Transpl Int (2003) 16: 154–160
DOI 10.1007/s00147-002-0510-1

ORIGINAL ARTICLE

Robert J. Stratta
Agnes Lo
M. Hosein Shokouh-Amiri
M. Francesca Egidi
Lillian W. Gaber
A. Osama Gaber

Improving results in solitary pancreas transplantation with portal-enteric drainage, thymoglobin induction, and tacrolimus/mycophenolate mofetil-based immunosuppression

Received: 10 October 2001
Revised: 29 September 2002
Accepted: 11 October 2002
Published online: 13 February 2003

R.J. Stratta (✉)
Department of General Surgery,
Wake Forest University,
Medical Center Boulevard, Winston-Salem,
NC 27157, North Carolina, USA
E-mail: rsratta@wfubmc.edu
Tel.: +1-336-7164241
Fax: +1-336-7165414

R.J. Stratta · M.H. Shokouh-Amiri
A.O. Gaber
Departments of Surgery-Transplant,
University of Tennessee, Memphis,
Tennessee, USA

A. Lo
Department of Clinical Pharmacy,
University of Tennessee, Memphis,
Tennessee, USA

M.F. Egidi
Department of Medicine,
University of Tennessee,
Memphis, Tennessee, USA

L.W. Gaber
Department of Pathology,
University of Tennessee,
Memphis, Tennessee, USA

Abstract Advances in surgical techniques and clinical immunosuppression have led to steadily improving results in pancreas transplantation (PTX). The purpose of this study was to analyze retrospectively the outcomes in patients undergoing solitary PTX with portal-enteric (P-E) drainage and contemporary immunosuppression. From June 1998 through December 2000, we performed 28 solitary PTXs with antibody induction and tacrolimus/mycophenolate mofetil maintenance therapy. The first 13 patients received daclizumab (DAC) induction, while the next 15 received thymoglobulin (rabbit anti-human thymocyte gamma globulin; Thymo) induction. The study group included 13 pancreas alone (PA) and 15 sequential pancreas-after-kidney-transplantations (PAKT). Solitary PTX was performed with P-E drainage in 18 patients and systemic-enteric (S-E) drainage in ten. Patient and pancreas graft survival rates were 96% and 79%, respectively, with a mean follow-up of 22 (range 1–39) months. The 1-year actual death-censored pancreas graft survival rate was 89%. One PAKT patient died with a functioning graft at 1 month; three patients (11%) experienced early graft loss due to thrombosis and were excluded from the immunological analysis, leaving 24 evaluable patients. The incidence of acute rejection was 54%, including 50% in PA and 58% in PAKT recipients (P = NS). In patients receiving Thymo induction, the rate of acute rejection was slightly lower (43% Thymo vs 70% DAC). Moreover, P-E drainage was associated with a slightly lower rate of acute rejection (44% P-E vs 75% S-E; P = NS). In patients with both Thymo induction and P-E drainage (n = 11), there was a tendency toward less rejection (the incidence of acute rejection was 36%). Two immunological graft losses occurred (one due to non-compliance), both in patients with P-E drainage. Only one patient had a cytomegalovirus (CMV) infection. Event-free survival (no rejection, graft loss, or death) was slightly higher in patients receiving Thymo (47%) than in those on DAC (23%) induction (P = NS). We can conclude that solitary PTX with P-E drainage and Thymo induction may be associated with improved intermediate-term outcomes and a possible immunological advantage.

Keywords Antibody induction · Daclizumab · Pancreas-after-kidney transplantation · Pancreas-alone transplantation · Surgical technique

Introduction

After decades of controversy surrounding the therapeutic validity of pancreas transplantation (PTX), the procedure has become accepted as the preferred treatment for patients with insulin-dependent diabetes mellitus and advanced diabetic nephropathy. Moreover, advances in surgical techniques and immunosuppression have enabled solitary PTX to become a viable option for the treatment of patients suffering from complication-prone or hyperlabile diabetes [31, 32]. Through October 2000, more than 15,000 PTXs were performed worldwide and reported to the International Pancreas Transplant Registry (IPTR) [9]. In the past decade, the majority (83%) of PTXs were performed in combination with a kidney transplantation (simultaneous kidney-PTX; SKPT) in patients with end-stage diabetic nephropathy. Solitary PTXs comprised the remaining activity, including either sequential pancreas-after-kidney transplantations (PAKT) (12%) or PTX alone (PA) (5%) [9]. The current 1-year patient survival rate after solitary PTX is 95%, and the 1-year actuarial pancreas graft survival rates (with complete insulin independence) are 72% for PAKT and 71% for PA [9].

