Transplant Int (1988) 1: 6-12

TRANSPLANT
International

Early diagnosis and treatment of pancreas allograft rejection

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Abstract. A major problem in vascularized pancreas transplantation is the lack of reliable methods for the early diagnosis and effective treatment of allograft rejection. Over a 2-year period, 54 rejection episodes occurred in 31 patients (13 isolated pancreas, 18 simultaneous pancreas-kidney recipients) with pancreaticoduodenocystostomy. A total of 253 radionuclide pancreas examinations were performed (mean 8.4 per patient) utilizing ^{99m}technetium-DTPA. Computer analysis generated a quantitative measure of blood flow to the allograft caused the technetium index (TI). Rejection episodes were characterized as isolated pancreas (22), combined pancreas-kidney (16), or isolated renal (16) allograft rejection in combined engraftments. The majority of rejection episodes occurred early (within 3 months of transplant, $N=47$) and were more responsive than late rejection to anti-rejection therapy (89.4% vs 42.9%, $P=0.01$). Mean urinary amylase (UA) levels and TI during normal allograft function were 29,398 U/l and 0.55%, while levels heralding rejection were 6,528 U/l and 0.40%, respectively ($P<0.05$). The treatment of rejection based upon renal dysfunction or combined renal and pancreas dysfunction resulted in significantly higher graft salvage with a lower incidence of hyperglycemia when compared to isolated pancreas allograft rejection. Of the 11 patients who developed hyperglycemia, 8 (72.7%) ultimately lost their pancreas grafts ($P<0.001$). Following therapy, a TI above 0.3% was associated with 97.4% graft survival, while levels below 0.3% resulted in a 70% rate of graft loss ($P<0.001$). Similarly, pancreas allografts with a UA above 10,000 U/l had 91.1% functional survival, while levels below 10,000 U/l resulted in a 66.7% rate of graft loss ($P<0.001$). Overall, reversal of rejection occurred in 83.3% of cases, with 9 grafts lost due to rejection at a mean of 4.7 months post-transplant. Therapy with ALG or OKT_3 was more effective in reversing allograft rejection than pulsed corticosteroids alone (68.8% vs 47.9%, $P=0.05$). Patient and pancreas allograft survival is 96.8% and 67.7%, respectively, after a mean follow-up interval of 14.9 months. Monitoring pancreas allograft function by UA, TI, and renal function (in simultaneous transplants) allows for the timely diagnosis and successful treatment of pancreas allograft rejection.

Key words: Monoclonal antibody OKT_3 - Pancreas transplantation - Rejection - Technetium scanning - Urinary amylase.

With advances in immunosuppression, refinements in surgical techniques, and increased clinical experience, allograft survival rates have improved dramatically and a resurgence of interest has occurred in vascularized pancreas transplantation. However, these achievements have been tempered by the continuing formidable challenge of the early detection and effective treatment of rejection. Rejection is the major cause of graft loss at present, accounting for about 40% of graft failures according to registry statistics [25]. The current dilemmas in pancreas transplantation are the lack of a reliable technique for the early detection of rejection and differentiating rejection from other causes of graft failure, such as pancreatitis, vascular thrombosis, and disease recurrence.

Simultaneous pancreas and kidney transplantation from the same donor has partially circumvented this problem, since numerous studies have dem-

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onstrated that the manifestations of renal allograft rejection precede pancreas rejection [1, 6, 30]. The major advantage of simultaneous pancreas and kidney transplantation is the "protective" effect of the renal allograft in terms of following renal function as an early monitor for subsequent pancreas allograft rejection. Although episodes of kidney rejection may occur independently and without concomitant detectable pancreas rejection, isolated pancreas rejection in combined engraftments is uncommon [1, 5, 32].

