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Use of tacrolimus and mycophenolate mofetil as induction and maintenance in simultaneous pancreas-kidney transplantation

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Abstract Clinical trials using quadruple immunosuppression that include the combination of tacrolimus and mycophenolate mofetil have been shown to reduce the incidence of acute rejection episodes in simultaneous pancreas-kidney (SPK) transplantation. In an attempt to obtain a low rejection rate without antibody induction therapy, we undertook a prospective study of combined tacrolimus and mycophenolate mofetil and steroids as primary immunosuppression for SPK transplantation. In this study, we analyzed 17 patients who received low-dose intravenous tacrolimus as induction therapy. This was combined with oral tacrolimus, mycophenolate mofetil, and steroids as the primary immunosuppression regimen. There was a significant reduction of empirically and biopsy-proven rejection with an incidence of 23% (4 patients). Leukopenia, gastroparesis, and gastrointestinal side-effects were the cause of discontinuation of mycophenolate mofetil, or low tacrolimus trough level in those patients who developed rejection. All rejection episodes were easy to treat, and none of them required antibody therapy. The combination of tacrolimus with mycophenolate mofetil without antibody induction therapy is effective in preventing early acute rejection. This combination is safe and effective as an alternative immunosuppressive regimen after SPK transplantation.

Key words Induction therapy · Tacrolimus · Simultaneous pancreas-kidney transplantation · Acute rejection · Mycophenolate mofetil

Introduction

One of the major problems facing simultaneous pancreas-kidney (SPK) transplantation is graft loss due to rejection. In the early 1990s, episodes of acute rejection were reported to occur in about 80% of patients [1], varying from 64% [2] to 100% [3], a rate higher than that for other organ transplants.

The use of antibody therapy in combination with a base immunosuppressive regimen has been standard in SPK transplantation. Recently, tacrolimus (T) has been used with antibody therapy in SPK transplant recipients with a 35% incidence of first reversible rejection episode by 6 months [4]. By adding mycophenolate mofetil (MMF) in combination with tacrolimus or cyclosporine and antibody therapy, the incidence of biopsy proven rejection decreased to 11% in the first 3 months [5].

Lately, the use of antibody therapy has become controversial, due to the introduction of these new potent immunosuppressive agents.

In an effort to decrease the morbidity associated with antibody therapy without increasing the acute rejection rate, we report our experience in SPK transplantation without antibody therapy induction using tacrolimus and mycophenolate mofetil as the base immunosuppressive regimen.

Table 1 Recipient immunosuppression for simultaneous pancreas/kidney transplantation (SPK)

Induction immunosuppression:	
Tacrolimus	Start immediately after surgery at 1 mg/over 24 h, along with oral tacrolimus at 0.1–0.2 mg/kg/day
Steroids	750 mg the day of surgery tapered to 0.1 mg/kg/day over 3 months
Mycophenolate mofetil (MMF)	1 g twice a day
Maintenance immunosuppression:	
Steroids	4 mg/day by 3–6 months
Tacrolimus	Aiming at maintaining level of 5–15 ng/ml (whole blood) for the first 12 months post-transplant
MMF	1 g twice a day
Treatment of rejection episodes:	
Biopsy-proven rejection episodes: solumedrol, and/or tacrolimus IV. Antibody therapy in case of resistant rejection	

Patients and methods

From May 1997 through December 1997, 17 SPK were performed using pancreatic exocrine bladder drainage. The recipient group included 8 men and 9 women , with a mean age 34.7 years (range 26–48 years), and mean duration of diabetes of 24 years (range 15–34 years). The mean duration of end-stage renal disease was 10 months (range 2–24 months), and three patients underwent preemptive SPK. Two patients had undergone prior living related kidney transplant with islet cell infusion. Mean follow-up time was 20.3 months (range 17–24 months).

Immunosuppression

Induction immunosuppression (Table 1) consisted of low dose tacrolismus T intravenous (iv), along with oral tacrolismus. The intravenous dose was started immediately after surgery by continuous iv infusion at doses of 1 mg/24 h, and continued for a mean of 6 days (range 4–8 days). The iv dose was adjusted with an oral dose of tacrolismus (0.1–0.2 mg/kg/day) to maintain a trough level of 10–15 ng/ml. Methylprednisolone (750 mg on the date of surgery tapered to 0.1 mg/kg/day over 3 months) and MMF (1 g twice a day) were given concurrently.