Although the annual number of PTXs has steadily risen, the proportion of solitary PTXs (PAKT and PA) has increased significantly in recent years [9]. Despite increasing activity and improving results, rejection remains a major cause of morbidity and graft loss after solitary PTX [9, 27, 31, 32]. In contrast to the low 1-year rate of immunological pancreas graft loss (2%) after SKPT, the 1-year rates of pancreas graft loss due to rejection in sequential PAKT and PA transplantation are 7% and 10%, respectively [9]. Further improvements in immunosuppressive regimens after solitary PTX are needed in order for reproducible results to be attained that are comparable to SKPT.

According to IPTR data, most solitary PTXs are performed with systemic venous delivery of insulin and either bladder (systemic-bladder) or enteric (systemic-enteric; S-E) drainage of the exocrine secretions [9]. The majority of PTXs with enteric drainage are performed with systemic venous drainage, resulting in peripheral hyperinsulinemia and antigen delivery. To improve the physiology of PTX, a new surgical technique was developed at our center, combining portal venous delivery of insulin with enteric drainage of the exocrine secretions (portal-enteric; P-E) [7, 25, 30]. The method of splanchnic venous drainage in this technique differed from an alternative technique of whole-organ pancreaticoduodenal transplantation with enteric exocrine drainage that was also first described in 1992 [23]. According to IPTR data, the proportion of enteric-drained PTXs with portal venous delivery of insulin currently accounts for 21% of cases [9].

The introduction of tacrolimus (TAC) (Prograf) and mycophenolate mofetil (MMF) into clinical transplantation raised the benchmark of maintenance immunosuppression by lowering rates of rejection. Initial experience with TAC and MMF after PTX has been favorable [2, 3, 10, 13, 26, 28], and this particular drug combination has become the mainstay of contemporary immunosuppression after solitary PTX [9]. Newer antibody therapies, such as the polyclonal agent thymoglobulin (rabbit anti-human thymocyte gamma globulin; (Thymo) [12, 24] and the monoclonal antibody daclizumab (DAC) [12, 29] directed against the interleukin-2 receptor (IL-2R), have been added to the immunosuppressive armamentarium. At the present time, however, there is no consensus as to the optimal immunosuppressive regimen for preventing rejection and improving graft survival after solitary PTX. The purpose of this study was to evaluate intermediate-term outcomes in solitary PTX recipients with P-E drainage receiving antibody induction with either Thymo or DAC and standardized maintenance immunosuppression with TAC, MMF, and steroids.

Methods

Study design and population

Beginning in 1995, our group began preferentially performing the technique of P-E drainage after solitary PTX [5, 30]. Since 1996, our standard immunosuppressive regimen for PTX has been TAC, MMF, and steroids, either with or without antibody induction [22, 30]. When DAC and Thymo became available, we selectively added these agents to our standard protocol in a chronological fashion. From June 1998 through December 2000 we performed 28 solitary PTXs with antibody induction and TAC/MMF maintenance therapy. For purposes of this study, a retrospective analysis was performed of a prospective entry PTX database. The first 13 patients received DAC induction, while the next 15received Thymo induction. The study group included 15 sequential PAKT and 13 PA recipients. Solitary PTX was performed with P-E drainage in 18 patients and S-E drainage in ten. Minimum follow-up was 9 months.

Recipient selection and operating procedure

Patients were selected for solitary PTX based on ABO blood type compatibility, waiting time, human leukocyte antigen (HLA) matching, and a negative T-lymphocytotoxic crossmatch, in accordance with United Network for Organ Sharing (UNOS) guidelines. After preparation of the organ, the recipient operation was performed through a midline intraperitoneal approach. The surgical techniques for S-E and P-E drainage have previously been reported by our group [7, 30].

Peri-operative management and immunosuppression

Peri-operative antibiotic prophylaxis was attained with a single preoperative dose, an intra-operative dose, and three postoperative doses of cefazolin (1°g intravenously). All patients received single-

strength sulfamethoxazole/trimethoprim (1 tablet/day) for 6–12 months as prophylaxis against *Pneumocystis* pneumonia. Antifungal prophylaxis consisted of oral fluconazole (200°mg/day) for 2–3 months. Anti-viral prophylaxis included intravenous ganciclovir (2.5–5°mg/kg twice daily) during the initial hospital stay, followed by oral ganciclovir (1°g three times daily) for 3 months (for 6 months if the donor was seropositive for cytomegalovirus (CMV) and the recipient was seronegative) [16, 30].