With regard to isolated pancreas transplantation, the prediction of rejection episodes remains difficult. Multiple reports have shown that loss of glucose homeostasis occurs rather late in the sequence of immunological rejection, with successful reversal of rejection achieved in only 30% of cases after the onset of hyperglycemia [17, 19, 27]. Fortunately, other studies have demonstrated that the exocrine pancreas is more sensitive to rejection than the endocrine pancreas, with a reduction in exocrine function preceding the onset of hyperglycemia [8, 17, 19]. Histological studies have noted mononuclear cell infiltration of acinar tissue and vasculitis prior to any islet cell changes [8, 19, 20].

Pancreas rejection is subtle and occult; its clinical presentation may be characterized by fever ($T \geq 37.8\,^{\circ}C$), leukocytosis, ileus, graft swelling and tenderness, and abdominal pain. Differentiation from pancreatitis is difficult and none of these features is consistently present or pathognomonic of the rejection process. By utilizing ductal drainage techniques that permit easy access and analysis of pancreatic exocrine secretions (pancreaticocystostomy), one can monitor exocrine function and detect rejection. Evidence is accumulating that reductions in urinary amylase levels are an early marker of rejection crises [7, 16, 17, 22]. Serological assays of exocrine and endocrine function as applied to rejection are not very sensitive. Serum amylase concentrations do not seem to correlate well with allograft rejection [26, 31, 32]. A number of metabolic profiles and provocative tests (such as arginine- or glucagon-stimulated C-peptide output) have been examined but are of limited value in the early diagnosis of rejection [9, 26, 27].

Radionuclide imaging provides useful information as to the physiologic status of the pancreas. Perfusion indices generated by radionuclide flow studies with ^{99m}technetium-diethylene triamine pentaacetic acid (^{99m}Tc-DTPA) are currently being investigated in the detection of pancreas rejection [15].

The detection and progression of pancreas allograft rejection are extremely dependent upon the transplantation technique. With the development of pancreaticocystostomy at our institution, we have employed urinary monitoring of pancreatic exocrine secretions as an index of allograft function [23]. The objectives of this study were to determine: (1) if urinary amylase levels are a reliable and sensitive indicator of pancreas allograft rejection; (2) if radionuclide imaging and the calculation of a technetium flow index is useful in the detection of rejection; (3) if renal allograft rejection in simultaneous pancreas-kidney transplants is an accurate harbinger of pancreas rejection; (4) if the above diagnostic studies can be employed to monitor antirejection therapy; and (5) the efficacy of various therapeutic agents on pancreas allograft rejection.

Materials and methods

Patient population

Over a 2-year period, 40 technically successful intraperitoneal whole-organ vascularized pancreas transplants with pancreaticoduodenocystostomy, with or without simultaneous kidney transplant, were performed by a technique described previously [22]. This included 18 isolated pancreas transplants and 22 combined pancreas-kidney transplants. Rejection was detected in 31 patients (77.5%), including 13 isolated pancreas and 18 simultaneous pancreas-kidney recipients. The study group consisted of the patients experiencing allograft rejection. The mean age of the patient population was 32.9 years (range 24–43) with a mean duration of insulin-dependent diabetes mellitus of 21.3 years (range 10–28). Twenty patients were male (64.5%) and 11 were female (35.5%). The entire population was Caucasian. All patients receiving an isolated pancreas allograft ($N = 13$) had previously undergone successful renal transplantation, either living-donor ($N = 10$) or cadaveric donor ($N = 3$). All recipients had retinopathy and nearly half had clinically significant neuropathy.

Recipient selection and monitoring

Recipient selection was based upon blood type ABO compatibility. Prospective tissue typing for A, B, and DR antigens was not routinely performed. In patients receiving a simultaneous pancreas-kidney transplant, prospective T-cell cross-matching was performed. In all other patients (all had low-panel reactive antibody titers), no prospective T-cell cross-match was performed. After transplantation, recipients were serially monitored with daily fasting serum glucose, amylase, blood urea nitrogen, creatinine, and beta-2-microglobulin levels, performed by standard laboratory techniques. Daily urinary amylase levels (units/liter) were likewise obtained. Pancreas scans were performed on the first postoperative day (portable) to confirm graft viability, the second postoperative day (in combination with ^{131}I-Hippuran renal scan), and when clinically indicated. The diagnosis of rejection was a composite decision based upon clinical criteria (fever, ileus, allograft swelling and tenderness), a reduction in urinary amylase levels (usually below 10,000 U/l), hypoperfusion or a reduction in the technetium index on radionuclide scan, hyperglycemia (serum glucose above 180 mg/dl), or associated renal allograft dysfunction in combined engraftments. Renal and pancreas allograft biopsies were not performed. Serum amylase and beta-2 microglobulin levels were not consistently helpful in determining the presence of rejection.

