Expanding the Kidney Allograft Donor Pool in the Tacrolimus Era

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Kidney transplantation is the most satisfactory modality of treatment for end-stage renal disease. Over the past decade, the results of kidney transplantation have improved dramatically, due to the availability of new immunosuppressive drugs. A newer, more potent drug, Tacrolimus (TAC), approved by the United States Food and Drug Administration on April 12, 1994, is very promising also in renal transplantation, with one-year patient and graft survival equal or superior to results of recipients treated with cyclosporine (CyA).[1,2] However, the number of patients on dialysis and awaiting kidney transplantation has increased more than five-fold during the past 15 years and now exceeds 26,000.[3]

As kidney transplantation has become more successful and widely practiced, older patients are now more likely to be considered as candidates for allograft transplantation. Unfortunately, in the United States, the number of cadaver donors has declined over the past few years, now being at about 4,800 per year.[3]

Several factors have had a significant impact in the shortage of donor organ supply, such as the enforcement of the speed limit at 55 miles per hour, the use of seat belts, motorcycle and bike helmets, child restraint seats, and improved trauma care. A study conducted in Pennsylvania, concerning the characterization of the potential renal organ donor pool, concluded that there is a potential for the current ratio of organ donation to increase by at least a factor of 2, with the families' refusal to donate being responsible for a significant number of missed potential donors.[4] Ultimately, the organ supply has remained unchanged.[3] Although financial incentives are being considered for the family of the organ donor, it is felt that educational programs for both healthcare personnel and the general public are needed to improve organ donation.[4] There are important economic advantages in expanding the donor pool. According to the Health Care Financing Administration, a 25% increase in organ donation would result in approximately 2,000 kidney transplants and a saving of $68 million over the next 10 years.[5]

After a brief description of TAC, this chapter will focus on the critical issue of expanding the cadaver donor pool, by considering both the very young and the older kidney donors.

TACROLIMUS

TAC (Prograf™ formerly FK506) is a macrolide antibiotic, with potent immunosupressive activity, isolated as a fermentation product from the soil fungus *Streptomyces tsukubaensis*.[6-7] It is exclusively

metabolized in the liver, with less than 1% being excreted in the bile and urine.[8] Ochiai et al. first reported the results of a preclinical trial in the heterotopic cardiac allotransplantation in the rat at the Transplantation Society meeting in 1986.[9] In the United States, the first results of basic and clinical research were presented at the First International Congress on FK506, held in Pittsburgh, Pennsylvania, in 1991.[10]

As of today, TAC is the most potent immunosuppressive drug used in humans and has been shown to be very effective in all solid organ transplants.[11,12] Although its intracellular mechanism of action is similar to that of Cyclosporine (CyA), with equal or higher patient and graft survival in kidney transplants, TAC has several advantages over CyA. TAC is associated with the ability to be weaned from steroids in up to 60% of the allograft recipients, lower serum cholesterol levels, and lower incidence of hypertension.[13-15] Used intravenously, TAC has been shown to be effective in treating acute cellular rejection in both liver and kidney allografts,[16,17] although the mechanism is still not completely understood. One could speculate that this is due to the fact that TAC is substantially more potent than Cyclosporine (CyA) in suppressing B cell activation.[18,19] The ability to be weaned from steroids, under TAC, is definitely a marked advancement in the management of immunosuppressed patients, especially children[20] who notably suffer a significant growth deficit when treated with CyA. When using CyA, the addition of steroids is required almost universally to keep the allograft rejection-free. Even more impressive have been the reports of successful rescue, by TAC, of renal allografts that were failing under conventional immunosuppressive agents. The success ratio was reported to be 74%, in both adults and children, with some patients already in dialysis treatment, at the time of the switch to TAC.[21-24]

THE PEDIATRIC DONOR

Despite a crucial organ shortage, pediatric donors have been underestimated as a potential source of renal allografts. The report by Yuge et al. showed that pediatric donors, under the age of 10 years, represented less than 10% of first cadaver donor kidneys.[25] The recipients of kidneys from donors 5 years of age or younger scored a significantly lower graft survival at one year (68%), when compared to recipients of pediatric donors ages 16 to 18 (81%).