All patients received antibody induction with either DAC or Thymo. DAC 1°mg/kg was administered intravenously over 15–30°min within 24°h of transplantation and then every 14 days (post-operative days 14, 28, 42, and 56) for a total of five doses. Thymo was administered at 1.5°mg/kg per day based on actual body weight. The recommended duration of therapy was 5–7 days. Administration was through a central line over 6°h for the first dose, which was started intra-operatively. Subsequent doses were administered over 4°h as tolerated. Premedication for both DAC and Thymo included the administration of up to 500°mg of intravenous methylprednisolone, 650°mg of acetaminophen, and 25–50°mg of diphenhydramine.

The Thymo dose was adjusted to maintain the total white blood cell count at above 3,000/mm^3 and the total platelet count at above 80,000/mm^3.

All patients received TAC, MMF, and steroids for maintenance immunosuppression [28]. TAC was started at 0.15°mg/kg orally in two divided doses on post-operative day 1, and the 12-h trough levels were maintained at 15–25°ng/ml for the first 3 months after transplantation. After 3 months, TAC trough levels were maintained at 10–15°ng/ml in the absence of rejection or toxicity. Oral MMF was begun immediately post-operatively at 2°g/day in 2–4 divided doses. The MMF dose was reduced in patients with gastrointestinal intolerance (nausea, vomiting, or diarrhea) or when the total white blood cell count was less than 3,000/mm^3. MMF was discontinued temporarily in patients with active infection or septicemia, or when the total white blood cell count was less than 2,000/ mm^3; it was restarted later at a reduced dosage. After the first 3 months, the usual MMF dose was 1°g/day in the absence of rejection. Corticosteroids were administered as intravenous methylprednisolone 500–1,000°mg during surgery, followed by 250°mg on post-operative day°1, and then tapered to 30°mg/day oral prednisone by day 7. Gradual steroid taper was then used, aimed at an oral prednisone dose of 20°mg/day at 1 month, 15°mg/day at 2 months, 10°mg/day at 4 months, and 5°mg/day at 6 months, in the absence of rejection.

Anti-platelet therapy, consisting of oral aspirin (81°mg/day), was administered to all patients. In addition, 2,000–3,000°U of intravenous heparin were administered as a single dose during surgery before implantation of the pancreas. Heparin prophylaxis was continued after transplantation (continuous infusion of 300°U/h for 24°h, then 400°U/h for 24°h, and then 500°U/h until post-operative day°5). Oral warfarin in a single dose of 1°mg/day was administered to patients requiring prolonged vascular access or those with subsequent placement of a permanent central venous catheter. Patients with a history of deep venous thrombosis or hypercoagulable syndrome were maintained on therapeutic levels of warfarin.

Post-operative monitoring

Patients were monitored in the intensive care unit for 24–48°h before being transferred to the transplant unit. After transplantation, duplex ultrasonography of the pancreas was performed on the first post-operative day and whenever clinically indicated. Initially, recipients' serum glucose, amylase, lipase, and TAC levels were monitored frequently. Elevation of serum amylase or lipase concentrations or unexplained fluctuations in serum glucose levels were further evaluated by imaging studies such as ultrasonography and computerized tomography. If no clinical explanation could be identified, a diagnostic biopsy was obtained to determine the etiology of allograft dysfunction [6, 30]. Moreover, patients underwent surveillance monitoring with percutaneous, ultrasound-guided pancreas allograft biopsies performed at 2–3 weeks, 6–8 weeks, and 10–12 weeks after transplantation. We have previously described our technique of percutaneous allograft biopsy in detail [6]. The severity of rejection was graded according to the University of Maryland classification system [14]. The presence of subclinical rejection by surveillance biopsy was an indication for therapy, as was clinical rejection confirmed by biopsy. Borderline or minor pancreas allograft rejection was treated with intravenous methylprednisolone at 500–1,000°mg/day for three doses. Mild, moderate, or severe pancreas allograft rejection was treated with Thymo, ATGAM, or OKT3 for 5–10 days. Steroid-resistant rejection was also treated with anti-lymphocyte therapy. The presence of mild or persistent rejection on follow-up biopsy was treated with pulsed steroids.

Statistical analysis

Data are reported as mean and range. Pancreas graft loss was defined as death with function, pancreatectomy, or the need for daily scheduled insulin therapy. Outcomes and adverse events were recorded prospectively into a database. For study purposes, the database was examined retrospectively, with confirmation by medical record review. Univariate analysis of categorical variables was performed either by the chi-square test or Fisher's exact test, when data were sparse.