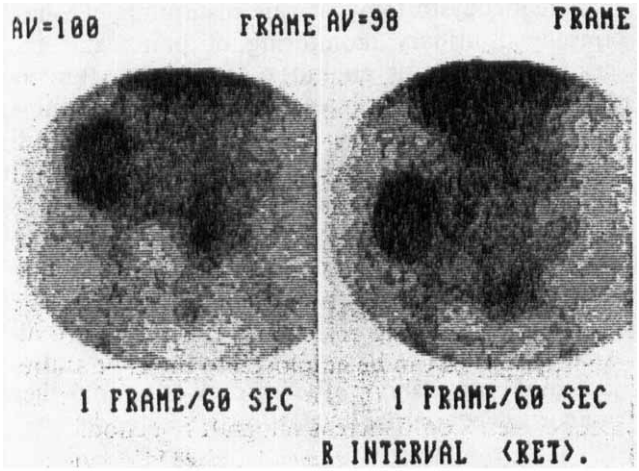

Fig. 1. A typical ^{99m}Tc-DTPA perfusion scan during isolated pancreas allograft rejection demonstrating excellent perfusion of the renal allograft in the right and pancreas hypoperfusion in the left iliac fossa (pre-OKT_3, *left*). With OKT_3 *(right)* therapy, pancreas perfusion returns to normal

Serum glucose and urinary amylase levels were determined every 2-4 h during the first 5 days after transplant. Patients with a well-functioning allograft exhibited normoglycemia without further insulin requirements within 6 h of transplantation. Urinary amylase concentrations usually reached a value of 2,000-10,000 U/l within the first 48 h postoperatively. Urinary amylase levels below 600-800 U/l indicated severe preservation injury, vascular impairment, or massive diuresis. In the ensuing weeks, urinary amylase determinations were monitored daily until hospital discharge and then biweekly. Stable long-term grafts achieved urinary amylase concentrations well above 10,000 U/l.

Radionuclide imaging

Five mCi of ^{99m}Tc-DTPA was administered intravenously and flow images of the pancreas allograft were obtained. Data were acquired on a computer at 1 frame/s × 60 s, then 1 frame/min × 4 min. After the 5-min computer analysis was processed, a perfusion scan of the allograft was generated. Following interpolative background subtraction, computer analysis of the percentage of tracer present in the pancreas allograft in the third minute of scanning was employed to generate a technetium index (TI). The TI is a quantitative measure of blood pooling in the allograft and is followed over sequential examinations. A standard "region of interest" corresponding to pancreas allograft borders is determined for each patient. In addition, the TI was compared to the percentage of tracer accumulation in the renal allograft during the same time period. Characteristics of rejection demonstrated by nuclear scanning include hypoperfusion with diminished visualization, graft swelling and haziness, and loss of border resolution, especially in the tail of the pancreas (Fig. 1).

