Further Experiences with Tacrolimus and Bone Marrow Augmentation in Renal Transplant Patients

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This chapter will serve to update last year's report, published in SURGICAL TECHNOLOGY INTERNATIONAL™ III[1] and will discuss our experience at the University of Pittsburgh with the use of tacrolimus as the primary immunosuppressive agent after renal transplantation, and our program of combined kidney–bone marrow transplantation to augment chimerism.

TACROLIMUS IN RENAL TRANSPLANTATION

Tacrolimus, known as FK506 when it was still an investigational agent, was first used clinically in renal transplant patients in 1989.[2] An initial pilot experience was followed by a small randomized trial comparing FK506 with cyclosporine, and a larger non-randomized experience for higher risk cases.[3,4] This initial two-year experience with over 200 patients was presented at the First International Conference on FK506 in August 1991, and showed comparable patient and graft survival, when compared with cyclosporine-based therapy, but lower steroid and hypertensive requirements and lower cholesterol levels in the FK506-treated patients.[4] On the basis of these data, a prospective, randomized trial was begun in August 1991, comparing FK506/prednisone with FK506/azathioprine/prednisone.[5-7] Three hundred ninety-five patients undergoing 397 transplants were entered into this trial which ended in December 1993.[8] Overall one- and two-year actuarial patient survival rates were, respectively, 95% and 93%, and one- and two-year actuarial graft survival rates 89% and 83% respectively. No significant differences were seen between the double and triple therapy group in terms of either patient or graft survival (a poorer one-year graft survival rate was seen in the triple therapy group in the first half of this trial,[7] but this difference disappeared by the end of the trial). Rejection was seen less frequently in the triple therapy group (44% vs. 54%, $p<.04$), but a crossover rate from triple to double therapy of 40% was also noted. Forty-nine percent of successfully transplanted patients were withdrawn from steroids, and 35% were not taking any antihypertensive medications. The completed study confirmed earlier reports of the efficacy of FK506 in renal transplant patients and called into question again the utility of azathioprine as a routine third agent. Currently, a trial examining the role of a short course of low-dose cyclophosphamide is currently in progress, and a preliminary analysis is pending. It

should be noted that tacrolimus has been used in renal transplant patients in many other centers with equally encouraging results,[9-12] and a recent multicenter analysis has concluded that it is associated with a significantly longer graft half-life than has been seen with cyclosporine, 13.8 vs. 9 years.[13]

Tacrolimus has also been used in patients undergoing simultaneous kidney–pancreas transplantation, with promising early results. Of the first 27 cases, only two pancreases have been lost to rejection, and there have been no patient deaths.[14]

In pediatric kidney transplantation under tacrolimus, there has been no substantial change in the results previously reported of one- and three-year actuarial patient survival of 100% and one- and three-year actuarial graft survival of 98% and 85%.[15] In subsequent follow-up, one patient has died for unclear reasons, 38 months following transplantation and 17 months after losing her allograft to noncompliance. As she had been off immunosuppression following the loss of her kidney, it is unlikely that tacrolimus played any role as a cause of death. Two additional patients have lost their allografts to chronic rejection, 33 and 50 months after transplantation. In the ensuing 12 months, 19 children have undergone kidney transplantation with 100% patient and graft survival. One patient developed an early posttransplant lymphoproliferative disorder five months after transplantation, which resolved with temporary cessation of immunosuppression and antiviral therapy. One patient who developed a late (46 months) posttransplant lymphoproliferative disorder, with a Burkett's lymphoma-type histologic appearance, has required chemotherapy; this PTLD arose after an increase in maintenance immunosuppression. Fortunately, the lesion seems to have regressed completely, and renal function has remained normal. Thus, careful dosing adjustment remains important in pediatric renal transplant patients receiving tacrolimus.

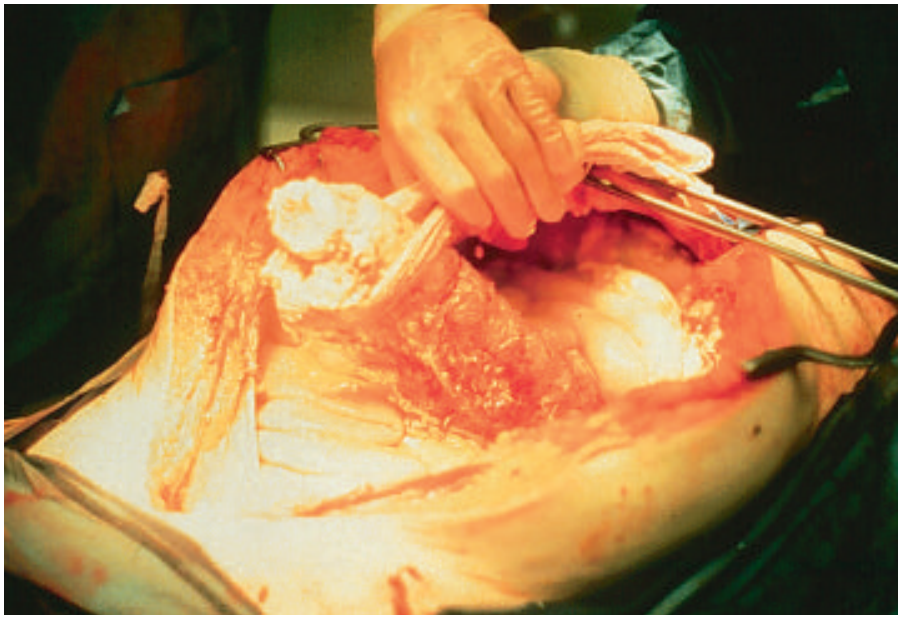

Figure 1. Recovery of donor vertebral bodies after removal of solid organs in a cadaveric donor.