Results

Over a 30-month period, we performed 28 solitary PTXs with antibody induction and TAC/MMF maintenance therapy. Demographic, immunological, and transplant characteristics of the study group are listed in Table 1. The first 13 patients received DAC induction, while the next 15 received Thymo induction. The study group consisted of 15 sequential PAKT and 13 PA recipients, including eight cases of pancreas retransplantation (six second, two third). Solitary PTX was performed with P-E drainage in 18 patients, and S-E drainage in ten.

Results are depicted in Table 2. Actual patient and pancreas graft survival rates were 96% and 79%, respectively, with a mean follow-up of 22 months. The 1-year actual death-censored pancreas graft survival rate was 89%. One PAKT patient died with a functioning graft at 1 month due to bacterial sepsis and peritonitis; three patients (11%) experienced early graft loss due to thrombosis and were excluded from the immunological analysis, leaving 24 evaluable patients. None of the explant specimens showed evidence of rejection. The incidence of acute rejection was 54%, including 50% in PA and 58% in PAKT recipients (P = NS). In patients receiving Thymo induction, the rate of acute rejection was slightly lower (43% Thymo vs 70% DAC, P = NS). Moreover, P-E drainage was associated with a slightly lower rate of acute rejection (44% P-E vs 75% S-E, P = NS). In patients with both Thymo induction and P-E

Table 1 Group characteristics. Data are reported as mean(range). P = NS for all variables. *PRA* panel reactive antibody

Characteristic	DAC (n = 13)	Thymo (n = 15)	Total (n = 28)
Age (years)	41.6 (34–54)	37.5 (24–53)	39.3 (24–54)
Gender			
Male	8 (62%)	8 (53%)	16 (57%)
Female	5 (38%)	7 (47%)	12 (43%)
Ethnicity: Caucasian	13 (100%)	14 (93%)	27 (96%)
Years of diabetes	27.2 (15–44)	25.7 (8–40)	26.3 (8–44)
Weight (kg)	75.8 (60–105)	65.9 (50–81)	70.3 (50–105)
Daily insulin dose (U)	46 (31–75)	37 (20–70)	41 (20–75)
Waiting Time (months)	1.8 (0.5–5)	2.0 (0.1–5)	1.9 (0.1–5)
PRA > 10%	1 (8%)	2 (13%)	3 (11%)
HLA-match			
AB	1.54 (0–3)	1.53 (0–3)	1.54 (0–3)
DR	0.92 (0–2)	0.73 (0–2)	0.82 (0–2)
Total	2.5 (1–5)	2.3 (1–4)	2.4 (1–5)
Cold ischemia (h)	15.0 (7–21)	15.5 (11–22)	15.3 (7–22)
CMV D+/R−	3 (23%)	3 (20%)	6 (21%)
Retransplants	5 (38%)	3 (20%)	8 (29%)
Surgical technique			
P-E	6 (46%)	12 (80%)	18 (64%)
S-E	7 (54%)	3 (20%)	10 (36%)
Type of transplant			
PA	4 (31%)	9 (60%)	13 (46%)
PAK	9 (69%)	6 (40%)	15 (54%)

Table 2 Results. Data reported as mean (range). P = NS for all variables

Parameter	DAC (n = 13)	Thymo (n = 15)	Total (n = 28)
Patient survival	12 (92%)	15 (100%)	27 (96%)
Pancreas graft survival			
Actual	10 (77%)	12 (80%)	22 (79%)
1 Year	10 (77%)	14 (93%)	24 (86%)
Death-censored 1 year	10/12 (83%)	14 (93%)	24/27 (89%)
Follow-up (months)	27 (1–39)	18 (10–27)	22 (1–39)
Pancreas thrombosis	2 (15%)	1 (7%)	3 (11%)
Acute rejection: total	7/10 (70%)	6/14 (43%)	13/24 (54%)
P-E	3/5 (60%)	4/11 (36%)	7/16 (44%)
S-E	4/5 (80%)	2/3 (67%)	6/8 (75%)
PA	3/4 (75%)	3/8 (38%)	6/12 (50%)
PAKT	4/6 (67%)	3/6 (50%)	7/12 (58%)
Initial hospitalization			
Length of stay (days)	11 (7–29)	11 (6–25)	11 (6–29)
Charges ($)	84,458	86,279	85,434
Number of re-admissions	2.3 (0–9)	1.7 (0–5)	2.0 (0–9)
CMV infection	1 (8%)	0	1 (4%)
Major infection	3 (23%)	4 (27%)	7 (25%)
Re-laparotomy	9 (69%)	7 (47%)	16 (57%)
Event-free survival (no rejection, graft loss, or death)	3 (23%)	7 (47%)	10 (36%)