Historically, pediatric cadaver kidney allografts have been considered difficult because of a higher incidence of primary non-functioning kidneys and technical complications,[26,27] especially with donors under the age of 3 years.[28] More recently, some centers started to perform en-bloc paired allograft transplantion with acceptable results, although the initial series was comprised of a relatively small number of patients.[29] Darras et al. reported the first Pittsburgh Transplant experience of 39 pediatric en-bloc kidneys, from donors under 4 years of age, with TAC as primary immunosuppression. The overall patient and graft survival rate was 92% and 74% respectively, with 45% of patients being on tacrolimus monotherapy.[30] Memel et al. in a larger retrospective review study of pediatric en-bloc kidneys transplanted at our institution over a 10-year period showed an overall graft survival of 70%.[31] Presently, the pediatric en-bloc kidney donors at our institution represent 20% of the total number of cadaver donors, and this is a significant difference, when compared to less than 10% of all kidney transplants across the United States.[25] By utilizing pediatric allografts, including the donors under 3 years of age, we have been able to achieve a graft and patient survival not significantly different from those of the adult kidneys seen at most institutions.[30,31] The age-old arguments supporting the discarding of very young pediatric cadaver kidneys are no longer tenable. Recent improvements in immunosuppression, surgical and radiologic techniques, and organ preservation have shown that these organs may afford patients graft survival comparable to those of adult kidneys.

THE OLDER DONOR

No less debated is the question of transplanting the allografts from older donors. Nevertheless, when carefully selected, these may represent a significant source of adequate organs. The serum creatinine is the most common laboratory test to assess the renal function; however, it does not reflect an accurate estimation, in older individuals, of the glomerular filtration rate. This may decline for both physiologic and pathologic changes in the senescent kidney, despite a normal or near normal serum creatinine value.[34] Wesson demonstrated a significant decrease in renal plasma flow,[35] while Ljunquist and Lagergren were able to detect, in a postmortem study, an age-related increase in the number of blind aglomerular arterioles, especially in the cortex, concluding that in the aged kidney a significant amount of blood flow is shunted from cortical to medullary areas.[36]

It appears clear that, when evaluating the graft function of older donors, the serum creatinine alone is not satisfactory, and additional parameters should be taken into consideration. Despite near universal agreement that the number of sclerotic glomeruli slowly advances after the age of 40,[37,38] these changes, as well as interstitial fibrosis, may not be universally present, and it is imperative that each older kidney allograft be evaluated on an individual basis. In this regard, the pre-transplant wedge biopsy, performed in the allografts of the older donor, may represent an important tool in gathering detailed histological information, especially in the hypertensive donors with no adequate medical follow-up, or in those who suffered unrecognized renal injuries.

The results of the frozen section, obtainable within 10 to 15 minutes, may allow an early evaluation of the degree of glomerulosclerosis, intestinal fibrosis, and arteriosclerosis. When combined with other clinical parameters, the wedge biopsy may significantly contribute to a better assessment of the allograft functional status. Unfortunately, this safe, simple procedure is not done routinely in the older donors, and many good functional grafts may be discarded, solely on the basis of the donor's age.

As of today, the selection of the allografts is left to the discretion of the individual surgeon, and is therefore center-dependent. No standard guidelines have been defined for choosing the older kidney allografts carefully. The studies published so far have been suffering from methodological discrepancies with regard to statistical methods, parameters under consideration, and immunosuppression protocols, making it difficult to draw firm conclusions. One of the earlier reports on the outcome of cadaver kidney allografts from older donors was published two decades ago in the azathioprine era by Darmady,[39] who showed that cumulative graft survival was inferior to that with younger donors. These findings must have had a significantly negative impact on the use of this age group donors, for, during the decade that followed, the transplanta-

tion literature has had very few publications on this important issue.

With the advent of newer immunosuppressive drugs and better understanding of the immunologic mechanisms in the immunosuppressed patient, surgeons have attempted reconsidering older donor kidney allografts. According to data published by UNOS, the number of donors from age group 55 and older increased by 67% in the period from 1988 to 1990.[5] Although in the early 1990s the literature has been flourishing with several papers, the debate on whether or not to utilize kidney grafts from older donors has not been resolved yet.

We have performed in our institution since 1990 pre-transplant wedge biopsy in most cadaver kidney allografts from donors age 50 years and older. The preliminary results of a retrospective study were recently presented,[40] comprising 77 recipients who received allografts from older donors (age 50-75) between 1990 and 1992. Allografts were considered for transplantation if the wedge biopsy showed glomerulosclerosis less than 30%, and if the serum creatinine was less than 2.0 mg/dL at the time of harvesting. Results were compared to those of recipients, who received the allografts from younger donors during the same time period. Ninety percent of all patients were under TAC. The rest were under CyA, as primary immunosuppression. The one-year graft survival rate was 77% in the study group, not significantly different from that of the control group (84%).

Although long-term follow-up is needed, the use of the older donor kidneys seems encouraging and promising. These allografts, when carefully selected, may help reduce the ever-increasing gap between organ demand and availability. STI

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