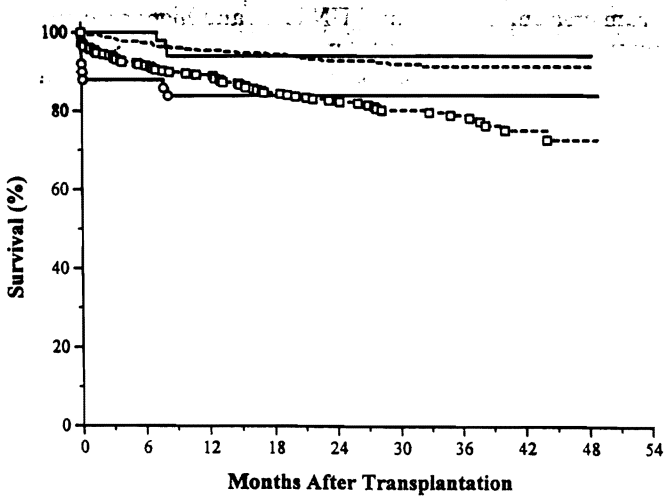

FIGURE 2. Patient and graft survival rates in recipients of en bloc kidneys from pediatric donors versus other cadaveric donors. For patient survival: ——— = en bloc (n=50), - - - - - = other cadaveric (n=306), $P=0.596$ (log rank). For graft survival: O—O = en bloc (n=50), □- - -□ = other cadaveric (n=308), $P=0.440$ (log rank).

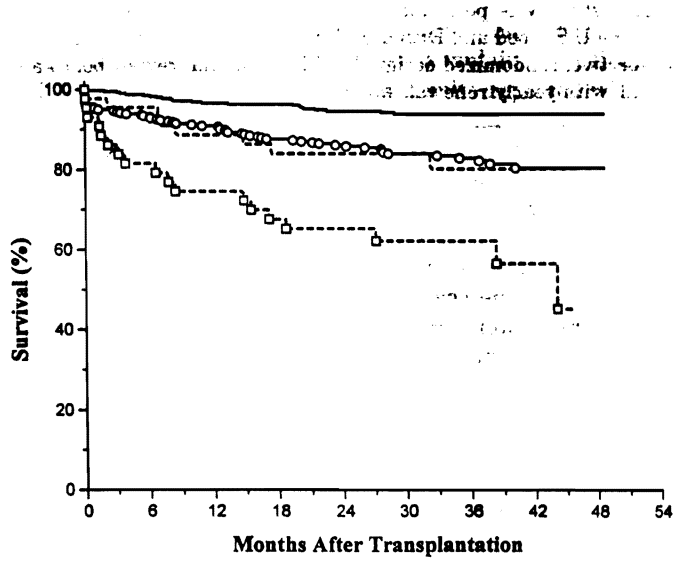

FIGURE 3. Patient and graft survival rates in recipients of kidneys from donors over or under the age of 60. For patient survival: ——— = donor age ≤60 (n=352), - - - - - = donor age >60 (n=43), $P=0.003$ (log rank). For graft survival: O—O = donor age ≤60 (n=354), □- - -□ = donor age >60 (n=43), $P=0.0001$ (log rank).

cyclosporine, and decreased renal mass, or "nephron dose," of female donors (*16, 17*). We have seen no evidence of any such effect under tacrolimus, an agent that is generally thought to exhibit nephrotoxicity comparable to that seen with cyclosporine (*27–31*). The lack of donor sex effect may well be simply a function of the superiority of tacrolimus as an immunosuppressive agent, evidence for which is becoming increasingly apparent (*20, 21, 23*). Since the donor sex effect has largely been confined to the first 3 months after transplantation, perhaps the more efficacious immunosuppression offered by tacrolimus has been associated with less early graft loss to rejection.

This greater protection against rejection of an organ with less renal mass could also explain the excellent outcomes obtained with en bloc kidneys. It is worth noting that there was a slight decrement at 1 year in the en bloc cases, possibly related to an increased number of technical losses or cases of primary nonfunction; these were, however, not sufficient to degrade the overall outcome with these kidneys. The fact that the renal function is actually better with en bloc kidneys is probably a function of the fact that two kidneys are being transplanted. In the absence of overwhelming rejection and excessive toxicity, these kidneys can grow and provide excellent renal function over time (*32, 33*). An argument could be made that these small kidneys could be separated and used singly (*34*), and these results are sufficiently encouraging that this idea could perhaps be considered for donors over the age of 1½ or 2 years. At present, we have little data of our own on this issue and have been reluctant to separate kidneys from donors less than 3 or 4 years of age.