drainage (n = 11), there was a tendency toward less rejection (the incidence of acute rejection was 36%). Conversely, in patients without Thymo induction and P-E drainage, the incidence of acute rejection was 69% (P = 0.22). Two immunological graft losses occurred: one due to non-compliance, 12 months after PA transplantation with P-E drainage, and one due to chronic rejection, 13 months after PA transplantation with P-E drainage. Only one patient (3.6%) had a documented CMV infection. Other morbidity, such as length of stay, hospital charges, re-admission, major infection, and re-laparotomy, was comparable among the DAC and Thymo groups (Table 2). The composite endpoint of no rejection, graft loss, or death (event-free survival rate) was highest in patients receiving Thymo (47%) vs DAC (23%) induction (P = NS).

Discussion

According to IPTR data, there are an increasing number (greater than 1,500 to date, greater than 250 per year) and proportion (25% of activity) of solitary PTXs being performed in the US [9]. Historically, the results of solitary PTX have been inferior to the excellent results achieved after SKPT, due to an increased rate of early graft loss due to rejection and thrombosis after solitary PTX [9]. Although enteric drainage has emerged as the preferred method of managing the pancreatic exocrine secretions in SKPT, the majority of solitary PTXs continue to be performed with bladder drainage. In the absence of a simultaneous kidney transplantation in which serum creatinine may be used as a surrogate marker for the diagnosis of rejection, it has been speculated that bladder drainage may provide the advantage of urine amylase monitoring after solitary PTX [9, 31, 32]. Consequently, there are few data available on the results of solitary PTX with enteric drainage, particularly in the setting of contemporary immunosuppression.

Independent of registry data, previous experience with solitary PTX is limited and almost exclusive to the transplant centers at the University of Minnesota and the University of Maryland. In 1997, Gruessner et al. reported outcomes in 225 solitary PTXs during three immunosuppressive eras: the pre-cyclosporine era (n = 83), the cyclosporine era (n = 118), and the TAC era (n = 24) [11]. The 1-year pancreas graft survival rate improved in each successive era, from 34% to 52% to 80% with TAC (P = 0.002). The 1-year rate of pancreas graft loss due to rejection decreased from 50% to 34% to 9% with TAC (P = 0.008). In addition, the technical failure rate decreased from 30% to 14% to 0% in the TAC era (P = 0.001). The 1-year patient survival rates in all three eras ranged from 88%–95%. However, the rates of rejection were over 67% in all three eras. The authors concluded that outcomes after solitary PTX have improved markedly with the use of bladder drainage, HLA-matching, TAC-based therapy, and biopsy-directed immunosuppression. In a follow-up study, the Minnesota group reported on 464 solitary PTXs

including 88 performed from 1994 to 1997 [32]. In this latter group, the 1-year graft survival rate was 72%, with a technical failure rate of 7%. The rate of acute rejection ranged from 10% in PAKT to 30% in PA transplant recipients.

In their most recent analysis [31], the University of Minnesota analyzed 404 PAKT and 291 PA recipients divided into four eras. Era 3 ranged from 1994–1998 and included 103 PAKT and 36 PA recipients. Era 4 ranged from 1998–2000 and included 123 PAKT and 46 PA recipients. Era 4 was characterized by TAC and MMF-based therapy, the use of DAC induction, and the administration of pre-transplant immunosuppression in candidates awaiting PA. In era 4, the PAKT patient and graft survival rates at both 1 and 2 years were 98% and 81%, respectively. Similarly, in era 4, the 1-year patient and graft survival rates after PA were 100% and 88%, respectively; at 2 years, they were 100% and 83%, respectively. The 1-year rates of immunological graft loss were 10% in PAKT and 9% in PA recipients. In these combined analyses, virtually all PA and the majority of PAKT recipients underwent PTX with systemic-bladder drainage.

In 1997, Kuo et al. [14] reported on 35 solitary PTXs (30 PAKT and five PA) performed at the University of Maryland with biopsy-directed immunosuppression. All patients received ATGAM induction and either cyclosporine or TAC-based therapy. The 1- and 2-year actuarial pancreas graft survival rates were 70% and 66%, respectively. The incidence of biopsy-proven acute rejection was 74%. In another study by the Maryland group [1], Bartlett et al. compared 15 consecutive PA transplantations performed between 1992 and 1994 with cyclosporine-based therapy with the next 27 consecutive PA transplantations performed from 1994 to 1996 with TAC-based therapy and biopsy-directed immunosuppression. In patients with technically successful grafts, the 1-year pancreas graft survival rate was 90% with TAC vs 53% with cyclosporine-based therapy ($P=0.002$). Actual 1-year graft survival rates were 77% with TAC vs 53% with cyclosporine ($P=0.06$). The incidence of biopsy-proven or clinically presumed rejection was in excess of 80% in both groups. The authors concluded that the results of solitary PTX were now equivalent to SKPT with the advent of modern immunosuppression and biopsy techniques. Again, however, the majority of these solitary PTXs were performed with systemic-bladder drainage.