Results

In the 17 patients, the kidney and the pancreas are functioning. Current creatinine is 1.1 ± 0.21 mg/dl. Glycemic control remains normal, with fasting blood sugar 88 ± 16.8 mg/dl and normal serum amylase and lipase (70 ± 41.83 IU/l and 31 ± 51.8 IU/l, respectively). There were 5 rejection episodes in 4 patients (23%) (Table 2). All rejection episodes were treated easily, and none required antibody therapy. There were 2 episodes of biopsy-proven rejection (1 pancreas and the other kidney) (2 patients, 11.7%) that responded to steroid bolus (500 mg × 3 doses) plus iv tacrolismus ($n = 1$), and to steroid bolus alone (500 mg × 1 dose) ($n = 1$). Both patients were restarted on MMF. Steroids (500 mg × 3 doses) were given empirically for a rise in creatinine to 1 patient and for increased serum amylase/lipase and creatinine to 1 patient (Table 3). Only one patient was not on MMF, and he was restarted on MMF during the rejection episode. No graft was lost due to rejection. Two patients had rejection episodes in the first 3 months (11.7%) and the other two at 6 months (11.7%). Three of the four patients had MMF discontinued for gastrointestinal intolerance and one for leukopenia during a viral syndrome. Two of the four patients had a tacrolismus trough level < 8 ng/dl during the rejection episode, one of them due to a severe gastroparesis. One patient developed cytomegalovirus (CMV) gastritis and the other CMV + by polymerase chain reaction (PCR) that responded to ganciclovir iv and stopping MMF.

Table 2 Incidence of rejection episodes

	n	Patients (%)
Rejections[a]	5	4 (23)
Biopsy-proven rejection	2	2 (11.7)
Empirically treated rejection	3[b]	2 (11.7)

[a] Biopsy-proven and/or empirically treated rejection episodes
[b] One patient had increased creatinine and serum amylase and lipase. He had a low trough level of tacrolimus due to severe gastroparesis (he had had a gastrojejunostomy feeding tube for 2 years prior to SPK)

Table 3 Type and treatment of rejection (*IV* intravenous, *MMF* mycophenolate mofetil, *ACR* acute cellular rejection, *VC* vascular component)

	n	Tacrolimus IV	Steroids	MMF
Biopsy-proven				
Kidney: Mild ACR with VC	1	Yes[a]	500 mg × 3	Yes[b]
Pancreas: Mild ACR	1		500 mg × 1	Yes[b]
Empirically treated rejection				
Increased creatinine	1		500 mg × 3	
Increased creatinine and serum amylase and lipase	1		500 mg × 3	Yes[b]

[a] Treated with tacrolimus iv
[b] Restarted on MMF

Discussion

This preliminary study demonstrates the effectiveness of low dose tacrolimus given intravenously as induction therapy combined with oral tacrolimus, MMF, and steroids. The most significant clinical finding was the reduction of early acute rejection episodes. Initially, we reported the potency of the use of low dose iv tacrolismus to treat rejection in SPK and to reverse vascular rejection in kidney and SPK recipients, sparing these

patients an extra course of monoclonal or polyclonal antibody [6, 7]. Since then, it has been used as induction and maintenance in some renal transplant recipients over the age of 60 years, with a rejection rate of 20% [8], and lately as induction and maintenance in SPK [9].

The results indicate that iv tacrolismus associated with a base immunosuppressive regimen of oral tacrolismus, MMF, and steroids may be an effective approach. The combination of tacrolismus and MMF has been used before in SPK, with rejection episodes of between 19% and 50% [10–12]. All these clinical studies included antibody as induction therapy. In the current study, 23% (11.7% at 3 and 6 months, respectively) empirically and biopsy-confirmed acute rejection is in a comfortable range when compared with studies that use quadruple therapy protocol [10–12] or without antibody therapy [13].

None of the rejection episodes were steroid-resistant, and all were treated successfully, including the patient with a kidney biopsy-proven vascular component. This rejection episode was treated with iv tacrolismus as previously described [6, 7].

The addition of MMF to tacrolimus therapy has allowed us to eliminate induction antibody therapy from our protocol. This regimen may be potent enough to reduce rejection episodes without resorting to the use of antibody therapy as induction therapy and/or for treatment of rejection. The markedly low incidence of acute rejection in this group of recipients reflects the results of combining two potent immunosuppressive agents. The net immunosuppressive effect of this combination was likely further enhanced by the interaction of tacrolismus with MMF metabolism. Zucker et al. [14] reported an augmentation of mycophenolic acid pK in renal transplant recipients receiving tacrolimus rather than cyclosporine. This resulted in a significant increase in both the mycophenolic acid trough and area under the curve (AUC) values. Thus, the low rate of acute rejection in these groups of patients probably represents the net effect of interaction of tacrolismus with MMF pharmacokinetics.

In summary, tacrolismus and MMF are potent immunosuppressive agents, which may reduce acute rejection episodes in the first postoperative year. Hyperglycemia has not been identified in this group of patients. In fact, euglycemia (normal fasting blood glucose) was achieved. Further follow-up and a larger number of patients will be needed to evaluate the efficacy of this protocol.

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