Recent Developments in Renal Transplantation - FK506 and Bone Marrow Augmentation

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In the past 40 years, clinical renal transplantation has evolved from a risky, highly speculative endeavor to a fairly mature, well-established service. There are hundreds of programs around the world, transplanting thousands of patients annually, and reasonably good success rates have been achieved. Current expectations are of one year patient survival of 90 - 98%, and one year graft survival of 75 -90%.[1] In addition, patients who have been successfully transplanted have a markedly improved quality of life compared with patients on dialysis.[2,3] However, in spite of these encouraging results, there remain significant problems. Among them are acute rejection, which still occurs in 40 - 75% of cases,[4,5] and graft loss secondary to rejection, acute or chronic, which limits the half-life of cadaveric kidneys to 8 years.[1] As part of an effort to address these issues, there have been a number of new immunosuppressive agents and therapeutic modalities that have been investigated over the past several years. This chapter will focus on 2 areas of ongoing research in our institution, the use of FK506 in renal transplant patients, and the program of combined kidney/bone marrow transplantation.

FK506

FK506, now known as Tacrolimus (Prograf™), is a new immunosuppressive agent that has recently been approved by the United States Food and Drug Administration. Isolated as a fermentation product from the soil fungus, Streptomyces Tsukubaensis, as part of a deliberate screening program to search for new immunosuppressive agents, it is a macrolide antibiotic with a molecular weight of 822[6] It was first discovered in 1982/83, by the Fujisawa Pharmaceutical Company, Ltd. in Osaka, Japan. The first pre-clinical report, by Ochiai and his associates, was presented at the Transplantation Society meetings in 1986.[7] A large number of pre-clinical reports were subsequently presented and published in 1987.[8] These led to the first clinical trials at the University of Pittsburgh, reported in October, 1989,[9] followed by a number of papers presented at the Transplantation Society meetings in 1990.[10-13] By the time of the First International Congress on FK506, held in August, 1991, in Pittsburgh, which summarized a great deal of basic and clinical research,[14] 2 clinical multi-center trials of FK506 in liver transplantation were well underway. These confirmed the earlier reports of the Pittsburgh group[15,16] and led to eventual approval by the FDA.

The progress of research with FK506 in clinical renal transplantation lagged behind the work in liver transplantation. The early papers from Pittsburgh, published in 1990 and 1991,[11,17,18] demonstrated comparable patient and graft survival between FK506 and cyclosporine-based therapies. However, FK506 was associated with the ability to wean steroids in over 40% of patients, a somewhat lower need for antihypertensive medications, and lower serum cholesterol levels, when compared with cyclosporine-treated patients. On the basis of these findings, two multicenter randomized trials were begun, in Japan[19,20] and in the United States,[21] and a randomized trial of FK506-based immunosuppression was begun in Pittsburgh, comparing FK506 and prednisone with and without azathioprine.[22,23] This latter trial has confirmed and extended the earlier work. In 204 unselected adult patients randomized and followed for a minimum of 12 months, one year actual patient and graft survival of 94% and 87% were seen.[24] In addition, 56% of patients were weaned off steroids. The benefit of azathioprine was uncertain, and in fact, worse graft survival outcomes were seen in patients initially randomized to triple therapy. However, lower rates of rejection in certain subgroups and lower new onset diabetes were seen in patients randomized to triple therapy, and 27% of patients randomized to double therapy required the addition of azathioprine because of rejection. Thus, a third agent may be needed in a subset of patients receiving FK506 after renal transplantation. Azathioprine may not be the ideal agent, and perhaps one of the new azathioprine substitutes currently under clinical evaluation, such as mycophenolate mofetil[25] or Brequinar,[26] or other new agents, such as Rapamycin,[27] Leflunomide,[28] or Deoxyspergualin,[29] may be more useful.