In the past few years, experience has begun to accumulate in solitary PTX with enteric drainage, including portal venous delivery of insulin. In 1998, Eubanks et al. from our group compared 12 solitary PTXs with systemic-bladder drainage performed from 1991–1995 with 16 solitary PTXs with P-E drainage performed between July 1995 and March 1997 [5]. The former group was managed with cyclosporine, and the latter with TAC-based immunosuppression. One patient in each group experience graft loss as a result of thrombosis. In the remaining patients, the incidence and density of rejection were lower in the more recent era, leading to an improvement in the 1-year pancreas graft survival rate to 80% [5].

In 1999, Philosophe et al. [19] from the University of Maryland reported their initial experience with 66 PTXs with P-E drainage compared with 183 PTXs with S-E drainage. Graft survival rates for SKPT, PAKT, and PA recipients were similar according to technique. However, when stratified for HLA-matching, the incidence of rejection was lower in patients with P-E drainage. In a follow-up report in 2000 [20], Philosophe et al. compared 117 solitary PTXs with P-E drainage vs 70 with S-E drainage. The authors noted not only an improvement in the pancreas graft survival rate, but also a decrease in the incidence and severity of rejection in patients with P-E drainage. The authors concluded that P-E drainage may be associated with an immunological advantage.

In 2000, Gruber et al. [8] reported a pancreas graft survival rate of 79% and a 50% incidence of acute rejection in 14 solitary PTX (seven PAKT, seven PA) recipients managed with OKT3 induction, TAC and MMF-based therapy, and without regard to donor/recipient HLA-matching. The majority of these transplantations were performed with bladder drainage. In 2001, Odorico et al. [17] reported on 37 solitary PTXs (28 PAKT, nine PA) with S-E drainage, antibody induction, and TAC/MMF-based immunosuppression. Although the accumulated incidence of biopsy-proven acute rejection was 42%, the 2-year pancreas graft survival rate was 92%. In 2001, Larson et al. [15] from the Mayo Clinic performed surveillance biopsies in 29 solitary PTX recipients, including 17 PA and 12 PAKT. All patients received antibody induction (DAC [$n=6$], OKT3 [$n=10$], or Thymo [$n=13$]) in combination with TAC, MMF, and steroids. The overall 1-year pancreas graft survival rate was 89%. The incidence of acute rejection was 50% with either DAC or OKT3 induction, but only one of 13 patients (8%) receiving Thymo induction experienced a rejection episode.

Similarly to the previous literature, our study reports improving outcomes after solitary PTX associated with antibody induction, TAC/MMF-based therapy, and biopsy-directed immunosuppression. Moreover, a tendency toward a lower rate of rejection was seen with Thymo induction and P-E drainage. In spite of heavy, front-loaded immunosuppression, the incidences of infectious complications and other morbidity were not excessive. Although our numbers are small and the study groups are not randomized, the data certainly suggest that excellent outcomes and rejection rates below 50% may be achieved after solitary PTX with advances in immunosuppression and refinements in surgical tech-

niques. The use of surveillance biopsy monitoring facilitates the safe application of enteric drainage after solitary PTX. In our experience, the rates of either undetected rejection or immunological graft loss are low after solitary PTX with P-E drainage, although two immunological graft losses did occur. The addition of Thymo induction may further lower immunological morbidity in this otherwise high-risk population. A number of previous studies have suggested that portal venous delivery of antigen may have a possible immunological advantage [4, 5, 7, 18, 19, 20, 21, 30]. However, this question can be answered only by a well-designed, prospective, randomized study comparing systemic vs portal venous drainage in the setting of standardized immunosuppression. In the absence of such a study design, we conclude that solitary PTX with P-E drainage and Thymo induction may be associated with excellent intermediate-term outcomes and possibly an immunological advantage.

Acknowledgement We gratefully acknowledge the technical expertise of Joyce Lariviere in the preparation of the manuscript.

