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INITIAL SUCCESS OF SOLITARY PANCREAS TRANSPLANTS WITHOUT REGARD TO DONOR/RECIPIENT HLA MISMATCHING

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Background. Despite Rristry data indicating that an increasing number of HLA mismatches (MM) significantly increases rejection risk and lowers graft survival, we hypothesized that solitary pancreas transplants could be successfully performed even in the presence of poor HLA matching if an aggressive approach were taken with regard to both immunosupperssive protocol and allograft biopsy.

Methods. Seven panceas-after-kidney (PAK) Transplants and 7 pancreas transplants alone (PTA) were performed from to 10/98 without consideration given to the degree of HLA MM using tacrolimus (FK506)/ mycophenolate mofetil (MMF)/ prednisone maintenance therapy. Mean (± SD) A/B, DR, and total HLA MM were 3.3 ± 0.9, 1.5 ± 0.5, and 4.8 ± 1.2, respectively. All patients were followed for at least 6 months. The first cases were induced with ATGAM for 7 to 10 days. In the remaining 10 cases, an ultrasound-guided percutaneous needle biopsy was attempted when possible on a protocol basis 10 days after completing induction with OKT3 for 7 (n = 2) or 14 (n=8) days.

Results. Overall patient survival, graft survival, and incidence of acute rejection requiring treatment were 86 %, 79 %, and 50 % respectively. Both deaths occurred in PAK Transplant recipients, one from pulmonary embolism at 6 months and the other from necrotizing candidal transplant pancreatitis and sepsis at 2 months. Two patients receiving ATGAM Developed grade III-V rejection at 3 weeks (one with graft loss), and both patients receiving OKT3 for 7 days developed early grade III rejection, Suggesting failure of induction in both these groups. Only 3 of 8 patients receiving OKT3 For 14 days developed rejection requiring treatment. Protocol biopsy was successfully performed in 6 of 7 patients and uncovered 3 cases of otherwise undetectable grade III-IV rejection.

Conclusions: Solitary pancreas transplants with a poor match can be successfully performed with an acceptable morbidity and rejection incidence using an OKT3/FK506/MMF/ prednisone regimen with protocol and as-needed percutaneous needle biopsy, particulary in PTA patients.

Abbreviations:FK506, tacrolimus, HLA MM, HLA mismatches; MMF, mycophenolate mofetil; PAK,Pancreas-after-kidney; PTA, pancreas transplant alone; SPK, simultaneous pancreas/kidney

Keywords: HLA, pancreas, transplants, matching, clonar, recipient.

INTRODUTION

In the past, graft survival rates for pancreas-after-kidney (PAK) Transplants and pancreas transplants alone (PTA) in nonuremic patients with labile insulin-dependent diabetes mellitus have been significantly lower than those obtained with simultaneous pancreas/kidney (SPK) transplantation. Indeed, according to recently released International Pancreas Transplant Registry/United Network for Organ Sharing data from the 1994-97 era, one-year graft survival rates for PAK transplants (71%) and PTA (62%) Began to approach but were still quite less favorable than those for SPK Transplantation (82%) [(1)].This difference in graft survival between combined and solitary pancreas transplant recipients was mainly attributable to increased graft loss from rejection at one year in the later (PAK Transplant: 9%; PTA: 16%) when compared with the former (2%). Interestingly, the one factor which was

identified by muutivariate analysis to be the most significant predictor of risk for pancreas graft loss in general and for graft loss due to rejection in particular in both PAK transplant and PTA patients, but not in SPK transplant recipients, was the number of HLA mismatches (MM) [1]. Along these lines, recently-reported single-center data from the University of Minnesota has also continued to demonstrate a significant detrimental effect of an increasing number of HLA MM on graft survival; graft loss due to rejection; and incidence of first rejection episodes in solitary pancreas transplant recipients [2-4].

In 1996, Bartlett el al. [5] reported equivalent success of SPK and solitary pancreas transplantation (84% and 77% one-year graft survival, respectivel) with tacrollimus (FK506) based immunosuppression and liberal application of ultrasound-guided percutaneous needle biopsy for diagnosis of isolated pancreatic rejection. In their study, the maximum allowable mismatch for solitary transplants was two A/B and one DR antigens; polyclonal antilymphocyte antibody (10 days) was used for induction; and initially azathioprine and subsequently mycophenolate mofetil (MMF) was combined with FK506 for maintenance therapy. Despite the aforementioned registry data, these excellent results led us to believe that solitary pancreas transplants could be successfully performed even in the presence of poor HLA matching if an aggressive approach were taken with regard to both immunosuppressive protocol and allograft biopsy. The purpose of this report is review our initial experience with 14 solitary pancreas transplants (7 PAK transplants, 7 PTA) performed regardless of the degree of donor/recipient HLA MM using FK506/MMF/prednisone maintenance immunosuppression.