KIDNEY–BONE MARROW TRANSPLANTATION

The goal of kidney–bone marrow transplantation has been to augment the naturally occurring chimerism that is seen after every organ transplantation,[16-19] with the aim of improving long-term graft survival. Between December 13, 1992, and September 30, 1994, 30 patients underwent combined, simultaneous bone marrow transplantation, under tacrolimus-based immunosuppression. Six also received pancreatic islets, and four received pancreases, all from the same donors. Figures 1 through 6 demonstrate the process of recovering donor vertebral bodies and isolating donor bone marrow, which is infused intravenously into the recipient at the conclusion of the

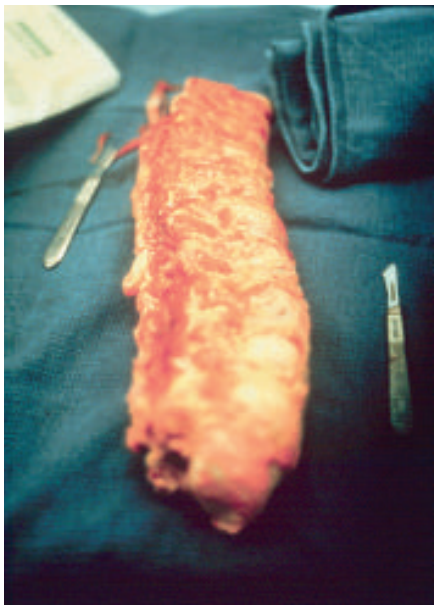

Figure 2. The intact donor vertebral bodies after recovery.

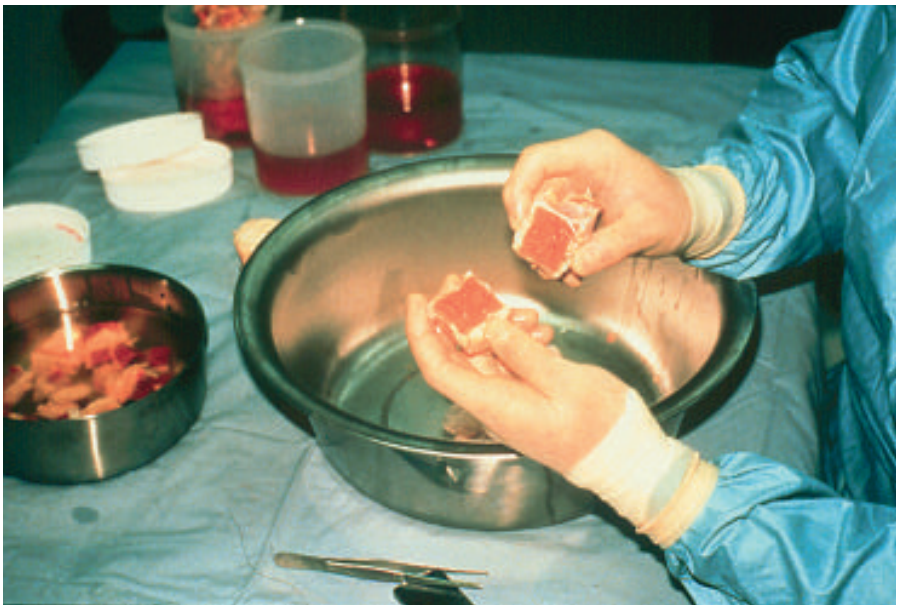

Figure 3. Open vertebral body, showing bone marrow-containing cancellous bone.

Figure 4. Cancellous bone chips prior to processing.

Figure 5. Bone marrow after initial processing and centrifugation.

Figure 6. Resuspended bone marrow at a dose of 3.5 x 108 unmodified cell/kg, ready to be infused into the recipient.

transplant procedure. With a mean follow-up of 8 ± 6.4 months, all patients are alive, and 28 (93%) have functioning allografts, with a mean serum creatinine of 1.8 ± 0.6 mg/dl and a BUN of 30 ± 9 mg/dl. The chimerism data are still being analyzed, but are not thought to be substantially different from those reported earlier.[20-23] Graft versus host disease has not been observed in any patient. This project is ongoing and continues to accrue patients.

The evaluation of new immunosuppressive agents and other new modalities continues to be an important theme in the Renal Transplantation Program at the University of Pittsburgh, as part of an effort to optimize patient outcomes after transplantation. Tacrolimus and bone marrow augmentation have been the main focus of our clinical research efforts thus far. Other new agents, (e.g., mycophenolate mofetil[24]) may also be studied, as they become available. STI

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