References

1. Bartlett ST, Schweitzer EJ, Johnson LB, Kuo PC, Papadimitriou JC, Drachenberg CB, Klassen DK, Hoehn-Saric EW, Weir MR, Imbembo AL (1996) Equivalent success of simultaneous pancreas kidney and solitary pancreas transplantation: a prospective trial of tacrolimus immunosuppression with percutaneous biopsy. Ann Surg 224:440–452
2. Bruce DS, Woodle ES, Newell KA, Millis JM, Cronin DC, Loss GE, Grewal HP, Siegel CT, Pellar S, Josephson MA, Thistlethwaite JR Jr (1998) Tacrolimus/mycophenolate mofetil provides superior immunosuppression relative to Neoral/mycophenolate in synchronous pancreas-kidney transplantation. Transplant Proc 30:1538–1540
3. Burke GW, Ciancio G, Alejandro R, Roth D, Ricordi C, Tzakis A, Miller J (1998) Use of tacrolimus and mycophenolate mofetil for pancreas-kidney transplantation with or without OKT3 induction. Transplant Proc 30:1544–1545
4. Cattral MS, Bigam DL, Hemming AW, Carpentier A, Greig PD, Wright E, Cole E, Donat D, Lewis GF (2000) Portal venous and enteric exocrine drainage versus systemic venous and bladder exocrine drainage of pancreas grafts: clinical outcome of 40 consecutive transplant recipients. Ann Surg 232:688–695
5. Eubanks JW, Shokouh-Amiri MH, Elmer D, Hathaway D, Gaber AO (1998) Solitary pancreas transplantation using the portal-enteric technique. Transplant Proc 30:446–447
6. Gaber AO, Gaber LW, Shokouh-Amiri MH, Hathaway DH. (1992) Percutaneous biopsy of pancreas transplants. Transplantation 54:548–550
7. Gaber AO, Shokouh-Amiri MH, Hathaway DK, Hammontree L, Kitabchi AE, Gaber LW, Saad MF, Britt LG (1995) Results of pancreas transplantation with portal venous and enteric drainage. Ann Surg 221:613–624
8. Gruber SA, Katz S, Kaplan B, Clark JH 3rd, Chen PC, El-Sabrout R, Kerman RH (2000) Initial results of solitary pancreas transplants performed without regard to donor/recipient HLA-mismatching. Transplantation 70:388–391
9. Gruessner AC, Sutherland DER (2001) Pancreas transplant outcomes for United States cases reported to the United Network for Organ Sharing (UNOS) and non-US cases reported to the International Pancreas Transplant Registry (IPTR) as of October 2000. In: Cecka JM, Terasaki PI (eds) Clinical transplants 2000. UCLA Immunogenetics Center, Los Angeles, pp 45–72
10. Gruessner RWG, Sutherland DER, Drangstveit MB, West M, Gruessner AC (1998) Mycophenolate mofetil and tacrolimus for induction and maintenance therapy after pancreas transplantation. Transplant Proc 30:518–520
11. Gruessner RWG, Sutherland DER, Najarian JS, Dunn DL, Gruessner AC (1997) Solitary pancreas transplantation for non-uremic patients with labile insulin-dependent diabetes mellitus. Transplantation 64:1572–1577
12. Kaufman DB, Burke G, Bruce D, Sutherland D, Johnson C, Gaber AO, Merion RM, Schweitzer E, Marsh Cl, Gruber SA, Alfery E, Leone JP, Conception W, Stegall MD, Gores PS, Danovitch G, Nunnally PJ, Henning AK, Fitzsimmons WE (2000) The role of antibody induction in simultaneous pancreas-kidney transplant patients receiving tacrolimus and mycophenolate mofetil immunosuppression. Transplantation 69:206
13. Kaufman DB, Leventhal JR, Koffron A, Gheorghiade M, Elliott MD, Parker MA, Abecassis MM, Fryer JP, Stuart FP (2000) Simultaneous pancreas-kidney transplantation in the mycophenolate mofetil/tacrolimus era: evolution from induction therapy with bladder drainage to non-induction therapy with enteric drainage. Surgery 128:726–737
14. Kuo PC, Johnson LB, Schweitzer EJ, Klassen DK, Hoehn-Saric EW, Weir MR, Drachenberg CB, Papadimitriou JC, Bartlett ST (1997) Solitary pancreas allografts: the role of percutaneous biopsy in standardized histologic grading of rejection. Arch Surg 132:52–57
15. Larson TS, Kim DY, Carpenter HA, Burgart LJ, Velosa JA, Stegall MD (2001) Utility of surveillance biopsies following solitary pancreas transplantation. Am J Transplant 1:286
16. Lo A, Stratta RJ, Egidi MF, Shokouh-Amiri MH, HP Grewal, Kisilizik AT, Trofe J, Alloway RR, Gaber LW, Gaber AO (2001) Patterns of cytomegalovirus infection in simultaneous kidney-pancreas transplant recipients receiving tacrolimus, mycophenolate mofetil, and prednisone with ganciclovir prophylaxis. Transplant Infect Dis 3:8–15
17. Odorico JS, Pirsch JD, Becker YT, Knechtle SJ, D'Alessandro A, Werwinski C, Sollinger HW (2001) Results of solitary pancreas transplantation with enteric drainage: is there a benefit from monitoring urinary amylase levels? Transplant Proc 33:1700
18. Perez R, Troppmann C, Mcvicar J, Cecka JM (2001) The immunologic advantage of portal venous drainage of the pancreas allograft in simultaneous pancreas-kidney transplantation. Am J Transplantation 1 [Suppl 2]:286

