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Pancreas Transplantation Without Antibody Therapy

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AFTER whole organ pancreas transplantation with duodenojejunostomy to drain the exocrine secretions was reintroduced in 1984,¹ a few centers adopted this technique to replace transplantation of the body and tail of the pancreas, which had been the procedure of choice in the 1970s and early 1980s. Although in the early clinical trials using cyclosporine in whole organ pancreas transplantation, the incidence of thrombosis appeared to be less than with transplantation of the tail or "pancreatic segment," it was by no means insignificant, and it was considered that cyclosporine, given its vasoconstrictive properties, might be a contributing factor.² However, there were other reasons why the pancreas was more prone to thrombosis than either the kidney or the liver, in both of which there is a much higher blood flow by comparison with the pancreas. These factors include twisting or compression of the portal vein, ischemic injury, pancreatitis, and reperfusion injury. In addition, acute rejection played a role in early pancreas allograft loss.

Therefore, it was believed that if a lower dose of cyclosporine (or no cyclosporine at all) was used in combination with an anti-T cell antibody administered during the first 10 days following transplantation, the incidence of acute rejection and thrombosis would be reduced. Most pancreas transplant centers in the United States and Europe adopted this immunosuppression regimen with delayed introduction of cyclosporine, the so-called "quadruple sequential immunosuppressive therapy," introduced by Sollinger.³

In the late 1980s and 1990s, both patient and graft survival improved with this regimen, probably more as a result of technical refinements and a more restrictive policy of donor and recipient selection, than improvement in immunosuppression. In spite of these better results, surgically-related morbidity remained high,⁴ but this phenomenon was not related to the choice of immunosuppressive regimen.

By mid-1995, experience had been gained in a few centers using tacrolimus-based immunosuppression in pancreas transplantation, and a multicenter analysis was presented in a preliminary fashion in 1996 by Gruessner,⁵ and again, with more complete data and greater patient accrual in 1997 at the annual meeting of the American Society of Transplant Surgeons (ASTS).⁶ All of the contributing centers but one (Pittsburgh) used tacrolimus in combination with antibody induction. Results of the retrospective multicenter analysis, presented by Gruessner, showed a 1 year

patient and graft survival of 97% and 85%, respectively.⁶ Although the Pittsburgh group, which did not use anti T-cell induction therapy, contributed more patients than each of the other centers, except the University of Minnesota, in the multicenter retrospective analysis, the majority of the patients in the study had received antibody induction. Graft success rates were better with tacrolimus-based immunosuppression than with other drug regimens. In addition, graft survival improved substantially with tacrolimus in patients receiving a pancreas without a kidney, ie, pancreas after kidney transplantation (PAK) and pancreas transplant alone (PTA).^{6,7} However, these "solitary" graft recipients also received anti T-cell induction therapy in addition to tacrolimus.

Although the data clearly showed that tacrolimus was superior to cyclosporine, it was difficult to conclude in a definitive fashion that the addition of an anti-T-cell preparation in combination with tacrolimus was necessary.

THE PITTSBURGH DATA

During a 3-year period, July 1994 through July 1997, 123 patients received pancreas transplants, 104 in combination with a kidney from the same donor (simultaneous pancreas kidney [SPK]). One year actuarial patient, kidney and pancreas survival (Kaplan-Meier) was 98%, 95%, and 83%, respectively. One patient, who was highly sensitized and whose lymphocytotoxic cross-match turned positive at 3 days, lost both grafts. Five other patients lost pancreas function at 3, 6, 9, 11, and 11 months, 2 had recurrent pancreatitis, and 3 had chronic rejection. All other losses were a result of other factors including early graft thrombosis (largely from high-risk donors), surgical complications, pancreatitis, and death in one patient from disseminated lymphoma with normal graft function.

Rejection episodes occurred in 64% of the patients which reversed with steroid therapy, except in 9 patients (7%) who responded to antibody treatment. Only 2 of the last 80 patients, who also received mycophenolate mofetil, required anti-T cell antibody.