Immunosuppressive protocol

In preparation for pancreas transplantation, a minimum of five random blood transfusions were required. Preoperatively, patients received 120 mg methylprednisolone intravenously and 300 mg azathioprine orally. The azathioprine dose was reduced for leukopenia. Recipients received 250 mg of intravenous methylprednisolone intraoperatively just prior to release of the vascular clamps. Postoperatively, 120 mg methylprednisolone was continued intravenously for 3 days and then rapidly tapered to 30 mg prednisone orally per day within 10 days. Minnesota antilymphoblast globulin was initiated on the 1st postoperative day at 10-20 mg/kg per day with dosage adjustments to maintain the WBC count above 3,000/mm^3 and the platelet count above 50,000/mm^3 in the absence of clinical sepsis or bleeding. A complete 10-14 day course of "prophylactic" ALG was given. Azathioprine was maintained at a level of 1 mg/kg per day with dose adjustments to maintain the WBC count above 5,000/mm^3. Cyclosporine was administered intravenously at a dose of 1-3 mg/kg per day for the first 3 days after transplantation and was then switched to an oral dose of 6-12 mg/kg per day. The dose of cyclosporine was adjusted daily to achieve 24-h trough whole-blood radioimmunoassay levels of 200-400 ng/ml. Long-term maintenance immunosuppression usually consisted of oral prednisone, 10-30 mg/day; cyclosporine, 4-12 mg/kg per day; and azathioprine, 1 mg/kg per day.

Acute rejection episodes were treated with pulsed corticosteroids (250-500 mg methylprednisolone intravenously) with rapid taper over 10 days to 30 mg oral prednisone. Treatment with ALG was usually initiated if rejection recurred following two courses of high-dose prednisone or if no response was seen after 5 days of initial treatment with steroids. Monoclonal antibody OKT_3 was reserved only for "rescue" therapy of rejection unresponsive to high-dose steroids and/or ALG. OKT_3 was administered for 14 consecutive days as a single daily intravenous bolus of 5 mg. Pulsed corticosteroid therapy (oral prednisone, 3 mg/kg per day) with rapid taper was given on days 0-3 and on days 12-16 of OKT_3 therapy. During days 4-11 of OKT_3 therapy, oral prednisone at 30 mg/day was given. Maintenance doses of azathioprine (1 mg/kg per day) were continued throughout the duration of monoclonal antibody therapy. Low-dose oral cyclosporine (4-6 mg/kg per day) was also maintained, with dosage adjustments near the end of OKT_3 therapy titrated to whole-blood radioimmunoassay levels of 200-400 ng/ml. At the completion of OKT_3 therapy, the pretreatment doses of immunosuppressive agents were resumed with rapid steroid taper.

Statistical analysis

Data are reported as mean ± standard error of the mean values. Differences between groups were compared statistically with Students' *t*-test for continuous variables and Fisher's exact test for categorical variables. A *P*-value less than 0.05 was considered significant.

Results

A total of 54 rejection episodes occurred in the 31 patients and were characterized as isolated pancreas ($N=22$), combined pancreas-kidney ($N=16$), or isolated renal ($N=16$) allograft rejection in combined engraftments. The majority of rejection episodes occurred early (within 4 months of transplant), with 47 episodes documented at a mean time post-transplant of 36.3 days (range 3-118 days). The remaining 7 rejection episodes occurred late (mean time post-transplant 10.8 months, range 5.5-29 months). A total of 253 radionuclide pancreas examinations were performed (mean 8.4 per patient). Results are depicted in Table 1.

Table 1. Laboratory parameters of rejection in pancreas and combined pancreas-kidney allografts (mean ± SEM). * $P<0.05$; ** $P<0.10$

Type of rejection	N	Urine amylase (U/l)			Technetium index (%)			Serum creatinine (mg/dl)		
		Pre	Rejection	Post	Pre	Rejection	Post	Pre	Rejection	Post
Isolated pancreas	22	30687± 4612	6277±* 995	22028± 3903	0.61± 0.10	0.41±** 0.04	0.41± 0.06			
Combined pancreas-kidney	16	28023± 4345	6870±* 1619	28769± 6053	0.47± 0.05	0.40± 0.06	0.52± 0.10	1.6± 0.1	3.2±* 0.2	1.9± 0.1
Total pancreas	38	29398± 3132	6528±* 880	25110± 3476	0.55± 0.07	0.40±* 0.03	0.45± 0.05			
Isolated renal (in simultaneous transplants)	16	45910± 8142	35263± 10562	50618± 7910	0.52± 0.04	0.51± 0.04	0.58± 0.07	2.0± 0.2	3.8±* 0.4	2.0± 0.1