PATIENTS AND METHODS

Patients. Seven patients undergoing PAK transplantation and seven patients undergoing PTA at the University of texas at Houston Health Science Center between March 18, 1997 and October 13, 1998 are included in this report. All patients were recipients of primary pancreas grafts and all PAK transplant patients had their first , functioning rental transplant in situ. (Table 1) gives the mean donor age and cold ischemia time, as well as mean recipient age; duration of IDDM; current (at time of transplant) and peak panel reactive antibody (PRA); and A/B, DR, and total donor/recipient HLA MM, for each transplant type and for the entire group of 14 patients. The median (range) time interval between transplantation of rental and pancreas allografts in PAK transplant patients was 53 (5-140) months. All recipients were white and had third-party insurance coverage. Criteria used to select and evaluate appropriate candidates for both procedures have been previously described in detail [6]. All patients were followed for at least six months posttransplant, with the data presented as of May 1, 1999.

Table(1): ***Donor and recipient demographics for solitary pancreas transplant patients***[a]

Transplant Type	*Donor Age*	*CIT*[b] *(hr)*	*Recipient Age*	*Duration IDDM*
PAK (n=7)	24 ± 9(12-41)	8 ± 3(5-11)	42 ± 4(34-47)	28 ± 7(17-35)
PTA (n=7)	18 ± 8(11-36)	8 ± 1(6-10)	35 ± 6(27-13)	26 ± 6(17-31)
Total (n-14)	21 ±9	8 ± 2	39 ± 6	26 ± 6

			HLAMM		
Transplant Type	*Current PRA (%)*	*Peak PRA (%)*	*A/B*	*DR*	*Total*
PAK (n=7)	1 ± 2(0-4)	11 ± 9(0-22)	3.4 ± 0.8	1.6 ± 0.5	5.0 ± 1.2
PTA (n=7)	1± 1(0-3)	2 ±3(0-7)	3.1 ± 1.1	1.4 ± 0.5	4.6 ± 1.3
Total (n=14)	1 ± 1	6 ± 8	3.3 ± 0.9	1.5 ± 0.5	4.8 ± 1.2

[a]Values given are mean ± SD (range).

Surgical procedure. All pancreas allografts were placed intraperitoneally in the right iliac fossa in PTA recipients and left iliac fossa in PAK transplant patients via a middle incision. Venous drainage was systemic, and no venous extension grafts were utilized. The first 12 cases were bladder-drained via an EEA-stapled duodenocystostomy overswen and inverted from inside the bladder [7]. The last three cases were enterically drained via a hand-sewn, open, two-layer, side-to-side duodenojejunostomy without a roux-en-Y limb. No attempt was made to place tacking sutures in the pancreas graft to facilitate postoperative localization and biopsy.

Induction protocol. Our antilymphocyte antibody induction regimen evolved in three phases over the two-year time period during which the transplants were

performed> The first four patients received antithymocyte globulin (ATGAM; Upjohn, Kalamazoo, MI) for 7 to 10 days, initially dosed at 15 mg/kg/d and subsequently adjusted to maintain the absolute lymphocyte count < 250 cells/Ul. The dose was reduced as necessary for thrombocytopenia. The next two patients received OKT3 (Muromonab; Ortho Biotech, Raritan, NJ) 5 mg/d for 7 days. Finally, the last eight patients received OKT3 5 mg/d for 14 days.

Maintenance immunosuppression. In All patients, MMF was initiated on the first postoperative day at a dose of 1 g twice daily given down the nasogastric tube. The daily total ethylperednisolone dose was 375 mg on day 0; 200 mg on day 1; and 160 mg on day2, tapering to 30 mg prednisone by day 9, 20 mg by 1 month, 15 mg by 6 months, and 10 mg by one year. In PAK transplant recipients, cyclosporin A (CSA) was discontinued just prior to surgery and FK506 was begun on the third postoperative day at a dose of 3 mg twice daily administered orally or per nasogastric tube, with the dose subsequently adjusted to keep 12 hr whole-blood trough levels 12-15 ng/ml by the Imx Tacrolimus II assay (Abbott Laboratories, Abbott Park, IL). In PTA patients. FK506 was begun on the first postoperative day and dosed as in PAK transplant recipients.