The lower rate of rejection observed with en bloc kidneys is harder to understand. Although there is a tendency to transplant these kidneys into low PRA recipients undergoing their first transplant, the en bloc group did not have significantly fewer retransplant or high PRA patients. It is hard to imagine these kidneys being less immunogenic than other cadaveric organs. Certainly, in the cyclosporine era, we have had anecdotal experience with early overwhelming rejection occasionally destroying these organs. Thus, this observation is a bit mysterious.

Finally, the worse outcomes with older donors are of significant concern. Both patient and graft survival were inferior, as was the quality of renal function. Delayed graft function and rejection were also seen more frequently than in

the under-60 group. These poor results could argue against the use of donors over 60 years of age under any circumstances. Parenthetically, these results under tacrolimus are substantially better than our experience with these donors under cyclosporine-based therapy (*35*, *36*). At present, our routine with older donors is to biopsy the kidneys and get an immediate frozen section reading, looking specifically at the percentage of glomerulosclerosis, as well as a qualitative assessment of arterionephrosclerosis and interstitial fibrosis. In addition, the urine output of the donor and the serum creatinine over time are also assessed. Anything over 20% glomerulosclerosis or more than mild arterionephrosclerosis or interstitial fibrosis, or evidence of a falling urine output, or a rising serum creatinine, will lead to rejection of the donor organ for transplantation. We are hopeful that these well-defined, somewhat more selective criteria will allow us to use organs from older donors more successfully, but clearly these results are grounds for increasing conservatism.

In summary, under tacrolimus-based immunosuppression, there was no penalty in using female or pediatric en bloc kidneys, and these two groups of donors should not be considerable suboptimal. Older donors, on the other hand, were associated with significantly inferior results. If kidneys from older donors are to be transplanted, they should be used with extreme caution and after careful screening.