Table 2. Incidence of hyperglycemia and success of therapy for rejection in isolated pancreas and combined pancreas-kidney transplantation. * $P<0.05$; ** $P<0.10$

Type of rejection	N (rejection episodes)	Hyperglycemia (fasting glucose > 180 mg/dl)	Reversal of rejection (%)	Graft survival (%)
Isolated pancreas	22	10 (45.4%)	15 (68.2%)	46.7%
Combined pancreas-kidney	16	3 (18.7%)**	14 (87.5%)	80%
Total pancreas	38	13 (34.2%)	29 (76.3%)	60%
Isolated renal (in simultaneous transplants)	16	1 (6.25%)*	16 (100%)*	100%*
Total	54	14 (25.9%)	45 (83.3%)	67.7%

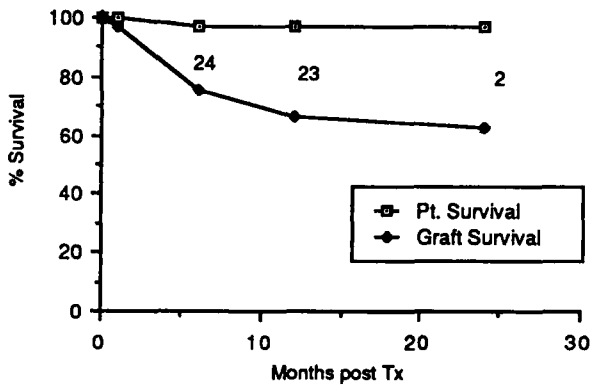

Fig. 2. Actuarial patient and pancreas allograft survival in 31 recipients who experienced rejection episodes (pancreas recipients without rejection not included)

A total of 38 episodes of pancreas allograft rejection were documented. The mean baseline or prerejection values for urine amylase and the TI were 29,398 U/l and 0.55%, respectively. Pancreas rejection was associated with significant reductions in the urine amylase and the TI to mean values of 6,528 U/l and 0.40%, respectively ($P<0.05$). Following antirejection therapy, urine amylase and the TI returned to normal (mean 25,110 U/l and 0.45%). Isolated renal allograft rejection in combined pancreas-kidney recipients was characterized by a significant rise in serum creatinine and no significant change in the urine amylase or pancreas TI. After therapy for renal allograft rejection, serum creatinine returned to normal and the urine amylase and TI continued to be unaffected. Only two cases of isolated pancreas allograft rejection in combined pancreas-kidney recipients were seen.

The treatment of isolated pancreas allograft rejection was associated with a 45.4% incidence of hyperglycemia and a 68.2% success rate (Table 2). Therapy for combined pancreas-kidney allograft rejection resulted in an 18.7% incidence of transient hyperglycemia ($P=0.08$) and an 87.5% rate of rejection reversal ($P=$ NS). In isolated renal allograft rejection, only one patient developed hyperglycemia with steroid therapy and no grafts were lost ($P=0.03$). Of 11 patients who developed hyperglycemia, 8 (72.7%) ultimately lost their pancreas grafts ($P<0.001$).

Antirejection therapy consisted of pulsed corticosteroids in 48 cases, with 23 (47.9%) successful. ALG was utilized in the treatment of rejection in 14 patients, with reversal of rejection occurring in 12 (85.7%). Monoclonal antibody OKT_3 was em-

ployed in 18 episodes of steroid- and/or ALG-resistant rejection, with successful rescue in 10 (55.5%). Therapy with ALG or OKT_3 was more effective in reversing allograft rejection than pulsed corticosteroids alone (68.8% versus 47.9%, $P=0.05$). Overall, 45 episodes of allograft rejection were successfully reversed (83.3%), with 9 pancreas allografts lost due to rejection. No renal allografts were lost from rejection, but 1 patient died due to sepsis. Actuarial patient and pancreas allograft survival is 96.8% and 67.7%, respectively, after a mean follow-up interval of 14.9 months (range 1-43) (see Fig. 2).