In pediatric renal transplantation, initial reports with FK506 showed excellent outcomes and an ability to wean steroids in a large percentage of children.[30,31] A larger comparative review of the pediatric renal transplant experience in Pittsburgh demonstrated an overall one and four year actuarial patient survival of 100% and 98%, and one and four year actuarial graft survival of 98% and 83%, with no differences between cyclosporine and FK506-treated children.[32,33] However, FK506 was associated with a greater freedom from steroids and antihypertensive medications than cyclosporine-based therapy.[32-34] In spite of a slightly higher incidence of viral complications, the experience with FK506 was felt to be encouraging, particularly in terms of improved growth and development in children off steroids. The most recent review, in 43 children receiving FK506, demonstrated 100% patient survival at one and three years, and 98% and 85% actuarial graft survival at one and three years, with over 60% of the children successfully weaned off steroids.[35] Growth in the pre-adolescent children who were off steroids was markedly improved, to the point where catch-up to normal or above average height was observed.

The final aspect of FK506 in renal transplantation, that has been perhaps even more dramatic than its utility in primary renal transplantation, has been the ability to rescue renal allografts that have failed conventional immunosuppressive agents and anti-rejection therapy.[35-38] Roughly three-fourths of unselected adults and children were successfully rescued by switching to FK506-based therapy. Some of these patients had even returned to dialysis and were successfully switched.

Thus, FK506 has demonstrated significant efficacy in renal transplant patients, with equal or better results than conventional therapy in adults and children and the ability to wean steroids in 50 - 60% of patients. In addition, it can salvage nearly 75% of allografts failing conventional therapy. Among the remaining challenges are the need to reduce the incidence of rejection and initial non-function in FK506-treated patients, and several trials attempting to deal with these issues are in progress or are in the planning stages.

KIDNEY/BONE MARROW TRANSPLANTATION

The original impetus for this idea came from observations based on a small number of patients who have kept their renal allografts for 27 - 29 years.[39-42] All of these patients were found to have evidence of microchimerism, i.e. donor cells were found not only in the transplanted organ, but also in the skin, peripheral blood, and lymph nodes of the recipient. This association of long-term graft survival with microchimerism led directly to trials of solid organ transplantation with bone marrow augmentation.[43-45] Conceptually simple, the procedure involved transplantation of a kidney (or liver, heart, or lung), followed immediately by the intravenous infusion of 3 x 10^8 unmodified donor bone marrow cells/kg. The bone marrow was isolated from the donor vertebral bodies. No recipient preconditioning was used, and immunosuppression was with FK506 and prednisone, without induction anti-lymphocyte therapy.

The results on the first ten kidney patients were recently presented,[45] although there are perhaps 50 recipients of various solid organs to date whose experience has generally paralleled that of the kidney patients. All ten kidney recipients are alive and have functioning allografts, with a mean follow-up of over 10 months. All 9 evaluable patients have evidence of systemic chimerism, demonstratable by flow cytometry, polymerase chain reaction, or Y-chromosome analysis; the latter was performed in female recipients of organs from male donors. One patient who is doing well is not evaluable because of a perfect DR match and lack of

donor/recipient sex disparity. In addition, at the time of the report, half of the evaluable patients had evidence of evolving donor-specific hyporeactivity. No evidence of graft versus host disease was seen. The incidence of early events, such as acute rejection, initial nonfunction, or cytomegalovirus, was not affected. A group of control patients not receiving bone marrow was also studied, and while good results were also noted in terms of patient and graft survival, the incidence of microchimerism was both lower (60%) and less intense. Thus, the procedure appeared to be straightforward, safe, and associated both with excellent results and uniform augmentation of chimerism. This project is ongoing; to date, 22 kidney/bone marrow, kidney/islet/bone marrow or kidney/pancreas/bone marrow transplants have been performed. One of the long-term goals will be to see if, eventually, these patients would become candidates for weaning of immunosuppression.

These two areas of clinical investigation represent an important part of the research interest of a single institution. There are obviously a large number of protocols investigating different new immunosuppressive agents and other modalities in many different centers around the world, and to detail them is beyond the scope of this chapter. It is clear, however, that despite its routine image, renal transplantation is continuing to move forward. It is our hope that the two recent developments described in this chapter help to give a sense of the work in progress. STI

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