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REFERENCES

1. Cecka JM, Terasaki PI. The UNOS Scientific Renal Transplant Registry. In: Terasaki PI, Cecka JM, eds. Clinical transplants 1993. Los Angeles: UCLA Tissue Typing Laboratory, 1994: 1.
2. Takiff H. Donor factors. In: Terasaki PI, ed. Clinical transplants 1989. Los Angeles: UCLA Tissue Typing Laboratory, 1990: 417.
3. Shibue T, Kondo K, Iwaki Y, Terasaki PI. Effect of sex on kidney transplants. In: Terasaki PI, ed. Clinical transplants 1987. Los Angeles: UCLA Tissue Typing Laboratory, 1987: 351.
4. Kenneally P. The impact of sex on kidney transplantation. In: Terasaki PI, ed. Clinical kidney transplant 1985. Los Angeles: UCLA Tissue Typing Laboratory, 1985: 147.
5. Zhou YC, Cecka JM. Effect of sex on kidney transplants. In: Terasaki PI, ed. Clinical transplant 1989. Los Angeles: UCLA Tissue Typing Laboratory 1989: 361.
6. Koka P, Cecka JM. Sex and age effects in renal transplantation. In: Terasaki PI, ed. Clinical transplants 1990. Los Angeles: UCLA Tissue Tying Laboratory, 1990: 437.
7. Cecka JM. Donor factors. In: Terasaki PI, ed. Clinical transplants 1987. los Angeles: UCLA Tissue Typing Laboratory, 1987: 423.
8. Yuge J, Cecka JM. Sex and age effects in renal transplantation. In: Terasaki PI, ed. Clinical transplants 1991. Los Angeles: UCLA Tissue Typing Laboratory, 1991: 257.
9. Thorogood J, van Houwelingen JC, van Rood JJ, Zantvoom FA, Schreuder GMT, Persign GG. Factors contributing to long-term kidney graft survival in Eurotransplantation. Transplantation 1992; 54: 152.
10. Hong JH, Shirani K, Arshad A, et al. Influence of cadaver donor age on the success of kidney transplants. Transplantation 1981; 32: 532.
11. Ploeg RJ, Visser MJT, Stijnen T, Persijn GG, van Schilfgaarde R. Impact of donor age and quality of donor kidneys on graft survival. Transplant Proc 1987; 19: 1532.
12. Opelz G. Influence of recipient and donor age in pediatric renal transplantation. Transpl Int 1988; 1: 95.
13. Yuge J, Cecka JM. Pediatric recipients and donors. In: Terasaki PI, ed. Clinical transplants 1990. Los Angeles: UCLA Tissue Typing Laboratory, 1990: 425.
14. Alexander JW, Vaughn WK, Carey MA. The use of marginal donors for organ transplantation: the older and younger donors. Transplant Proc 1991; 23: 905.
15. Smith AY, van Buren CT, Lewis RM, Kerman RH, Kahan BD. Short-term and long-term function of cadaveric kidneys from pediatric donors in recipients treated with cyclosporine. Transplantation 1988; 45: 360.
16. Brenner BM, Milford EL. Nephron underdosing: a programmed cause of chronic renal allograft failure. Am J Kidney Dis 1993; 21 (suppl 2):66.
17. Brenner BM, Cohen RA, Milford EL. In renal transplantation, one size may not fit all. J Am Soc Nephrol 1992; 3: 162.
18. Shapiro R, Jordan M, Scantlebury V, et al. A prospective, randomized trial of FK506 in renal transplantation: a comparison between double and triple drug therapy. Clin Transplant 1994; 8: 509.
19. Shapiro R, Jordan ML, Scantlebury VP, et al. A prospective, randomized trial of FK506-based immunosuppression after renal transplantation. Transplantation 1995; 59: 485.
20. Shapiro R, Jordan ML, Scantlebury VP, et al. A prospective, randomized trial of FK506/prednisone vs FK506/azathioprine/prednisone in renal transplant patients. Transplant Proc 1995; 27(1): 814.
21. Shapiro R, Scantlebury VP, Jordan ML, et al. FK506 in pediatric kidney transplantation—primary and rescue experience. Pediatr Nephrol 1995; 9 (suppl): S43.
22. Laskow DA, Vincenti F, Neylan J, Mendez R, Matas A. Phase II FK506 Multicenter Concentration Control Study: one-year follow-up. Transplant Proc 1995; 22(1): 809.
23. Gjertson DW, Cecka JM, Terasaki PI. The relative effects of FK506 and cyclosporine on short- and long-term kidney graft survival. Transplantation 1995; 60(12): 1384.
24. UNOS Update. 1995; 11(12): 26.
25. UNOS Update. 1994; 10(12): 27.
26. Neugarten J, Silbiger SR. The impact of gender on renal transplantation. Transplantation 1994; 58(11): 1145.
27. McCauley J, Takaya S, Fung J, et al. The question of FK506 nephrotoxicity after liver transplantation. Transplant Proc 1991; 23(1): 1444.
28. Starzl TE, Abu-Elmagd K, Tzakis A, et al. Selected topics on FK506, with special references to rescue of extrahepatic whole organ grafts, transplantation of "forbidden organs," side effects, mechanisms, and practical pharmacokinetics. Transplant Proc 1991; 23(1): 914.
29. Starzl TE. FK506 versus cyclosporine. Transplant Proc 1993; 25(1): 511.
30. Demetris AJ, Banner B, Fung JJ, et al. Histopathology of human renal allograft function under FK506: a comparison with cyclosporine. Transplant Proc 1991; 23: 944.
31. Randhawa PS, Shapiro R, Jordan ML, Starzl TE, Demetris AJ. The histopathological changes associated with allograft rejection and drug toxicity in renal transplant recipients maintained on FK506: clinical significance and comparison with cyclosporine. Am J Surg Pathol 1993; 17(1): 60.
32. Nghiem DD, Hsia S, Schlosser JD. Growth and function of en bloc infant kidney transplant: a preliminary study. J Urol 1995; 153(2): 326.

33. Darras F, Jordan ML, Shapiro R, et al. Transplantation of pediatric en bloc kidneys under FK 506 immunosuppression. Transplant Proc 1991; 23: 3089.
34. Gruessner RWG, Matas AJ, Lloveras G. A comparison of single and double pediatric cadaver donor kidneys for transplantation. Clin Transplant 1989; 3: 209.
35. Vivas CA, O'Donovan RM, Jordan ML, et al. Cadaveric renal transplantation using kidneys from donors greater than 60 years old. Clin Transplant 1992; 6: 77.
36. Vivas CA, Gritsch A, Shapiro R, et al. Cadaveric renal transplantation using donors over 60 years old: 5 year followup. Transplant Proc (in press).

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