The mean duration of antirejection therapy was 13.1 days (range 7-30). In successfully treated recipients, the mean time to rejection reversal was 6.3 days (range 2-18). The mean time to rejection reversal with monoclonal antibody OKT_3 was 9.0 days (range 4-14). Early rejection was successfully reversed in 42 of 47 instances (89.4%), while late rejection responded to therapy in 3 of 7 cases (42.9%; $P=0.01$). Of the 9 grafts lost to rejection, 8 were failures of monoclonal antibody OKT_3 therapy; the remaining patient failed steroid and ALG therapy.

Following therapy, a TI above 0.3% was associated with 97.4% graft survival, while levels below 0.3% resulted in a 70% rate of graft loss ($P<0.001$). Similarly, pancreas allografts with a urinary amylase level above 10,000 U/l after antirejection therapy had a 91.1% functional survival, while levels below 10,000 U/l resulted in a 66.7% rate of graft loss ($P<0.001$).

Discussion

The results of vascularized pancreas transplantation remain inferior to the excellent results now achieved in kidney, heart, and liver transplantation. As pancreas transplantation has evolved, technical problems have been overcome and the focus of attention has now shifted to the current limiting factor - allograft rejection. It is difficult to determine the susceptibility of the pancreas to rejection. The pancreas may be a highly immunogenic organ, not only vulnerable to rejection but also with a poor potential for recovery. In addition, current methods are not sensitive enough to detect early rejection crises. The diagnosis of pancreas allograft rejection is often made at a time when 90% or more of the graft has been irreversibly injured [17]. In the recent past, pancreas rejection was characterized as rapid, unpredictable, and irreversible. These clinical observations are supported by the histological sequence of pancreas allograft rejection [8, 19, 20, 26]. In the early phase of the rejection response, a focal, interstitial, lymphocytic infiltrate and perivascular cuffing are noted. During this stage, the patient remains normoglycemic. In the second stage, an intense, diffuse, mononuclear cell infiltration with islet sparing is seen, and again the patient is normoglycemic, with possibly an abnormal glucose tolerance test. In the final stage of the rejection response, fibrosis, loss of acinar tissue, and pronounced vascular changes with islet infiltration and destruction are seen. It is only in this stage that frank hyperglycemia is observed. When rejection is diagnosed at this stage, it is usually irreversible.

A major advance in the early diagnosis of pancreas allograft rejection came with the introduction of bladder drainage [22]. Using this technique, the pancreatic duct or a portion of the duodenum is directly anastomosed to the bladder. While this modification was initially developed at our institution in an attempt to create a safer surgical procedure available for exocrine drainage, clinical and laboratory experience has demonstrated that an additional advantage is the ability to monitor pancreatic exocrine secretions in the urine. Many clinicians are now relying on the excretion of urinary amylase for the diagnosis of pancreas rejection [7, 16, 17, 22, 23]. Urinary amylase concentration per unit time is currently being investigated as a more sensitive assay of pancreatic function. In addition to urinary amylase, urinary pH, lipase, protein, interleukin-2 receptors, thromboxanes, prostaglandins, neopterin, insulin, exfoliative cytology, and serum immunoreactive trypsins are currently under investigation as to their value in the early diagnosis of pancreas allograft rejection [2, 13, 14, 29]. Other diagnostic approaches, such as pancreas or duodenal biopsy via cystoscopy and the determination of shedded DR antigens in the urine (antigen capture test), are only possible with the use of the bladder technique.