In all patients, ultrasound-guided percutaneous needle biopsy of the pancreas allograft was performedrule out acute rejection whenever sufficient laboratory and/or clinical suspicion of the diagnosis was present, as well as to histologically document the resolution of acute rejection following a course of therapy or observation, if necessary. Beginning with the fifth case, biopsy was attempted on a protocol basis ten days following completion of induction therapy with OKT3. All biopsieswere performed by the same surgeon (S.A.G.) in conjunction with the same personal in the ultrasonography suite of the Department of radiology. An automatic 18-gauge core biopsy needle (ASAP, Miicrovasive Boston Scientific Corporation. Watertown, MA) was used to take samples from the distal pancreas (body/tial region) following clear identification of the vascular supply of the gland using Doppler ultrasound examination [8]. The severity of acute rejection was assessed using the 0 to V grading scheme described by Drachenberg et al. [9]. All rejection episodes of at least mild severity (grade III) were treated with 7 to 14 days of antilymphocyte antibody. Treatment of grade I-II (borderline to minimal) acute rejection episodes was dependent upon the time posttransplant rejection was diagnosed and upon the clinical course of the patient. One patient presenting with elevated amylase and lipase vaues at 5 months posttransplant in whom percutaneous needle biopsy was not technically feasible was treated empirically for acute rejection with bolus steroid therapy alone.

Medical therapy. Both cefazolin and fluconazole (200 mg) were administered preoperatively and continued for 3 days and 5 days, respectively , postoperatively. Preemptive cytomegalovirus (CMV) therapy consisted of intravenous ganciclovir 2.5 mg/kg every 12 hours while the patient was receiving antibody induction or treatment for acute rejection, followed by either oral ganciclovir 1000 mg thrice daily for the donor (+)/recipient (-) serologic status combination or oral acyclovir 400 mg thrice daily for all other serologic combinations for a total of 3 months postoperatively or six weeks post-rejection. Prophylactic anticoagulation consisted of subcutaneous heparin 5000 units twice daily for 72-96 hr postoperatively, followed by entericcoated aspirin, 80 mg/d. Oral trimethoprim/sulfamethoxazole prophylaxis was begun on postoperative day 4.

Data analysis. The mean number of A/B, DR, and total HLA MM were compared in patients with and without acute rejection using an unpaired students t-test. In those patients with rejection, Pearson correlation methods were used to assess the relationship between the number of HLA MM and the graded severity of the rejection episode. Glycosylated hemoglobin (HgbA1C) values were obtained at six month intervals posttransplant. All values are expressed as mean ± SD. $p \leq 0.05$ was regarded as statistically significant.

RESULTS

(Table 2) summarizes information regarding length of follow-up period, induction agent used, protocol biopsy results and occurrence of later rejection, and cause of graft loss for each recipient. Overall patient survival, graft survival, and incidence of acute rejection requiring treatment were 86%, 79%, and 50%, respectively. Both deaths occurred in PAK transplant recipients, one from massive pulmonary embolism at 6 months post transplant following clinical and enzymatic resolution of an episode of transplant pancreatitis (patient #2), and the other from necrotizing candidal transplant pancreatitis and sepsis at 2 months post transplant (following pancreatectomy at day 18) in a patient induced with 14 days of OKT3 (#6). Interestingly, patient #2 had previously required exploration 11 days post transplant for hypotension and leukocytosis, and was found to have a wound infection and transplant pancreatitis, the latter resolving with octreotide therapy. Another PAK transplant recipient (#4) who was induced with OKT3 for 7 days and subsequently received 14 days of ATGAM for grade III acute rejection, developed pulmonary aspergillosis at 4.5 months post transplant. This patient was successfully treated with Amphotericin B, along with discontinuation of MMF and significant reduction of KF506 and prednisone doses. One PTA recipient (#13) was converted from FK506 to CSA for psychosis and neurotoxicity developing 5 weeks post transplant. No patients required discontinuation of FK506

or MMF for hyperglycemia or gastrointestinal disturbances, respectively. Postoperative HgbAIC values for 10 patients with grafts surviving beyond 6 months are displayed in figure (1). There were no cases of CMV infection or PTLD

Fig (1) ***The postoperative HgbA1C value for the latest 6 month interval of follow – up is shown for each of the 11 solitary pancreas transplant recipients with grafts surviving beyond 6 months (normal<7.0%).***