19. Philosophe B, Taylor JP, Schweitzer EJ, Farney AC, Colonna JO, Foster C, Frank AM, Jarrell BE, Bartlett ST (1999) Portal venous drainage in pancreas transplantation: is there an immunologic advantage? Proceedings of the 7th World Congress of the International Pancreas and Islet Transplant Association 56 (A 15)
20. Philosophe B, Farney AC, Schweitzer EJ, Farney AC, Colonna JO, Foster C, Frank AM, Jarrell BE, Bartlett ST (2000) The superiority of portal venous drainage over systemic venous drainage in solitary pancreas transplantation. Proceedings of the 17th International Congress of the Transplantation Society 115 (A 0330)
21. Philosophe B, Wiland AM, Klassen DK, Schweitzer EJ, Farney AC, Colonna JO, Foster C, Frank AM, Jarrell BE, Bartlett ST (2001) Immunologic protection of kidneys by portal venous drainage of the pancreas in simultaneous pancreas-kidney transplantation. Am J Transplantation 1 [Suppl 1]:286 (A 601)
22. Reddy KS, Stratta RJ, Shokouh-Amiri MH, Alloway RR, Somerville T, Egidi MF, Gaber LW, Gaber AO (2000) Simultaneous kidney-pancreas transplantation without anti-lymphocyte induction. Transplantation 69:49–54
23. Rosenlof LK, Earnhardt RC, Pruett TL, Stevenson WC, Douglas MT, Cornett GC, Hanks JB (1992) Pancreatic transplantation: an initial experience with systemic and portal drainage of pancreatic allografts. Ann Surg 215:586–597
24. Schulz T, Martin D, Heimes M, Klempnauer J, Busing M (1998) Tacrolimus/mycophenolate mofetil/steroid-based immunosuppression after pancreas-kidney transplantation with single-shot anti-thymocyte globulin. Transplant Proc 30:1533–1535
25. Shokouh-Amiri MH, Gaber AO, Gaber LW, Jensen SL, Hughes TA, Elmer D, Britt LG (1992) Pancreas transplantation with portal venous drainage and enteric exocrine diversion: a new technique. Transplant Proc 24:776–777
26. Stegall MD, Simon M, Wachs ME, Chan L, Nolan C, Kam I (1997) Mycophenolate mofetil decreases rejection in simultaneous pancreas/kidney transplantation when combined with tacrolimus or cyclosporine. Transplantation 64:1695–1700
27. Stratta RJ (1998) Graft failure after solitary pancreas transplantation. Transplant Proc 30:289
28. Stratta RJ, for the FK/MMF Multicenter Study Group. (1997) Simultaneous use of tacrolimus and mycophenolate mofetil in combined pancreas-kidney transplant recipients: a multi-center report. Transplant Proc 29:654–655
29. Stratta RJ, Alloway RR, Lo A, Hodge E, for the PIVOT Study Group (2001) A multi-center trial of two daclizumab dosing strategies versus no antibody induction in simultaneous kidney-pancreas transplantation. Transplant Proc 33:1692–1693
30. Stratta RJ, Shokouh-Amiri MF, Egidi MF, Grewal HP, Gaber LW, Gaber AO (2001) Portal-enteric pancreas transplantation at the University of Tennessee, Memphis. In: Cecka JM, Terasaki PI, (eds) Clinical transplants 2000. UCLA Immunogenetics Center, Los Angeles, pp 217–237
31. Sutherland DE, Gruessner RW, Dunn DL, Matas AJ, Humar A, Kandaswamy R, Mauer SM, Kennedy WR, Goetz FC, Robertson RP, Gruessner AC, Najarian JS (2001) Lessons learned from more than 1,000 pancreas transplants at a single institution. Ann Surg 233:463–501
32. Sutherland DER, Gruessner RWG, Najarian JS, Gruessner AC (1998) Solitary pancreas transplants: a new era. Transplant Proc 30:280–281