There have been several attempts at pancreatic imaging. Imaging modalities, including nuclear scans, ultrasound, computed tomography, magnetic resonance imaging, and angiography, have met with some success [4, 21]. Since pancreas transplantation is a relatively new procedure, experience with the various imaging techniques is limited. At present, radionuclide scanning has shown the most promise in evaluating the transplanted pancreas [10, 11, 15]. The use of Tc-DTPA has the advantages of being inexpensive and readily available, with a low radiation dose to the patient. In addition, the 6-h half-life allows examinations to be repeated as needed. However, poor visualization of the pancreas may occasionally occur during radionuclide flow studies despite normal allograft function; thus, the results

must be interpreted in conjunction with clinical findings.

In this study, monitoring pancreas allograft function by urinary amylase determinations, TI, and renal function in combined engraftments enabled the timely diagnosis and successful treatment of rejection. Additionally, urinary amylase levels and TI were excellent indicators of the effectiveness of antirejection therapy. Despite quadruple immunosuppression in this population, early rejection was common after pancreas transplantation. Hyperglycemia was a valid, but delayed, parameter of pancreas allograft rejection and was associated with a high rate of graft loss. Urinary amylase and the TI consistently decreased prior to the onset of hyperglycemia in pancreas rejection, resulting in improved graft salvage and a reduced incidence of hyperglycemia when compared to previous reports [3, 9, 17, 24, 25, 27]. In simultaneous pancreas-kidney transplants, the advantage of renal function as an additional indicator of rejection was well demonstrated. Renal rejection was a reliable harbinger of pancreas rejection, as shown by significantly reduced rates of hyperglycemia and graft loss in this setting. This improvement in antirejection efficacy in combined pancreas-kidney recipients is most certainly due to the earlier diagnosis of allograft rejection in this population and is reflected in enhanced graft survival. Simultaneous pancreas-kidney transplantation is currently our preferred operative approach.

The mainstay of antirejection therapy is increased immunosuppression. In simultaneous allografts, aggressive treatment of kidney rejection results in functional survival of both organs [1]. Most centers employ pulsed corticosteroids and/or ALG preparations as initial therapy for rejection. A paradox of treatment is that bolus steroids, by inducing peripheral insulin resistance, may actually precipitate or worsen what is to be prevented, namely, hyperglycemia. ALG alone can reverse pancreas allograft rejection - even in cyclosporine-treated patients - and has a nondiabetogenic mode of action [19, 26]. Rejection episodes in patients on cyclosporine appear milder and acute severe vascular rejection episodes are rarely encountered [12]. For patients receiving ALG prophylactically, repeat courses of ALG have been used successfully to control rejection. However, monoclonal antibody therapy with OKT_3 is being increasingly employed not only for resistant or recurrent rejection but for primary therapy as well [28]. Contrary to prior studies, salvage therapy with OKT_3 is a safe and effective means of reversing rejection in pancreas allograft recipients [18]. The apparent discrepancy in the efficacy of OKT_3 in pancreas allograft rejection can be explained by the earlier diagnosis and treatment of allograft rejection in our population. Experience with the institution of early or prophylactic OKT_3 therapy requires further investigation as a therapeutic modality.

In summary, vascularized pancreas transplantation has assumed an emerging role in the treatment of diabetes mellitus. Immunological rejection has been the greatest obstacle to successful pancreas transplantation and is currently the major cause of graft failure. The tendency toward sudden deterioration in allograft function with irreversible islet destruction underscores the importance of the early diagnosis and implementation of effective therapeutic regimens. In simultaneous pancreas-kidney allografts, renal rejection occurs first and heralds pancreas rejection. With secretory drainage techniques, the exocrine pancreas has been shown to be more susceptible to rejection than islet cells. Urinary amylase monitoring is a sensitive indicator of exocrine rejection and impending endocrine dysfunction, and therapeutic interventions are most successful when initiated at this point in time. Hyperglycemia is a terminal event in the sequence of immunologic rejection; reversal of rejection is difficult after its onset. Radionuclide imaging provides useful information regarding pancreas perfusion, and refinements in current techniques will hopefully improve our ability to diagnose rejection early. Modifications in existing diagnostic and immunosuppressive regimens are currently being explored to further improve pancreas allograft survival and to control rejection with acceptable morbidity and mortality.

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