While it is not the intent of this presentation to detail the prescription for preventing and managing surgical complication-related graft loss, which is presented elsewhere,⁸ it is important to note that, as the program matured, these types of graft losses were

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minimal. The important point here is that only one pancreas was lost to early rejection (antibody-mediated), which could not have been prevented by any immunosuppressive regimen with or without anti-T cell induction. It is also possible that in the two graft losses to recurrent pancreatitis (bladder-drained), chronic rejection may have played a role. However, no pancreases were lost within the first year to acute cellular rejection. Of even greater significance, is the fact that only 5 kidneys, transplanted from the same donors, were lost within the first year, 2 to sepsis following discontinuation of immunosuppressive agents, 1 death to posttransplant lymphoproliferative disorder with normal renal and pancreatic function, 1 to hyperacute rejection, and 1 to arterial thrombosis, but none from acute rejection.

Although a positive pp 65 CMV antigen was observed in many of the cytomegalovirus (CMV) seronegative patients who received organs from seropositive donors, only one patient was hospitalized with a febrile illness for 1 week without pulmonary or liver disease. A few of the seropositive to seronegative patients were given prophylactic Ganciclovir during the early part of the program, but the majority of these patients were not given prophylaxis for CMV. All seronegative recipients who had received seropositive donors were tested weekly for pp 65 CMV antigen, and if the test turned positive, were treated with a course of Ganciclovir predominately as an out patient, for 2 weeks or longer until the pp 65 antigen was undetectable. The association of CMV disease and the use of anti-T cell antibodies, either monoclonal or polyclonal, is well recognized, and it is clear from this series of over a 120 patients, in whom an anti-T cell agent was not used prophylactically, that the incidence of clinically significant CMV disease was low.

DISCUSSION

Whether anti T-cell induction therapy played a role in preventing graft loss from cyclosporine treated pancreas transplant recipients cannot be stated definitively. However, even in our first series of 20 SPK patients, treated with cyclosporine, azathioprine and prednisone performed more than a decade ago, pancreas graft loss to acute rejection occurred in only one patient within the first year.⁹ In the current Pittsburgh series, graft loss to rejection was minimal.¹⁰

Adequate blood trough levels of tacrolimus are required, particularly within the first 2 to 3 months after transplantation. Patients are given intravenous tacrolimus 0.05 mg/kg for 5 to 7 days followed by an initial oral dose of 0.15 mg/kg twice a day. The dose is adjusted daily to achieve whole blood trough levels of 20 to 25 ng/mL for the first 2 weeks, 15 to 20 ng/mL by one month, 10 to 15 ng/mL by 3 months, and 7 to 12 ng/mL chronically. Patients received either azathioprine or mycophenolate mofetil (the latter in the

second half of the Pittsburgh series) as well as tapering steroid doses, which were withdrawn in about a third of the patients between 6 months and 1 year. The use of intravenous tacrolimus for the first 5 to 7 days was well tolerated, with little drug toxicity. Only one patient had significant neurological symptoms, and one required hemodialysis postoperatively which was related to acute tubular necrosis. A few had hyperglycemia, which recovered after reduction in both the tacrolimus and prednisone dosages. The importance of achieving adequate target blood levels of tacrolimus, particularly during the first few months, together with an appropriate tapering strategy as outlined above, should be underscored. To achieve these optimal target trough blood levels, the actual dose of tacrolimus varied widely from patient to patient.

In conclusion, the use of tacrolimus without anti-T cell preparations for induction in pancreas transplantation is largely limited to the Pittsburgh data, which confirms the fact that antibody induction is not necessary to prevent acute rejection-related graft loss. Furthermore, the incidence of clinical CMV disease is low in this series, a potential benefit of avoiding the use of prophylactic or induction anti T-cell antibody drug therapy. Whether either mycophenolate mofetil or azathioprine is necessary as a third drug has not been addressed, but the requirement for anti-T cell antibody for refractory rejection was less when mycophenolate mofetil was used.

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