The only graft loss from rejection occurred in a fourth PAK transplant patient (#3), who was induced with ATGAM and presented acutely with arterial thrombosis 19 days post transplant secondary to grade IV rejection (moderate with vasculitis) and required pancreatectomy. Of the other two patients (#1 and #8) receiving ATGAM for induction, one (#8) developed grade III rejection at 17 days, requiring OKT3 treatment. While both patient receiving OKT3 for days (#4 and #9) developed early grade III rejection, only 3 of the remaining 7 patients receiving OKT3 for 14 days developed rejection felt to require treatment (#5, #13, and #14). There were no significant differences in mean A/B, DR or total HLA MM in patients with and without rejection, and in the seven patients with rejection, there was no significant correlation between the number of HLA MM and the histologic severity of the rejection episode.

Percutaneous needle biopsy was attempted on 22 occasions in 11 patients, nine of which were performed on a protocol basis. Of the 22 attempts, biopsy was ultimately not performed in two instances because of overlying bowel (patients #12 and #13 (Table 2)) and yielded an inadequate specimen in two cases (both follow-up biopsies on patient #5), for an overall success rate of 82%. There were no complications from the procedure. Repeat needle biopsy confirmed resolution of acute rejection following treatment in patients #4, #9, and #14, but was not attempted in patients #8 and #13. The histologic findings were the only sign of rejection in 5 patients with a positive protocol biopsy. Both patients with grade III acute rejection on protocol biopsy (#4 and 14) were treated with ATGAM and did not develop recurrent rejection. The remaining 3 patients with grade I-II rejection on protocol biopsy (#5, #7, and #11) were not immediately treated, but were followed by repeat biopsy 1 week later. Only one patient (#5) progressed to grade III rejection requiring therapy.

Table 2. *Results of solitary pancreas transplantation*

Patient#	Type	Follow-up (mo)	Introduction Agent # Days	Protocol Biopsy Grade/Treatment	Later Rejection time/Grade/Treatment	Cause of Graft Loss/Time
1	PAK	25.8	ATGAM/10	Not Done	---	---
2	PAK		ATGAM/7	Not Done	---	Death/PE [a]/6.0 mo
3	PAK		ATGAM/7	Not Done	0.7mo/IV/Px [b]	Rejection/0.7 mo
4	PAK	16.2	OKT3/7	III/ATGAM	---	---
5	PAK	15.2	OKT3/14	I-II/--	1.0 mo/III/ATGAM	---
6	PAK		OKT3/14	Px	---	Death/inf [c]/2.0/mo
7	PAK	11.0	OKT3/14	I-II/--	---	---
8	PTA	22.7	ATGAM/10	Not Done	0.6 mo/III/OKT3	---
9	PTA	17.5	OKT3/7	0/--	2.5 mo/III/ATGAM	---
10	PTA	15.3	OKT3/14	0/--	---	---
11	PTA	13.3	OKT3/14	I-II/--	---	---
12	PTA	12.1	OKT3/14	NTF [d]	---	---
13	PTA	7.2	OKT3/14	Not Done [c]	0.7 mo/I-II/ATGAM [e] 5.0 mo/NTF/steroids	---
14	PTA	6.7	OKT3/14	III-IV/ATGAM	---	---

[a]PE = pulmonary embolism; [b]Px = pancreatectomy; [c]inf = infection; [d]NTF = not technically feasible;

[e]Biopsy performed for hyperamylasemia on day 20, prior to scheduled protocol biopsy.

DISCUSSION

To our knowledge, the only previous report of solitary pancreas transplantation performed without regard to donor/recipient HLA MM was a very abbreviated of the outcome of 6 PAK transplant patients receiving OKT3 induction and either FK506 or CSA-based maintenance immunosuppression [(10)]. It was not stated whether MMF or azathioprine was used cocurrently. Although graft survival was 83 % (follow-up period not stated), mean HLA MM was only 3, so these patients were significantly better-matched than were the group presented herein.

In the aforementioned report from the university of Maryland [(5)], one year graft survival for the 27 solitary pancreas transplant patients receiving FK506-based immunosuppression was 76.7 % overall, but was 90.1 %in technically successful cases with only one graft lost to rejection due to patient noncompliance (4 to early thrombosis and one to PTLD). Of the 23 technically-successful cases, 19 patients (83 %) were treated for rejection, even though the mean number of HLA A/B and DR MM were 1.7 and 0.7, respectively, significantly lower than in our study (3.3 and 1.5, respectively).

In the recently-reported Minnesota experience [(11)], 44 patients underwent PAK transplantation and 15 PTA using combination FK506/MMF/prednisone maintenance therapy, with the vast majority of patients receiving 5 to 7 days of ATGAM for induction. One-year graft survival rates were 77 % for PAK and 50 % for PTA. These patients had significantly better matched grafts than 61 concurrently-performed SPK transplant recipients, with a median HLA MM of 4 for the entire cohort of 120 patients. At one year follow-up, the incidence of first rejection episodes, the percent of grafts lost to rejection, and the incidence of CMV infection were 50 %, 11 %, and 23 % respectively, in the PAK transplant group and 67 %, 47 %, and 13 %, respectively, in the PTA group. Even with an attempt to use better-matched grafts, there was a similar incidence of, but more graft loss from, acute rejection when compared with our series,

perhaps attributable to the use of a short course of ATGAM, rather than a full course of OKT3, for induction.

Stratta[12] recently compared the results of using OKT3 induction (number of days not stated) in 6 versus no induction in 12 PAK transplant recipients treated with CSA, azathioprine, and prednisone maintenance immunosuppression in whom a minimum two-antigen HLA match was required for organ acceptance. Given the finding that the incidence of rejection and immunologic graft loss was similar between the groups but the rates of operative complications, allograft pancreatectomy, peri-graft infection, and graft loss from infection were all significantly higher in the OKT3 induction group, he cobcluded that the overall results favored omission of induction therapy in PAK transplant recipients. In contrast, we felt induction would be necessary in poorly-matched PAK transplant patients. Indeed, following a graft loss from grade IV rejection at 19 days posttransplant in patient #3 as well as the development of early grade III rejection in PTA patient #8, we switched from ATGAM to OKT3 (7 days) and initiated the performance of protocol BIOPSIES. However, our very next PAK transplant patient placed on the new regimen (#4) was noted to have grade III rejection on protocol biopsy. This result, combined with the occurrence of an early grade III rejection in PTA recipient #9 stimulated us to further intensify our induction period to 14 days of OKT3. However, the subsequent loss of patient #6 and development of aspergillosis in patient #4 do strike a note of caution with regard to the use of a heavy induction regimen in PAK transplant patients, who have been previously immunosuppressed by virtue of both their prior rental transplant and antecedent period of rental failure, often for long periods of time. We are currently exploring the use of an interleukin-2 receptor antagonist for induction in PAK transplant recipients, which we feel represents an intermediate step between OKT3 induction and nine at all.

Although limited to 7 cases, our experience with protocol biopsy was very favorable, enabling immediate detection of two and ultimate detection of a third patient with grade III acute rejection that was not otherwise diagnosable .It would appear that patients with grade I-II rejection noted on protocol biopsy can be initially observed and followed with subsequent biopsies at weekly intervals as necessary to determine the need for subsequent antirejection therapy.

In addition to continually improving graft survival , several other factors have interacted to produce an increase in the number of PAK transplants performed in the United States over the past several years , and will continue to do so in the foreseeable future . Fist , the introduction of laparoscopic donor nephrectomy ; increased willingness to use unrelated donors ; and the continued organ shortage have all increased the number of living – donor renal transplants being performed , and thus the need for PAK transplants . Second. Medicare coverage of PAK transplants appears to be forthcoming. Finally , willingness ay the local organ procurement organization (OPO) level to give some form of preference to SPK transplant over kidney- transplant- alone candidates with regard to kidney allocation in the form of separate list or other criteria is not universal and indeed , may be diminishing . Along these line , our own experience within an OPO in which no preference is given to SPK transplant recipients demonstrates that rapid development of a solitary pancreas transplant program without regard to HLA matching is not only feasible , but also permits more suitable donor pancreata to be used locally , rather than be shipped elsewhere or (not infrequently) discarded , decreases waiting time (mean 45 ± 38 days for our 14 patients!) , and increases organ utilization . We agree with the Maryland group that the difficult issue of national pancreas transplant sharing will be greatly simplified and expedited if HLA matching is no longer necessary.

We conclude that solitary pancreas transplants with a poor match can be successfully performed with an acceptable morbidity and rejection incidence using an OKT3/FK506/MMF/prednisone with ultrasound – guided percutaneous needle biopsy on both a protocol and as needed basis, particularly in PTA patients.

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